REGULATION (EC) NO 1272/2008 (CLP REGULATION),

ANNEX VI, PART 2

Proposal for Harmonised Classification and Labelling for a biocidal active substance

CLH REPORT

Tetrahydro-3,5-dimethyl-1,3,5-thiadia-zine-2-thione (Dazomet)

EC Number: 208-576-7

CAS Number: 533-74-4

Index Number: 613-008-00-X

Contact details of evaluating CA: : Competent Authority Belgium

Contact details dossier submitter:

FPS Public Health, Food Chain Safety and Environment

DG 5/ Department of Product Policy and chemical Substances / Management of Chemical Substances

BELGIUM

Version number: 4.0 **Date: May 2024**

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STATEMENT

This CLH report has been established as a result of the renewal of approval of the active substance Dazomet (CAS no: 533-74-4) as product-type 8 (Wood Preservatives), carried out in the context of Biocidal Products Regulation (EC) No 528/2012 (BPR).

Important to note that Dazomet is already listed in Annex VI of Regulation (EC) no 1272/2008. Without assessing all hazard classes, this CLH report addresses only the endpoints for which a revision is proposed based on data received from the Applicant, Kanesho Soil Treatment SRL/BV.

As indicated in the template of the CLH report, the key studies are written in **green** (see tables).

SUMMARY

1 PRESENTATION OF THE ACTIVE SUBSTANCE

1.1 IDENTITY OF THE ACTIVE SUBSTANCE

Table 1-1: Main constituent(s)

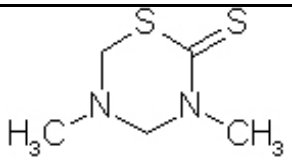
Main constituent(s)	
ISO name	Dazomet
IUPAC or EC name	Tetrahydro-3,5-dimethyl-1,3,5-thiadiazine-2-thione
EC number	208-576-7
CAS number	533-74-4
Index number in Annex VI of CLP	613-008-00-X
Minimum purity / content	960 g/kg
Structural formula	

Table 1-2: Relevant impurities and additives

Relevant impurities and additives
None of the impurities contribute to the classification. Please see Confidential Annex for more information on the impurities.

1.2 INTENDED USES AND EFFECTIVENESS

Table 1-3: Use of the active substance

Product type	Product Type 8: Wood preservatives
Intended use pattern(s)	-
Users	Professional

Table 1-4: Effectiveness of the active substance

Function	PT 8 Wood preservatives (curative effect)
Organisms to be controlled	Wood destroying fungi (brown rot, white rot and soft rot). Typical representatives of these fungi are *Poria spp., Coriolus spp., Gloeophyllum spp., Chaetomium spp..*
Limitation of efficacy including resistance	There is no evidence of practical fungal resistance to Dazomet. Due to the relative unspecific binding spectrum (binding to amines and SH-groups), a resistance development seems extremely unlikely.
Mode of action	In contact with moisture, the active ingredient Dazomet hydrolyses to methyl-isothiocyanate (MITC). The hydrolysis product MITC, which is the active form of Dazomet, binds to amines and SH-groups. This relatively unspecific effect will inhibit the metabolism of the fungi.

2. PROPOSED HARMONISED CLASSIFICATION AND LABELLING OF THE ACTIVE SUBSTANCE ACCORDING TO THE CLP CRITERIA

2.1 PROPOSED HARMONISED CLASSIFICATION AND LABELLING FOR THE ACTIVE

Table 2-1: Proposed harmonised classification and labelling of the substance

	Index No	Chemical name	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors and ATEs	Notes
					Hazard Class and Category Code(s)	Hazard statement Code(s)	Pictogram, Signal Word Code(s)	Hazard statement Code(s)	Suppl. Hazard statement Code(s)		
Current Annex VI entry	613-008-00-X	Dazomet (ISO) tetrahydro-3,5-dimethyl-1,3,5-thiadiazine-2-thione	208-576-7	533-74-4	Acute Tox. 4* Eye Irrit. 2 Aquatic Acute 1 Aquatic Chronic 1	H302 H319 H400 H410	GHS07 GHS09 Wng	H302 H319 H400 H410			
Dossier submitter's proposal	613-008-00-X	Dazomet (ISO) tetrahydro-3,5-dimethyl-1,3,5-thiadiazine-2-thione	208-576-7	533-74-4	**Retain** Eye Irrit. 2 Aquatic Acute 1 Aquatic Chronic 1 **Modify** Acute Tox. 4 **Add** STOT SE 3 STOT RE 1 Skin Irrit. 2 Skin Sens. 1	**Retain** H319 H400 H410 **Modify** H302 **Add** H335 H372 (liver) H315 H317	**Retain** GHS07 GHS09 **Modify** Dgr **Add** GHS08	**Retain** H319 H410 **Modify** H302 **Add** H335 H372 (liver) H315 H317 **Remove** H400		**Add** oral: ATE = 415 mg/kg bw M = 10	
Resulting entry in Annex VI if adopted by RAC and agreed by Commission	613-008-00-X	Dazomet (ISO) tetrahydro-3,5-dimethyl-1,3,5-thiadiazine-2-thione	208-576-7	533-74-4	Acute Tox. 4 STOT SE 3 STOT RE 1 Skin Irrit. 2 Eye Irrit. 2 Skin Sens. 1 Aquatic Acute 1 Aquatic Chronic 1	H302 H335 H372 (liver) H315 H319 H317 H400 H410	GHS07 GHS08 GHS09 Dgr	H302 H335 H372 (liver) H315 H319 H317 H410		oral: ATE = 415 mg/kg bw M = 10	

Table 2-2: Reason for not proposing harmonised classification and labelling and the status under CLH consultation

Hazard class	Reason for not proposing classification and labelling	Within the scope of consultation *(please select YES or NO from the drop down list)* (yes/no)
Explosives	Data conclusive but not sufficient for classification	Yes
Flammable gases (including chemically unstable gases)	Hazard class not applicable (e.g. physical state or chemical structure)	No
Oxidising gases	Hazard class not applicable (e.g. physical state or chemical structure)	No
Gases under pressure	Hazard class not applicable (e.g. physical state or chemical structure)	No
Flammable liquids	Hazard class not applicable (e.g. physical state or chemical structure)	No
Flammable solids	Data conclusive but not sufficient for classification	Yes
Self-reactive substances and mixtures	Data conclusive but not sufficient for classification	Yes
Pyrophoric liquids	Hazard class not applicable (e.g. physical state or chemical structure)	No
Pyrophoric solids	Data conclusive but not sufficient for classification	Yes
Self-heating substances and mixtures	Data conclusive but not sufficient for classification	Yes
Substances which in contact with water emit flammable gases	Data conclusive but not sufficient for classification	Yes
Oxidising liquids	Hazard class not applicable (e.g. physical state or chemical structure)	No
Oxidising solids	Data conclusive but not sufficient for classification	Yes
Organic peroxides	Data conclusive but not sufficient for classification	Yes
Corrosive to metals	Data conclusive but not sufficient for classification	Yes
Desensitised explosives	Hazard class not applicable (e.g. physical state or chemical structure)	Yes
Acute toxicity via oral route	Already harmonised on ATP00: Acute toxicity.4	Yes
Acute toxicity via dermal route	Data conclusive but not sufficient for classification	Yes
Acute toxicity via inhalation route	Data conclusive but not sufficient for classification	Yes
Skin corrosion/irritation	Harmonised classification proposed	Yes
Serious eye damage/eye irritation	Already harmonised on ATP00: Eye irritant.2	Yes
Respiratory sensitisation	Data conclusive but not sufficient for classification	Yes
Skin sensitisation	Harmonised classification proposed	Yes
Germ cell mutagenicity	Data conclusive but not sufficient for classification	Yes
Carcinogenicity	Data conclusive but not sufficient for classification	Yes

Reproductive toxicity	Data conclusive but not sufficient for classification	Yes
Specific target organ toxicity-single exposure	Harmonised classification proposed	Yes
Specific target organ toxicity-repeated exposure	Harmonised classification proposed	Yes
Aspiration hazard	Data conclusive but not sufficient for classification	No
Hazardous to the aquatic environment	Harmonised classification proposed	Yes
Hazardous to the ozone layer	Data conclusive but not sufficient for classification	Yes

2.1.1 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

BE CA was the evaluation CA for the approval of Dazomet. There is current harmonized classification for the active substance Dazomet according to Annex VI of Regulation (EC) no 1272/2008.

Proposed classification/labelling for the active substance, Dazomet, following the initial approval/evaluation:

On the basis of a review of the data submitted, the BE CA concludes that the current classification of Dazomet on Annex 1 to Directive 67/548/EEC cannot be maintained. The available published human data does give evidence that Dazomet should be classified as a skin, eye, and respiratory tract irritant and a skin sensitizer through MITC formation. With regard to reproductive toxicity, Dazomet showed some effects (variations and runts) but with the data available, it cannot be ruled out that classification is warranted. We want to inform that possible classification as toxic to reproduction Cat.3 is not excluded.
Regarding environment, a completely new data package has been submitted to comply with the current guidelines. However, based on the new information, the classification has not been changed. However, M-factors have now been taken into account. Therefore, Dazomet is still classified as aquatic acute 1, with a M-factor of 10, and aquatic chronic 1, with a M-factor of 1.

According to CLP:	
Acute Tox. 4	H302
STOT SE 3	H335
Skin Sens. 1	H317
Aquatic Acute 1	H400
Eye Irrit 2	H319
Skin Irrit 2	H315
Repr. 2	H361d
Aquatic Chronic 1	H410

Justification that action is needed at community level

Justification that action is needed at Community level is required.

Reason for a need for action at Community level for the specific endpoints:

- Human Health:

    1. Skin irritation, skin sensitization and STOT SE 3: a change in an existing entry is considered justified due to a new interpretation and/or evaluation of existing data.

    2. STOT RE 1: where there is a harmonised classification entry in Annex VI to CLP containing a minimum classification and it is concluded that a refinement of the classification based on new available data is justified.

- Environment:

  The endpoints were revised due to new available data in order to comply with the updated guidelines but the classification of Dazomet does not change (Aquatic Acute 1 and Aquatic Chronic 1).

2.2 PROPOSED CLASSIFICATION AND LABELLING AND PACKAGING FOR THE REPRESENTATIVE PRODUCT(S)

Not applicable for the CLH report.

Table 2-3: Proposed Classification and Labelling according to Regulation (EC) No 1272/2008

Not applicable for the CLH report.

Table 2-4: Packaging of the biocidal product

Not applicable for the CLH report.

2.3 DATA SOURCES

See the reference list in part D of Appendix V of this CLH report and the IUCLID dossier (UUID: e06cd6d2-aa99-40ea-b1ff-a5424d0e8b93). All the relevant data from PPP Dazomet (Bulgaria) have been taken into account.

Additional relevant information, which could be considered for the harmonized classification process for Dazomet, can be found in the adequate CLH dossiers for MITC and Metam Sodium. The ongoing public consultations for the relevant substances can be consulted from the following links:

- Metam-sodium

  https://echa.europa.eu/harmonised-classification-and-labelling-consultation/-/substance-rev/75214/term

- MITC (methyl isothiocyanate)

  https://echa.europa.eu/harmonised-classification-and-labelling-consultation/-/substance-rev/75215/term

- Dazomet

  https://www.efsa.europa.eu/en/consultations/call/public-consultation-active-substance-dazomet

3. SUMMARY OF THE HUMAN HEALTH RISK ASSESSMENT

Not applicable for the CLH report.

3.1 SUMMARY OF THE ASSESSMENT OF EFFECTS ON HUMAN HEALTH

Table 3-1: Summary of the assessment of effects on human health

Not applicable for the CLH report.

3.2 REFERENCE VALUES

Table 3-2: Reference values

Not applicable for the CLH report.

3.3 RISK CHARACTERISATION

Not applicable for the CLH report.

Table 3-3: Summary of exposure scenarios

Not applicable for the CLH report.

Table 3-4: Conclusion of risk characterisation for industrial user

Not applicable for the CLH report.

Table 3-5: Conclusion of risk characterisation for professional user

Not applicable for the CLH report.

Table 3-6: Conclusion of risk characterisation for non-professional user

Not applicable for the CLH report.

Table 3-7: Conclusion of risk characterisation for indirect exposure

Not applicable for the CLH report.

4. SUMMARY OF THE ENVIRONMENTAL RISK ASSESSMENT

Not applicable for the CLH report.

4.1 FATE AND BEHAVIOUR IN THE ENVIRONMENT

Table 4-1: Summary table on compartments exposed and assessed

Not applicable for the CLH report.

Table 4-2: Summary table on relevant metabolites/degradants

Not applicable for the CLH report.

Table 4-3: Summary table on relevant physico-chemical and fate and behaviour parameter of the active substance and of the relevant metabolite MITC

Not applicable for the CLH report.

4.2 EFFECTS ASSESSMENT

Table 4-4: Summary table on calculated PNEC values

Not applicable for the CLH report.

4.3 EXPOSURE ASSESSMENT

Table 4-5: Summary table on calculated PEC values

Not applicable for the CLH report.

4.4 RISK CHARACTERISATION

Table 4-6: Summary table on calculated PEC/PNEC values

Not applicable for the CLH report.

5. ASSESSMENT OF EXCLUSION CRITERIA, SUBSTITUTION CRITERIA AND POP

Not applicable for the CLH report.

Table 5-1: Assessment of exclusion criteria, substitution criteria and POP

Not applicable for the CLH report.

A Assessment of intrinsic properties and effects of the active substance

A.1 General substance information

A.1.1 Identity of the Substance

Table A-1: Summary table on substance identity

Summary table on substance identity	
Common name (ISO name, synonyms)	Dazomet
Chemical name (EC name, CA name, IUPAC name)	IUPAC: Tetrahydro-3,5-dimethyl-2H-1,3,5-thiadiazine-2-thione CA: 2H-l ,3,5-thiadiazine-2-thione, tetrahydro-3,5-dimethyl-
EC number	208-576-7
CAS number	533-74-4
other CAS numbers (e.g. deleted, related, preferred, alternate)	n.a.
Molecular formula	$C_5H_{10}N_2S_2$
Molecular weight or molecular weight range	162.3
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	Not applicable.
Description of the manufacturing process and identity of the source (for UVCB substances only)	Please see Confidential Annex.
Degree of purity (%)	Minimum purity of active substance 960 g/kg Maximum content of the impurity Please see Confidential Annex.

Table A-2: Structural formula

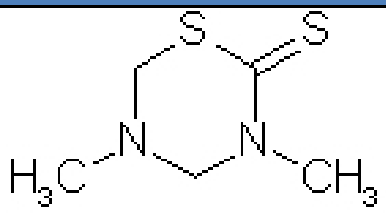
Structural formula


Table A-3: Origin of the natural active substance or precursor(s) of the active substance

Origin of the natural active substance or precursor(s) of the active substance
Please see Confidential Annex.

Table A-4: Method of manufacture

Method of manufacture
Please see Confidential Annex, table 92.

A.1.2 Composition of the substance (reference specifications)

Confidential information: For information on the composition of the substance (i.e., impurities and additives) please see Confidential Annex, table 91.

Table A-5: Main constituent(s)

Constituent (chemical name)	Typical concentration (% (w/w))	Concentration range (% (w/w))	Current CLH in Annex VI Table 3 (CLP)	Current self-classification and labelling (CLP)	Remarks / Discussion
Dazomet (CAS No. 533-74-4) IUPAC: Tetrahydro-3,5-dimethyl-2H-1,1,3,5-thiadiazine-2-thione	-	Minimum 96 %	See remark	See remark	See Section 2, Table 2.1 for Classification and Labelling

Table A-6: Impurities

Impurities do not contributes to the classification. Additional information can be found in the Confidential Annex, Table 93.

Table A-7: Additives

Dazomet contains no additives.

Table A-8: Concentration of constituents (main constituents, impurities, additives) in batches used for (eco)toxicity studies and proposed specification

See Confidential Annex, Table 94

Table A-9: Concentration of constituents (main constituents, impurities, additives) in batches used for (eco)toxicity studies and proposed specification

See Confidential Annex, Table 94

A.1.3 Physical and chemical properties of the active substance

Table A-10: Physical and chemical properties of the active substance

Property	Result	Test method applied or description in case of deviation	Remarks / Discussion / Justification for waiving	References
Aggregate state at 20°C and 101.3 kPA	Crystalline	Internal BASF methods, GLP	Dazomet Lot No. 39-155-2, purity 99.8 %	[redacted] (2000a) A3.1-001
Physical state (appearance) at 20°C and 101.3 kPA	Solid	Internal BASF methods, GLP	Dazomet Lot No. 39-155-2, purity 99.8 %	[redacted] (2000a) A3.1-001
Colour at 20°C and 101.3 kPA	Colourless	Internal BASF methods, GLP	Dazomet Lot No. 39-155-2, purity 99.8 %	[redacted] (2000a) A3.1-001
Odour at 20°C and 101.3 kPA	weak characteristic	Internal BASF methods, GLP	Dazomet Lot No. 39-155-2, purity 99.8 %	[redacted] (2000a) A3.1-001
Melting / freezing point	Melting Range 103.2 – 105.2 °C	OECD TG 102, GLP	Dazomet Lot No. 39-155-2, purity 99.8 %	[redacted] (2000a) A3.2-001
	35.9 °C	OECD TG 102, non-GLP	MITC	[redacted] (2002) A3.2-002
Boiling point at	Decomposition before boiling 119 °C	(OECD TG 102) + OECD TG 113, GLP (OECD TG 102) + OECD TG 113, non-GLP	Dazomet Lot No. 39-155-2, purity 99.8 % MITC	[redacted] (2000a) A3.4-001 [redacted] (2002) A3.4-002
Vapour pressure	0.0000058 hPa at 20 °C 0.000013 hPa at 25 °C	Thermo-gravimetric method based on evaporation rates (modified vapour pressure balance principles), non-GLP	Dazomet Lot No. CH 68 52 90 purity > 99.5 %	[redacted] (1988) A3.7.1-001

	25 hPa at 20 °C	Thermo-gravimetric method based on evaporation rates (modified vapour pressure balance principles), GLP	MITC	[redacted] (2001) A3.7.1-002
Henry's law constant	measured/calculated: result: 2.5 x 10-5 Pa*m³/mol at 20 °C measured/calculated: result: 22 Pa*m³/mol at 20 °C	Calculated on the basis to the vapour pressure and the water solubility (formula: H=p*MW/c , non-GLP Calculated on the basis to the vapour pressure and the water solubility (formula: H=p*MW/c , non-GLP	Dazomet MITC	[redacted] (2004) A3.7.2-001 [redacted] (2004) A3.7.2-002
Surface tension	69.4 mN/m at 20 °C (Concentration: 0.1 %) 69.9 mN/m at 20 °C (Concentration: 1.0 %) Dazomet is not surface active	Directive 92/69/EEC, A.5, GLP	BAS 002 01 N, Dazomet technical, purity 97 % Reviewers comment: BAS00201N [redacted]	[redacted] (2000a) A3.8-001
Water solubility at 20 °C	pH temperature result 5 10.3 +/- 0.1°C 2.7 g/L 5 20.2 +/- 0.1°C 3.5 g/L 5 30.3 +/- 0.1°C 5.0 g/L 7 10.3 +/- 0.1°C 2.7 g/L 7 20.2 +/- 0.1°C 3.7 g/L 7 30.3 +/- 0.1°C 5.3 g/L 9 10.3 +/- 0.1°C 2.9 g/L 9 20.2 +/- 0.1°C 3.9 g/L 9 30.3 +/- 0.1°C 5.6 g/L pH value: 6.6 – 7 8.36 g/L at 20 °C	including effects of pH (5-9) Directive 92/69/EEC, A.6 Japanese MAFF (12-Nousan-No. 8147, 2000) (Flask method); MITC was determined by HPLC with UV-spectro-photometer or photodiode array detector	Dazomet MITC, purity: 99.9 % (by the supplier)	[redacted] (2002a) A3.9-001 [redacted]. (2001a) A3.9-002
Partition coefficient (n-octanol/water) and its pH dependency	**pH temperature result** log Pow 5 24 +/- 1 °C 0.3 7 24 +/- 1 °C 0.3	including effects of pH (5-9) OECD TG 107 Theoretical value: 0.9	Dazomet	[redacted] (2002b) A3.10-001

	9 24 +/- 1 °C 0.3	(calculation with EPWIN-software, Syracuse Research Corp., 1992-1994, Merrill Lane, Syracuse, N. Y.		
	pH value: 6.8 – 7.1 Pow= 15.7+/-0.68 at 25 °C Log Pow= 1.2 at 25 °C	Japanese MAFF (12-Nousan-No. 8147, 2000) (Shake flask); MITC was determined by HPLC with UV detection	MITC, purity: 99.9 % (by the supplier)	[redacted]. (2001b) A3.10-002
Thermal stability and identity of breakdown products	Decomposition at > 150 °C Maximum at 180 °C	OECD TG 113, GLP	Dazomet Lot No. 39-155-2, purity 99.8 %	[redacted]. (2000a) A3.11-001
	Decomposition at > 160 °C	German DIN 51007, non-GLP	MITC	[redacted] (1988) A3.11-002
Reactivity towards container material	No leakage or rupture of the original container was observed during normal handling before and after storage.	BASF-internal standard CF/P 061.8 Visual examination of the container and sensing the plasticity of the container material. GLP Type of Storage Containers: paper bag, PE laminated Storage period: 24 months Storage temperature: 20 °C 50 % rel. humidity and at 30 °C	BAS 002 01 N, Dazomet technical, purity 97 %	[redacted] (2002) A3.12-001 [redacted] (2002) A3.12-002
Dissociation constant	The test substance does not dissociate. The determination of pKa involves a titration method carried out in deionized water at the concentrations of c. 1.33g/L (8.2 mmol/L) and at a	OECD TG 112, GLP	Dazomet Lot No. 39-155-1, purity 99.9 %	[redacted] (2000c) A3.13-001

	temperature of 20 °C.			
Viscosity			n.a. (solid)	
Solubility in organic solvents, including effect of temperature on solubility	**Temperature: 20 °C** **Result: g/L** Acetone 89.7 Ethyl acetate 28.5 Toluene 8.6 Dichloromethane 234 n-Heptane <0.1 Acetonitrile 112 Methanol 21.3 Iso-propanol 3.6 Octanol 2.2 Lutrol 43.0 Olive oil 1.7	EPA Guideline No. 63-8, GLP	Dazomet Lot No. 39-155-1, purity 99.9 %	[redacted] (1991) A3.16-001
Stability in organic solvents used in biocidal products and identity of relevant degradation products	-	-	Organic solvents not used in the biocidal products.	-

Dazomet presents a low vapour pressure and will not evaporate into the atmosphere. It does not dissociate and is not surface active. Dazomet is slightly soluble in water and many organic solvents.

MITC, the main hydrolysis degradation product of Dazomet, is soluble in water, has high vapour pressure and will rapidly evaporate into the atmosphere. From the water surface, MITC will evaporate into the atmosphere.

A.1.3.1 Physical hazards and respective characteristics

Table A-11: Physical hazards and respective characteristics

Hazard class / characteristics	Guideline and Method	Parameter(s)	Results / Waiver	Reference
Explosives	Directive 92/69/EEC, A.14	Explosive properties	BAS 002 01 N, Dazomet technical, purity 97 % Test A14 has not been carried out due to the chemical structure of the substance *Not Explosive* MITC The substance has no chemical groups indicating explosive properties. This statement agrees with the recommendations on the transport of dangerous goods, Manual of Tests and criteria, Appendix 6 (third revised edition) of the United Nations *Not Explosive*	[redacted] (2000) A4.1-001 [redacted] (1999), A4.1-002 [redacted] (2003), A4.1-003
Flammable gases			n.a.: Dazomet is a solid	
Flammable aerosols			n.a.: Dazomet is a solid	
Oxidising gases			n.a.: Dazomet is a solid	
Gases under pressure			n.a.: Dazomet is a solid	
Flammable liquids	Test A9 was not conducted because the test substance is a solid Directive 92/69/EEC, A.9, non-GLP	Flashpoint Flashpoint	BAS 002 01 N, Dazomet technical, purity 97 % *n.a. (solid)* MITC *32 °C*	[redacted] (2000) A4.6-001 [redacted] (2002) A4.6-002
Flammable solids	Directive 92/69/EEC, A.10, GLP	Flammability (solids)	BAS 002 01 N, Dazomet technical, purity 97 % *Preliminary test:* *The burning time was 33 min.* *Interpretation of the result:* *The test substance is not considered highly flammable*	[redacted] (2000) A4.2-001

Self-reactive substances and mixtures	Directive 92/69/EEC, A.16, GLP	Relative self-ignition temperature for solids	BAS 002 01 N, Dazomet technical, purity 97 % *No self-heating at temperatures up to the melting point*	[redacted] (2000) A4.8-001
Pyrophoric liquids	Regulation (EC) N° 440/2008 Method A13 UN Manual of tests and criteria UN Test N.2	Ignition in contact with air	n.a.: Dazomet is a solid	[redacted]
Pyrophoric solids			Dazomet, technical purity: 97.99 %	
Self-heating substances and mixtures	Directive 92/69/EEC, A.16, GLP	Relative self-ignition temperature for solids	BAS 002 01 N, Dazomet technical, purity 97 % *No self-heating at temperatures up to the melting point*	[redacted] (2000) A4.17-005
Substances and mixtures which in contact with water emit flammable gases	UN Manual of tests and Criteria UN model regulations Regulation (EC) N° 440/2008 Method A. 12	Amount of emitted gas	Dazomet, technical purity: 98 %	[redacted]
Oxidising liquids			n.a.: Dazomet is a solid	
Oxidising solids	Directive 92/69/EEC, A.17	Oxidizing properties (solids)	BAS 002 01 N, Dazomet technical, purity 97 % Test A17 has not been carried out because the chemical structure of the substance *No oxidizing properties* MITC The substance has no oxidizing properties, because the chemical structure does not contain oxygen, fluorine or chlorine. This statement agrees with the recommendations on the transport of dangerous goods, Manual of Tests and criteria, Appendix 6 (third revised edition) of the United Nations. *No oxidizing properties*	[redacted]2000) A4.4-003 [redacted] (1999) A4.4-004 [redacted] (2003) A4.4-005
Organic peroxides			Based on structure evaluation, Dazomet is not an organic peroxide.	

Corrosive to metals			Dazomet is a solid, and test of corrosion to metals for solids are complicated, since the relevant test is made for liquid. CLP regulation Annex I, 2.16 indicates that only substances for which the application of UN Test C1 is relevant need to be considered (liquids and solids that may become liquids). Dazomet, as stated above is a solid with a melting point higher than 100°C and that may not become liquid during transport. On the basis of expert judgement, the study does not need to be conducted. The pH is not extreme and dazomet does not contain acidic functional groups, it does not contain halogens, and it is not able to form complexes with metals Furthermore, the active substance Dazomet and formulation [redacted] have a neutral pH around 6-7. Corrosion to metals is therefore not expected.	
Desensitised explosives			n.a.: Dazomet has no explosive properties	
Auto-ignition temperature (liquids and gases)			n.a.: Dazomet is a solid	
Relative self-ignition temperature for solids	Directive 92/69/EEC, A.16, GLP	Relative self-ignition temperature for solids	BAS 002 01 N, Dazomet technical, purity 97 % *No self-heating at temperatures up to the melting point*	[redacted] (2000) A4.17.1-003
Dust explosion hazard	CIPAC MT 171.1 Basamid Batch No. 20180427-11 Purity: 97.5 %	Content of dust of a 30 g sample	Samples of Dazomet/[redacted] are “nearly dust free”, therefore there is no dust explosion hazard. Long term storage stability (2 years) Initial (t=0): 8.7 mg After 12 months: 7.6 mg i.e., “nearly After 24 months: 8.9 mg i.e., “nearly	[redacted](2020) A4.17-004

			i.e., “nearly dust free”	dust free”	dust free”	

A.1.3.2 Assessment of physical hazards according to the CLP criteria

Summary of physical hazards

Dazomet is not explosive, not considered highly flammable, not auto-flammable up to the melting point and has no oxidizing properties. It decomposes before boiling. MITC, the hydrolysis degradation product of Dazomet, is not explosive and has no oxidizing properties.

A.1.3.3 Explosives

Table A-12: Summary table of studies on explosive properties

Method	Results	Remarks	Reference
Directive 92/69/EEC, A.14	BAS 002 01 N, Dazomet technical, purity 97 % *Not Explosive*	Test A14 has not been carried out because of the chemical structure of the substance	[redacted] (2000) A4.1-001 [redacted] (1999) A4.1-002

A.1.3.3.1 Short summary and overall relevance of the provided information on explosive properties

Given the fact that Dazomet does not present any chemical group associated with explosive properties, and does not contain any metallic atom.

A.1.3.3.2 Comparison with the CLP criteria

Dazomet does not present or contain any chemical group associated with explosive properties, and therefore, does not meet the criteria for classification as explosive. Therefore, comparison with CLP criteria would not result in classification of the substance.

A.1.3.3.3 Conclusion on classification and labelling for explosive properties

Dazomet is not classified as explosive. Data conclusive but not sufficient for classification.

A.1.3.4 Flammable gases (including chemically unstable gases)

Table A-13: Summary table of studies on flammable gases (including chemically unstable gases)

Not applicable, Dazomet is a solid, not a gas.

A.1.3.4.1 Short summary and overall relevance of the provided information on flammable gases (including chemically unstable gases)

Not applicable.

A.1.3.4.2 Comparison with the CLP criteria

Not applicable.

A.1.3.4.3 Conclusion on classification and labelling for flammable gases

Not applicable.

A.1.3.5 Flammable aerosols and aerosols

Table A-14: Summary table of studies on flammable aerosols and aerosols

Not applicable, Dazomet is a solid and not provided as an aerosol.

A.1.3.5.1 Short summary and overall relevance of the provided information on flammable aerosols and aerosols

Not applicable.

A.1.3.5.2 Comparison with the CLP criteria

Not applicable.

A.1.3.5.3 Conclusion on classification and labelling for flammable aerosols and aerosols

Not applicable.

A.1.3.6 Oxidising gases

Table A-15: Summary table of studies on oxidising gases

Not applicable, Dazomet is a solid, not a gas.

A.1.3.6.1 Short summary and overall relevance of the provided information on oxidising gases

Not applicable.

A.1.3.6.2 Comparison with the CLP criteria

Not applicable.

A.1.3.6.3 Conclusion on classification and labelling for oxidising gases

Not applicable.

A.1.3.7 Gases under pressure

Table A-16: Summary table of studies on gases under pressure

Not applicable, Dazomet is a solid, not a gas.

A.1.3.7.1 Short summary and overall relevance of the provided information on gases under pressure

Not applicable.

A.1.3.7.2 Comparison with the CLP criteria

Not applicable.

A.1.3.7.3 Conclusion on classification and labelling for gases under pressure

Not applicable.

A.1.3.7.4 Flammable liquids

Table A-17: Summary table of studies on flammable liquids

Not applicable, Dazomet is a solid, not a liquid.

A.1.3.7.5 Short summary and overall relevance of the provided information on flammable liquids

Not applicable.

A.1.3.7.6 Comparison with the CLP criteria

Not applicable.

A.1.3.7.7 Conclusion on classification and labelling for flammable liquids

Not applicable.

A.1.3.8 Flammable solids

Table A-18: Summary table of studies on flammable solids

Method	Results	Remarks	Reference
Directive 92/69/EEC, A.10, Flammability (solids), GLP	BAS 002 01 N, Dazomet technical, purity 97 % Preliminary test: The burning time was 33 min. Interpretation of the result: The test substance is not considered highly flammable.	-	[redacted] (2000) A4.2-001

A.1.3.8.1 Short summary and overall relevance of the provided information on flammable solids

According to UN MTC 7th revised edition Part III section 33, “a preliminary screening test is performed to determine if, on ignition by a gas flame, propagation by burning with flame or smouldering occurs” and follows “If in the screening test, the substance does not ignite and propagate combustion either by burning with flame or smouldering, it is not necessary to perform the complete burning rate test as the substance is not a flammable solid”.
During the preliminary test, dazomet could not be ignited in the first minutes of the test. Consequently, Dazomet is not flammable.

A.1.3.8.2 Comparison with the CLP criteria

With a burning time of 33 minutes, dazomet does not meet the criteria to be considered highly flammable. According to the CLP Regulation, flammability is tested using UN test N.1. However, the screening procedure of methods N.1 and EC A.10 is equivalent, therefore a negative “not highly flammable” result from the A.10 method is conclusive for classification.

A.1.3.8.3 Conclusion on classification and labelling for flammable solids

Dazomet is not a flammable solid. Data conclusive but not sufficient for classification.

A.1.3.8.4 Self-reactive substances

Table A-19: Summary table of studies on self-reactivity.

According to CLP Annex I 2.8.4.2, no classification is required if:

a. no chemical groups associated with explosives and self-reactive properties, OR

b. exothermic decomposition energy < 300 J/g, OR

c. self-accelerating decomposition temperature (SADT) > 75°C for a 50 kg package.

Method	Results	Remarks	Reference
Directive 92/69/EEC, A.16, GLP **(Relative self-ignition temperature for solids)**	BAS 002 01 N, Dazomet technical, purity 97 %. *No self-heating at temperatures up to the melting point.*	Substance is not self-reactive	[redacted] (2000) A4.8-001

As Dazomet does not present any chemical group with explosive or self-reactive properties, and that it does not present any self-heating when submitted to an increase in temperature up to the melting point (103.2-105.2 °C) and present a decomposition temperature of 150 °C (above 75 °C), it is then considered that data conclusive but not sufficient for classification.

A.1.3.8.5 Short summary and overall relevance of the provided information on self-reactive substances

The substance Dazomet is not self-heating at temperatures up to the melting point.

A.1.3.8.6 Comparison with the CLP criteria

As no self-heating takes place at temperatures up to the melting point, there is no self-reaction, according to the CLP criteria.

A.1.3.8.7 Conclusion on classification and labelling for self-reactive substances

Dazomet is not classified for self-reactivity. Data conclusive but not sufficient for classification.

A.1.3.9 Pyrophoric liquids

Table A-20: Summary table of studies on pyrophoric liquids

Not applicable, Dazomet is a solid, not a liquid.

A.1.3.9.1 Short summary and overall relevance of the provided information on pyrophoric liquids

Not applicable.

A.1.3.9.2 Comparison with the CLP criteria

Not applicable.

A.1.3.9.3 Conclusion on classification and labelling for pyrophoric liquids

Not applicable.

A.1.3.10 Pyrophoric solids

Table A-21: Summary table of studies on pyrophoric solids

Method	Results	Remarks	Reference
Regulation (EC) No 440/2008 Method A.13 UN Manual of Tests and Criteria, Part III, Section 33, UN Test N.2	Dazomet technical, purity 98 % *The test item Basamid® has no pyrophoric properties*	-	[redacted] (2021a) A4.17-002

A.1.3.10.1 Short summary and overall relevance of the provided information on pyrophoric solids

The test item does not show an ignition when in contact with air in all six tests within 5 min.

A.1.3.10.2 Comparison with the CLP criteria

The test item does not show an ignition when in contact with air in all six tests within 5 min. Consequently, the test item Basamid® has **no pyrophoric properties** according to Regulation (EC) No. 440/2008, Method A.13. and UN Transport Regulations Test N.2, respectively.

A.1.3.10.3 Conclusion on classification and labelling for pyrophoric solids

Dazomet is not classified as a pyrophoric solid. Thus, the substance does not meet the criteria for classification and no further information is needed. Data conclusive but not sufficient for classification.

A.1.3.11 Self-heating substances

Table A-22: Summary table of studies on self-heating substances

Method	Results	Remarks	Reference
Directive 92/69/EEC, A.16, Relative self-ignition temperature for solids, GLP	BAS 002 01 N, Dazomet technical, purity 97 % *No self-heating at temperatures up to the melting point*	-	[redacted] (2000) A4.17-005

A.1.3.11.1 Short summary and overall relevance of the provided information on self-heating substances

Self-heating: No self-ignition of the test substance Dazomet was observed between room temperature and melting point. At the end of the test at 400 °C, the cube was empty. Dazomet is not considered to be auto-flammable.

A.1.3.11.2 Comparison with the CLP criteria

No self-ignition of Dazomet was observed between room temperature and the melting point, therefore the requirements for the CLP criteria are not met.

Screening procedure CLP guidance 2.11.4.2

Melting point: substances or mixtures with a low melting point (< 160 °C) should not be considered for classification in this hazard class since the melting process is endothermic and the substance-air surface is drastically reduced. However, this criterion is only applicable if the substance or mixture is completely molten up to this temperature.

Dazomet has a melting range of 103.2-105.2, and therefore does not meet the condition to be considered for classification for this endpoint.

A.1.3.11.3 Conclusion on classification and labelling for self-heating substances

Dazomet is not classified as a self-heating substance. Data conclusive but not sufficient for classification.

A.1.3.12 Substances which in contact with water emit flammable gases

Table A-23: Summary table of studies on substances which in contact with water emit flammable gases

Method	Results	Remarks	Reference
Regulation (EC) No 440/2008 Method A.12; UN Manual of Tests and Criteria, Part III, Section 33, Test N.5	Dazomet technical, purity 98 % *No emission of gases in contact with water*	-	[redacted] (2021b) A4.17-003

A.1.3.12.1 Short summary and overall relevance of the provided information on substances which in contact with water emit flammable gases

The test item Dazomet does not emit any gases in contact with water in any of the 4 steps of the test procedure.

A.1.3.12.2 Comparison with the CLP criteria

The test item Dazomet does not emit any gases in contact with water in any of the 4 steps of the test procedure. Consequently, the test item Dazomet has not to be classified according to Class 4, Division 4.3 “Substances which in contact with water emit flammable gases” according to the UN-Transport Regulations, the GHS / Regulation (EC) No 1272/2008 (CLP-Regulation), Annex I: 2.12 and the Regulation (EC) No 440/2008 Method A.12.

A.1.3.12.3 Conclusion on classification and labelling for substances which in contact with water emit flammable gases

Dazomet is not classified as a substance that emits flammable gas when in contact with water. Data conclusive but not sufficient for classification.

A.1.3.13 Oxidising liquids

Table A-24: Summary table of studies on oxidising liquids

Not applicable, Dazomet is a solid, not a liquid.

A.1.3.13.1 Short summary and overall relevance of the provided information on oxidising liquids

Not applicable.

A.1.3.13.2 Comparison with the CLP criteria

Not applicable.

A.1.3.13.3 Conclusion on classification and labelling for oxidising liquids

Not applicable.

A.1.3.14 Oxidising solids

Table A-25: Summary table of studies on oxidising solids

Method	Results	Remarks	Reference
Directive 92/69/EEC, A.17, Oxidizing properties (solids)	BAS 002 01 N, Dazomet technical, purity 97 % Test A17 has not been carried out because the chemical structure of the substance. *No oxidizing properties*	-	[redacted] (2000) A4.4-003 [redacted] (1999) A4.4-004

A.1.3.14.1 Short summary and overall relevance of the provided information on oxidising solids

Dazomet do not present any oxidising characteristics. As stated in the Guidance on the CLP criteria (2017), on page 207: "*For organic substances or mixtures the classification procedure for this hazard class need not be applied if:*

a. the substance or mixture does not contain oxygen, fluorine or chlorine;

or

b. the substance or mixture contains oxygen, fluorine or chlorine and these elements are chemically bonded only to carbon or hydrogen."

As Dazomet is an organic molecules that contains neither oxygen, nor fluorine or chlorine, testing is therefore not needed, and the classification need not to apply.

A.1.3.14.2 Comparison with the CLP criteria

Dazomet do not present any oxidising characteristics. As stated in the Guidance on the CLP criteria (2017), on page 207: "*For organic substances or mixtures the classification procedure for this hazard class need not be applied if:*

a. the substance or mixture does not contain oxygen, fluorine or chlorine;

or

b. the substance or mixture contains oxygen, fluorine or chlorine and these elements are chemically bonded only to carbon or hydrogen."

As Dazomet is an organic molecules that contains neither oxygen, nor fluorine or chlorine, testing is therefore not needed, and the classification need not to apply.

A.1.3.14.3 Conclusion on classification and labelling for oxidising solids

Dazomet is not classified as an oxidising solid. Data conclusive but not sufficient for classification.

A.1.3.15 Organic peroxides

Table A-26: Summary table of studies on organic peroxides

Not applicable as the chemical structure of the active substance does not exhibit a peroxide moiety.

A.1.3.15.1 Short summary and overall relevance of the provided information on organic peroxides

Not applicable.

A.1.3.15.2 Comparison with the CLP criteria

Not applicable.

A.1.3.15.3 Conclusion on classification and labelling for organic peroxides

Not applicable.

A.1.3.16 Corrosive to metals

Table A-27: Summary table of studies on the hazard class corrosive to metals

See information in section A.1.3.16.1.

A.1.3.16.1 Short summary and overall relevance of the provided information on the hazard class corrosive to metals

CLP Regulation Annex I, 2.16 indicates that only substances for which the application of UN Test C.1 is relevant need to be considered (liquids and solids that may become liquids). Dazomet is a solid with a melting point higher than 55 °C and that may not become liquid during transport. On the basis of expert judgement, the study does not need to be conducted. The pH is not extreme (6-7) and dazomet does not contain acidic or basic functional groups, it does not contain halogens, and it is not able to form complexes with metals.

A.1.3.16.2 Comparison with the CLP criteria

Only solids with a melting point below 55 °C need to be tested, see CLP Guidance 2.16.4.1. A “no classification” proposal based on a melting point > 55 °C is acceptable, and the overall conclusion is conclusive but not sufficient for classification.

A.1.3.16.3 Conclusion on classification and labelling for corrosive to metals

No classification, data conclusive but not sufficient for classification.

A.1.3.17 Desensitised explosives

Table A-28: Summary table of studies on the hazard class desensitised explosives

Not applicable: Dazomet is not an explosive.

A.1.3.17.1 Short summary and overall relevance of the provided information on the hazard class desensitised explosives

Given the fact that Dazomet does not present any chemical group associated with explosive properties, and does not contain any metallic atom.

A.1.3.17.2 Comparison with the CLP criteria

Dazomet does not present or contain any chemical group associated with explosive properties, and therefore, does not meet the criteria for classification as explosive. Therefore, comparison with CLP criteria would not result in classification of the substance.

A.1.3.17.3 Conclusion on classification and labelling for desensitised explosives

No classification, data conclusive but not sufficient for classification.

A.1.4 Analytical methods for detection and identification

Not applicable for the CLH report.

Table A-29: Analytical methods

Not applicable for the CLH report.

A.2 Effects against target organisms

Not applicable for the CLH report.

A.2.1 Intended uses

Short description of the use[1] : Dazomet active substance is recommended for the internal remedial treatment and protection of wood products such as utility poles, pilings, timbers, and other large solid or laminated wood products against fungal decay.

Mode of action : In contact with moisture, the active ingredient Dazomet is transformed into methyl-isothiocyanate (MITC). The hydrolysis product MITC which is the active form of Dazomet, binds to amines and SH-groups. This relatively unspecific effect will inhibit the metabolism of the fungi. Dazomet controls the mycelia growth. It has demonstrated fungitoxic and fungistatic effect.

Table A-30: Summary table of intended uses

Not applicable for the CLH report.

A.2.2 Summary on efficacy

Not applicable for the CLH report.

A.2.2.1 Efficacy

Table A-31: Experimental data on the efficacy of the active substance against target organism(s)

Not applicable for the CLH report.

A.2.2.2 Mode of action

Not applicable for the CLH report.

A.2.2.3 Resistance

Not applicable for the CLH report.

A.2.2.4 Conclusion on efficacy

Not applicable for the CLH report.

[1] Please note that the short description of use and mode of action has not changed since the first approval of the dossier.

A.3 Assessment of effects on Human Health

A.3.1 Toxicokinetics

Table A-32: Summary table of toxicokinetic studies

Method, Duration of study, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	Results	Remarks (e.g. major deviations)	Reference
Distribution and metabolism of 14C-Dazomet in rats. **OECD TG 417 GLP, unpublished** **Key study** **Reliability: 2**	Species Rat Strain Sprague-Dawley Rat Sex male/female No. of animals per sex: 12 rats/ sex/ test group	Concentration/Purity: 14C-Dazomet Batch No. 369-05 > 97.0 % Specific activity: 72.16 µCi/mmol Dazomet: Batch No. 39/155-1 purity not given Route of administration oral: gavage Vehicle: Sodium carboxymethylcellulose aqueous solution (1 %, w/v)	After oral administration, Dazomet is rapidly absorbed from the gastro-intestinal tract. The absorbed material is rapidly excreted mostly via urine, approximately 50 % within 24 h, regardless of the dose level. The highest amounts of radioactivity were found in the organs responsible for elimination and biotransformation (kidneys, urinary bladder, gastro-intestinal tract and liver) as well as in the thyroids.	Reliability with restriction: Deficiencies guideline study with acceptable restrictions The study is in good compliance also with the current version of OECD TG 417 with only minor deviations. The justifications for a number of decisions missing in the report were not required at the time of study conduction and do not confine its overall contemporary scientific reliability also from a present day's point of view. Therefore, we follow the	[redacted] *et al.* (1992-1993) IUCLID: A8.8.1-001

		Duration and frequency of treatment / exposure: single treatment, sacrifice time points 1, 6, 24 and 72 hours after dosing Dose level: Doses were prepared by suspending 14C-Dazomet in sodium carboxymethylcellulose aqueous solution (1 %, w/v) at rates of 2 mg/mL (10 mg/kg bw dose) and 20 mg/mL (100 mg/kg bw dose). Each rat received a single dose of suspension at a rate of 5 mL/kg by oral intubation at a nominal dose level of 10 or 100 mg/kg.	The rapid decline over time indicates that Dazomet has no bioaccumulation potential. The major metabolic pathway of Dazomet is the breakdown to a main intermediary, MITC, and the subsequent conjugation of MITC with amino acids. The major urinary metabolite is the N-acetyl cysteine conjugate of MITC. Within the study, no faeces or expired air was collected, thus the establishment of a mass-balance was impossible. This is not considered to affect the quality of the study, as the main intention was to assess the tissue distribution and the urine metabolites, as a complement on the existing study (KCA 5.1.1/03).	view of the previous evaluator and considers the study acceptable and reliable with only minor restrictions according to current requirements. Deviations No guideline stated; partly in compliance with test method B.36 (87/302/EEC): - Most deviations do not concern methodological, reporting or interpretation aspects, but rather the lack of justifications and rationales currently required for a number of decisions (e.g. choice of test species and strain, choice of vehicle, sample collection schedules, dose level selection). - Animal housing conditions not reported - Only one verification method for metabolite identification. - No pathway with molecular structures provided.	

The biokinetics and metabolism of 14C-Dazomet in the rat. **OECD TG 417 GLP, unpublished** **Key study** **Reliability: 2**	Species Rat Strain Sprague-Dawley Rat Sex male/female No. of animals per sex: 46 males and 43 females	Concentration/Purity: Lot/batch #: 61/23/1 14C-Dazomet > 99.0 % Specific activity: 79.5 µCi/mmol Dazomet Batch not stated <99.3 % Route of administration oral: gavage Vehicle: Sodium carboxymethylcellulose aqueous solution (1 %, w/v) Duration and frequency of treatment / exposure: Single treatment, sacrifice time points 0.5, 1, 6, 24 and 240 hours after dosing Dose level: Doses were prepared by suspending 14C-Dazomet in sodium carboxymethylcellulose aqueous solution (1 %, w/v) at rates of 2 mg/mL (10 mg/kg bw dose) and 20 mg/mL (100 mg/kg bw dose).	After oral administration Dazomet is rapidly absorbed from the gastro-intestinal tract. The absorbed material is rapidly excreted mostly via urine (approximately 65 %) and expired air (approximately 22 %). Elimination via the faces accounted for only 3%. There were no significant differences between the single oral high (100 mg/kg bw) and low (10 mg/kg bw) dose level as well as multiple low dose levels. Biliary excretion (approximately 7 %) was slightly higher than faecal elimination indicating that some of the material was re-absorbed from the G.I. tract. The bioavailability was approximately 100 %. No bioaccumulation potential could be identified. C_{max} increased slightly less than proportionally with dose, whereas the AUC did not increase proportionally with the dose, indicating that absorption was becoming saturated at the high	Reliability with restriction: The study is in good compliance with the current version of OECD TG 417 with only minor deviations. The justifications for a number of decisions missing in the report were not required at the time of study conduction and do not confine its overall contemporary scientific reliability also from a present day's point of view. Therefore, we follow the view of the previous evaluator and considers the study acceptable and reliable with only minor restrictions according to current requirements. Deviation: - Most deviations do not concern methodological, reporting or interpretation aspects, but rather the lack of justifications and rationales currently required for a number of decisions (e.g. choice of test species and strain, choice of vehicle, sample collection schedules, dose level selection). - Animal housing conditions	[redacted] *et al.* (1987b) [redacted] *et al.* (1988a) IUCILD: A8.8.1-002

		Each rat received a single dose of suspension at a rate of 5 mL/kg by oral intubation at a nominal dose level of 10 or 100 mg/kg.	dose level. At 72 hours after a seven-day treatment with 10 mg/kg bw the highest amounts of radioactivity were found in the thyroid gland and in the organs associated with the elimination and biotransformation of the test substance. There was a steady decline in the radioactivity in all organs and tissues indicating that Dazomet has no accumulating potential.	not reported - Only one verification method for metabolite identification	
The absorption and distribution of 14C-Dazomet in rats. **OECD TG 417 GLP, unpublished** **Key study** **Reliability: 2**	Species Rat Strain Sprague-Dawley Rat Sex male/female No. of animals per sex: 11 males and 11 females	Concentration/Purity: Lot/batch #: 61/22 RG1 61/22 RG2 14C-Dazomet > 99.0 % Specific activity: Batch1 (61/22 RG1): 0.117 mCi/mmol (preliminary study) Batch 2 (61/22 RG2): 0.119 mCi/mmol (main study) Dazomet Batch CH184290 <99.3 %	After oral administration Dazomet is rapidly absorbed from the gastro-intestinal tract. The absorbed material is rapidly excreted mostly via urine (approximately 60 %) and expired air (approximately 30 %). Elimination via the faeces accounted for only 2 – 3 %. The bioavailability was approximately 100 %. After a second plasma peak at 12 hours there was a steady decline in the radioactivity in all	Reliability with restriction: The study is in good compliance with the current version of OECD TG 417 with only minor deviations. The justifications for a number of decisions missing in the report were not required at the time of study conduction and do not confine its overall contemporary scientific reliability also from a present day's point of view. Therefore, we follow the view of the previous evaluator and consider the	[redacted] *et al.* (1985) IUCLID: A8.8.1-003

		Route of administration oral: oral intubation Vehicle: Sodium carboxymethylcellulose aqueous solution (1 %, w/v) Duration and frequency of treatment / exposure: single treatment, sacrifice time points 0, 0.5, 1, 2, 4, 6, 12, 24, 48, 72, 96, 120 and 168 hours after dosing. Dose level: Doses were prepared by suspending 14C-Dazomet in sodium carboxymethylcellulose aqueous solution (1 %, w/v) at a rate of 40 mg/mL. Each rat received a single dose (20 mg Dazomet in 0.5 mL) by oral intubation at a nominal dose level of 100 mg/kg.	organs and tissues indicating that Dazomet has no accumulating potential. Unchanged Dazomet was virtually not detected in this study indicating complete breakdown of the parent molecule. The main urinary metabolite was the N acetyl cysteine conjugate of MITC. There were at least four other metabolites present in the urine.	study acceptable and reliable with only minor restrictions according to current requirements. Deviations: - Most deviations do not concern methodological, reporting or interpretation aspects, but rather the lack of justifications and rationales currently required for a number of decisions (e.g. choice of test species and strain, choice of vehicle, sample collection schedules, dose level selection). - Animal housing conditions not reported - Age of test animals not reported - Spleen, thyroid not examined	
The biokinetics and metabolism of methyl isothiocyanate-14C in the rat.	Species Rat Strain Sprague-Dawley	Concentration/Purity: Methylisothio[14C]cyanate > 95.0 %	After oral administration MITC is rapidly absorbed from the gastro-intestinal tract. The absorbed material is rapidly	Reliability with restriction: The study is in good compliance also with the current version of OECD TG 417 with only minor	[redacted] *et al.* (1987a) [redacted] *et al.* (1988b) IUCILD:

OECD TG 417 **GLP,** **unpublished** **Key study** **Reliability: 2**	Rat Sex male/female No. of animals per sex: 22 males and 22 females	Specific activity: 16.33 µCi/mmol Route of administration oral: oral intubation Vehicle: Sodium carboxymethylcellulose aqueous solution (1 %, w/v) Duration and frequency of treatment / exposure: Single treatment, sacrifice time points 0, 0.25, 0.5, 1, 2, 4, 6, 12, 24, 48, 72, 96, 120, 168 and 240 hours after dosing. Dose level: Doses were prepared by dissolving 14C-MITC in sodium carboxymethylcellulose solution (1 % w/v) at rates of 0.79 µg/mL and 6.6 µg/mL for the 4.4 and 33 mg/kg dose levels respectively. Each rat received a single dose of dose suspension at a rate of 5 mL/kg by oral intubation at nominal dose level of 4.4 mg/kg and at a rate of 6 mL/kg at a nominal dose level of 33	excreted mostly via urine (approximately 85 %) and expired air (approximately 9 – 17 %). Elimination via the faeces accounted for only 2 %. There were no major differences between the single oral high (33 mg/kg bw) and low (4.4 mg/kg bw) dose level, with the exception of a reduction of radioactivity in expired air trap 2 at the high dose level. The bioavailability was approximately 100 %. At 168 hours the radioactivity in the organs was very low. The highest amounts of radioactivity were found in the thyroid gland and in the organs associated with the elimination and biotransformation of the test substance. There was a steady decline in the radioactivity in all organs and tissues indicating that MITC has no accumulating potential.	deviations. The justifications for a number of decisions missing in the report were not required at the time of study conduction and do not confine its overall contemporary scientific reliability also from a present day's point of view. Therefore, we follow the view of the previous evaluator and considers the study acceptable and reliable with only minor restrictions according to current requirements. Deviations: The study is in good compliance also with the current version of OECD TG 417 with only minor deviations. The justifications for a number of decisions missing in the report were not required at the time of study conduction and do not confine its overall contemporary scientific reliability also from a present day's point of view. Therefore, the applicant follows the view of the previous evaluator and	A8.8.1-004

		mg/kg.		considers the study acceptable and reliable with only minor restrictions according to current requirements.	
[Thiocarbonyl-2-14C] dazomet: the metabolic stability and comparative metabolism of [thiocarbonyl-2-14C]-dazomet in hepatic - microsomes from rat, dog and human. **No guideline is available GLP, unpublished** **Key study** **Reliability: 1**	Species Rat Dog Human Strain Sprague-Dawley Rat Tissues Hepatic microsomes Sex male/female	Concentration/Purity: Lot/batch #: 10180JLM001-8 14C-Dazomet 99.3 % Specific activity: 52.26 mCi/mmol Dazomet Batch BCBX4077 99.8 % Batch SZBD280XV 99.9 % 14C-Testosterone: Lot/batch #: QBC260 B15463-16325 99.2 % Specific activity: 59 mCi/mmol Duration and frequency of treatment / exposure: [14C]-Dazomet (10 µM) was incubated with hepatic microsomes from each species (mixed gender	Metabolism of [14C]-Dazomet (10 µM) was rapid and extensive with the highest levels of test item depletion being observed in rat and dog. Several regions of radioactivity were detected and quantified across the panel of samples. Of these, those designated as UK8, UK9, UK13, UK16, UK27 and UK31 were found to be potentially significant. In samples from incubations with [14C]-dazomet (10 µM) and rat microsomes, RegID8602 (A3 / MATM) was the major component formed, followed by MITC. Desmethyl hydroxy dazomet and M137/137 No.1 (dimer C) were also observed in these samples. In samples from incubations with [14C]-	Test procedure in accordance with generally accepted scientific standards and described in sufficient detail. No internationally agreed guideline available The study was conducted according to Charles River Protocol No. 180069 and Amendments 1 to 6. The objective of this study was to investigate the metabolic stability and compare the metabolic profiles of [thiocarbonyl-2-14C]-dazomet in hepatic microsomes from Sprague Dawley rat, Beagle dog and human. Therefore according to this study 99.3 % (14C-Dazomet) and 99.8 % (no radio-labelled dazomet) have been used. The [14C]-MITC has been also used like standard in order to confirm that one of	[redacted] (05 August 2020) IUCILD: A8.8.1-005

		preparations) for 0, 15, 30 and 60 min. Due to the potential volatile nature of some of the components formed, the incubations were performed in tubes with lids fitted with a rubber septum. The incubation supernatants were analyzed by HPLC with online radio detection to determine depletion of parent compound and quantify the major metabolites formed across species. [14C]-Dazomet (20 µM) was again incubated with hepatic microsomes form rat, dog and human for 0 and 60 min, to generate samples for metabolite identification experiments. Selected samples were analyzed by radio-chromatography and mass spectrometry, and the nature and identity of the components of interest was investigated.	dazomet (10 µM) and dog microsomes, desmethyl hydroxy dazomet was the most prominent component observed, followed by RegID8602 (A3 / MATM) and MITC. Formation of M137/137 No.1 (dimer C) was also observed in these samples. In samples from incubations with [14C]-dazomet (10 µM) and human microsomes, M137/137 No.1 (dimer C) was the major component formed followed by RegID8602 (A3 / MATM). MITC was also found to represent a significant region of radioactivity in these samples. Following review of these data (result on dazomet administer at 10 µM), [14C]-Dazomet (20 µM) was again incubated with hepatic microsomes form rat, dog and human for 0 and 60 min, to generate samples for metabolite Identification experiments.	the major metabolite produce by degradation on dazomet is well MITC.	

			Selected samples were analyzed by radio-chromatography and mass spectrometry, and the nature and identity of the components of interest was investigated. The component designated as UK13 was confirmed as the known degradation product RegID8602 (A3, also known as (methylamino)(thioxo) methanesulfenic acid, MATM, from previous studies), UK16 was confirmed as MITC (methyl isothiocyanate), the region of radioactivity spanning between UK27 and UK31 was confirmed as the known degradation product M137/137 No.1 (also known as dimer C). UK8 and UK9 were also confirmed to be the same component identified as desmethyl hydroxy dazomet. The presence of RegID8602 (A3 / MATM) was confirmed in all the species tested. M137/139 No.1 (dimer C) and MITC		

			were observed in rat and human samples only, and desmethyl hydroxy dazomet was confirmed in samples from incubations with dog microsomes.		
Dermal absorption. **OECD TG 427 (Draft version December 2000) US EPA OPPTS 870.7600 (1998)** **GLP** **Key study** **Reliable: 2**	Species Rat Strain CrlGlxBrlHan:WI Sex male No. of animals per sex: 4	Concentration/Purity: 14C-Dazomet (BAS 002 N) (> 98 %) Specific activity: 16.33 µCi/mmol Route of administration: Dermal Vehicle: Water Duration: 8 hours and 168 hours Dose level: 1.0 mg/cm² and 0.1 mg/cm² (corresponding nominally to about 10.0 mg/animal and 1.0 mg/animal and about 30 mg/kg body weight and 3 mg/kg body weight)	*In vivo* dermal absorption in the rat (8 hours topical application), after 168 hours: - 3 % for concentrate (formulation, 97 % pure a. s.) 9 % for aqueous 1/10 dilution - 3.6 % for concentrate based on re-evaluation in accordance with the EFSA Journal (2017);15(6):4873	Reliability: The study is nearly completely in-line with the current guideline, with the exemption of the housing conditions. In the study the dark light circle was not defined as 12 hour dark/light circle and the air condition turnover rates are not given in the report. The rest of the study, however, is in good compliance also to the current version of the test guideline. The minor deviations from the guideline are not considered relevant as only dermal absorption was measured in the study and temperature and humidity were in compliance with the guideline. Hence, the study is considered as reliable with restrictions by the	[redacted] (2004) IUCLID: A8.8.2-001

				applicant. In addition, being a vertebrate study, it is also considered for animal welfare reasons and the provided information is relied on and used for completion of the toxicological risk characterization. <u>Deviations:</u> No 12 hour dark/ light change - Housing conditions are not fully described concerning the turnover in air conditioning	

A.3.1.1 Short summary and overall relevance of the provided toxicokinetic information

After oral administration, Dazomet is rapidly absorbed from the gastro-intestinal tract. The absorbed material is rapidly excreted mostly via urine (approximately 65 %) and expired air (approximately 22 %; [redacted] *et al.* 1992 and [redacted] 1993, A8.8.1-001; [redacted] *et al.* 1987b, A8.8.1-002; [redacted] *et al.* 1988b, A8.8.1-004; [redacted] *et al.* 1985, A8.8.1-003). Elimination via the feces accounted for only 3 %. There were no significant differences between the single oral high (100 mg/kg bw) and low (10 mg/kg bw) dose levels as well as multiple low dose levels. Biliary excretion (approximately 7 %) was slightly higher than fecal elimination indicating that some of the material was re-absorbed from the gastro-intestinal (G.I.) tract. The bioavailability was approximately 100 %. The highest amounts of radioactivity were found in the organs responsible for elimination and biotransformation (kidneys, urinary bladder, gastro-intestinal tract and liver) as well as in the thyroids. The rapid decline over time indicates that Dazomet has no bioaccumulation potential.
From the pharmacological point of view, Cmax increased slightly less than proportionally with dose, whereas the AUC did not increase proportionally with the dose, indicating that absorption was becoming saturated at the high dose level.

MITC also is rapidly absorbed from the G.I. tract following oral administration ([redacted] *et al.* 1987a, A8.8.1-004; [redacted] *et al.* 1988a, A8.8.1-002). The absorbed material is rapidly excreted mostly via urine (approximately 85 %) and expired air (approximately 10 – 16 %). Elimination via the feces accounted for only 2 %. There were no major differences between the single oral high (33 mg/kg bw) and low (4.4 mg/kg bw) dose levels, with the exception of a reduction of radioactivity in the expired air at the high dose level (16.75 % at 4.4 mg/kg bw versus 8.9 % at 33 mg/kg bw). The bioavailability was approximately 100 %. The radioactivity in the organs was very low. The highest amounts of radioactivity were found in the thyroid gland and in the organs associated with the elimination and biotransformation of the test substance. There was a steady decline in the radioactivity in all organs and tissues indicating that MITC has no accumulating potential. Cmax increased slightly less than proportionally with dose.

Considering the biotransformation of Dazomet in rats, the major metabolic pathway of Dazomet is the breakdown to a main intermediary, MITC, and the subsequent conjugation of MITC with amino acids ([redacted] *et al.* 1992 and [redacted] 1993, A8.8.1-001). The general pattern of metabolites is similar in liver and kidney. For the plasma no specific metabolites were identified. In the liver the major important component was identified as a cysteine conjugate of MITC whereas the major urinary metabolite was an N-acetyl conjugate of MITC.

The metabolite patterns in urine for MITC and Dazomet were almost identical with 2 major metabolites being present ([redacted] *et al.* 1987a, A8.8.1-004; [redacted] *et al.* 1988a, A8.8.1-002). The principal component was the N acetylcysteine conjugate of MITC. Similar to Dazomet a total of five urinary metabolites were found. Radioactivity in the expired air is mainly associated with CO2.

Regarding dermal absorption of Dazomet according to the EFSA guidance 2017; a dermal absorption of 3.6 % has been derived from the *in vivo* study in rat (8 hours topical application), after 168 hours for concentrated formulation (formulation, 97 % pure a. s.) 9 % for aqueous 1/10 dilution.

A.3.1.2 Values and conclusions used for the risk assessment

Not applicable for the CLH report.

A.3.2 Acute toxicity / STOT SE

A full set of acute toxicity studies (acute toxicity via the oral, dermal or inhalation route, skin or eye irritation or skin sensitization) for the active substance Dazomet and its active metabolite MITC were provided for the Annex II inclusion and thus peer reviewed by European competent authorities and eCA Belgium.

During the last years, most of the guidelines for repeated dose toxicity testing have been reviewed and adapted to the state of science, a re-evaluation of existing studies was conducted to check for deviations which are no longer compatible with the current evaluation criteria.

For acute toxicity testing, almost all test guidelines changed fundamentally mainly due to the intended reduction of the number of test organisms to be used for animal welfare reasons and to the adaptation of the test design with regard to its future suitability for the revised GHS classification criteria. Due to these differences, a comparison of the old studies with the current guidelines would inevitably lead to the identification of a large number of inherent deviations, which would only be of limited informative value and could give a distorted picture of its contemporary reliability. When compared to the guideline in place at the time of study conduction, the applicant follows the assessment by the previous evaluator and considers the study reliable with restrictions. In any case, the study is also considered for animal welfare reasons and the provided results are relied on and used for completion of the toxicological risk characterization.

New information:

No new data was submitted for Dazomet and MITC with respect to acute toxicity via the oral, dermal or inhalation route, skin or eye irritation or skin sensitization. Nor have any new studies been found during the open literature search that would provide new data and/or question the results of the existing GLP studies. Even though the submitted studies no longer fully meet the standard of the current test guidelines, they do not deviate in such an extent that would justify the performance of new vertebrate tests. Thus, the evaluation in Dazomet Assessment Report (Belgium, 2010) remains valid.

A.3.2.1 Acute oral toxicity

Table A-33: Summary table of animal studies on acute oral toxicity

Method, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Type of administration (gavage, in diet, other)	Signs of toxicity (nature, onset, duration, severity, reversibility, include concentrations)	Value LD50	Remarks (e.g. major deviations)	Reference
Similar to OECD TG 401 **Reliability: 2** **Key study** **No GLP** **Chi² value for homogeneity-test was 0.09.** **A 95 % confidence limit was taken into consideration.**	Sprague-Dawley rats Males/Females 10 rats/sex/group	Dazomet 98 % 147, 215, 316, 464, 562, 681 mg/kg bw TS in 0.5 % aqueous CMC; Single gavage followed by an observation period of 14 days	In all dose groups: poor general state, piloerection, erythema, dyspnoea, apathy, staggering gait. Trembling and shaking was observed from 215 mg/kg bw and 464 mg/kg bw on, respectively. Occasionally, the following signs were noted (mostly at 464 mg/kg bw or higher): aggressiveness, abnormal position, atonia, twitching, tonus of the jaws, compulsive gnawing, fibrillary contractions, tonic convulsions, dehydration, salivation, lacrimation and paresis.	LD50= 415 mg/kg bw	LD50(m)= 596 mg/kg bw LD50(f)= 415 mg/kg bw	[redacted] (1983) IUCLID: A8.7.1-001

EPA 81-8 **Reliability: 2 (with restriction)** **GLP** **p≤0.05 (Anova and Mann-Whitney-U)** **p≤0.01(Dunnet)** **Key study**	Wistar rats Males/Females 10 rats/sex/group	Dazomet >96.3 % Aqueous 0, 50, 130, 450 (males), 0, 13, 50, 130 (females) mg/kg bw, in CMC; Single gavage followed by an observation period of 14 days	No abnormal signs were detected	Not calculated	Acute oral neurotoxicity study, see 2.6 (Neurotoxicity) See CLH Annex I	[redacted] (1994a) IUCLID: A8.7.1-002 and A8.13.2-003
OECD TG 401 before 2002 **Reliability: 2 (with restriction)** **Key study** **GLP** **Statistical value(s) not mentioned**	Wistar rats Males/Females 5 rats/sex/group	MITC >96.3 % 68.1, 100, 147, 215 mg/kg bw TS in olive oil; Single gavage followed by an observation period of 14 days	The following signs were observed at 147 mg/kg bw and higher: poor general state, piloerection, dyspnoea, apathy, staggering gait, twitching (females). Occasionally, following signs were noted at the top-dose or the next-lower dose: dehydration, salivation, lacrimation and paresis. All registered symptoms began from 30 min to 4 hours after substance administration. All surviving animals were free of symptoms from day 2 on.	LD50= 147 mg/kg bw	LD50 (m)= 163 mg/kg bw LD50 (f)= 147 mg/kg bw No vehicle control group was included in the study protocol.	[redacted] (1986c) IUCLID: A8.7.1-003

OECD TG 401 **Reliability: 2 (with restriction)** **Key study** **GLP** **Statistical value(s)not mentioned**	NMRI mice Males/Females 5 rats/sex/group	MITC 94.7 % 50, 100, 200 mg/kg bw TS in olive oil; Single gavage followed by an observation period of 14 days	The following signs were observed at 100 mg/kg bw and higher: poor general state, piloerection, dyspnoea, apathy, staggering. Occasionally, following signs were noted at the top-dose or the next-lower dose: abnormal position, twitching, tremors, dehydration (females) or paresis (females). All surviving animals were free of most symptoms from d3 on (piloerection until d6, males). No clinical signs could be observed in animals receiving dose level 50 mg/kg.	LD50= 114 mg/kg bw	LD50 (m)= 120 mg/kg bw LD50 (f)= 100 mg/kg bw See CLH annex I No vehicle control group was incorporated in the study protocol.	[redacted] (1987a) IUCLID: A8.7.1-004

Table A-34: Summary table of human data on acute oral toxicity

No human data is available.

Table A-35: Summary table of other studies relevant for acute oral toxicity

No other studies are available.

A.3.2.1.1 Short summary and overall relevance of the provided information on acute oral toxicity

Dazomet has an acute oral toxicity in rats (LD50 approximately 500 mg/kg bw; [redacted] 1983, A8.7.1-001). Acute oral toxicity studies with MITC indicate that this compound is toxic in rats (LD50 approximately 147 - 163 mg/kg bw; [redacted] 1986c, A8.7.1-003). Oral toxicity studies with MITC in mice indicate a similar level of toxicity level (LD50 approximately 100 - 120 mg/kg bw ([redacted] 1987a, A8.7.1-004).

A.3.2.1.2 Comparison with the CLP criteria

Dazomet : 300 mg/kg bw < LD50 = 596 mg/kg bw (m) - 415 mg/kg bw (f) < 2000 mg/kg bw (acute tox. 4)

MITC: 50 mg/kg bw < LD50 = 147 mg/kg bw - 163 mg/kg bw < 300 mg/kg bw (acute tox. 3)

A.3.2.1.3 Conclusion on classification and labelling for acute oral toxicity

The acute toxicity by oral route of Dazomet was shown, in both the rat and the mouse. The toxicity administered via oral route was comparable to that after administration via intraperitoneal or subcutaneous route, which was an indication of the rapid and complete oral absorption of the compound. Based upon the obtained oral LD_{50}, Dazomet should be classified “Harmful if swallowed” (Acute Tox. 4, H302, ATE 300-2000 mg/kg bw). According to the data provided an ATE of 415 mg/kg bw has been proposed in the context of harmonized classification.

For MITC, taking into account that the ATE is between 50 and 300 mg/kg bw, it should be classified “Toxic if swallowed” (Acute Tox. 3, H301), but in the context of the CLH dossier of dazomet the MITC classification doesn’t change anything (MITC was tested in pure form, the level of MITC generated form the metabolization/hydrolysation of dazomet is much lower which may explain this difference in toxicological effects observed) on the classification derived from the data provided for Dazomet. That’s why the conclusion of the classification of Dazomet for acute toxicity previously proposed remain valid.

A.3.2.3.3 Conclusion on classification and labelling for acute oral toxicity

Value used in the Risk Assessment – Acute oral toxicity	
Value	Dazomet: Classified for acute oral toxicity category 4 (H302) ATE: 415 mg/kg bw
Justification for the selected value	Dazomet has an acute oral toxicity in rats with LD50 of 415 mg/kg bw. Therefore according to the CLP regulation, this LD50 value is between the range 300-2000 mg/kg bw triggering the classification H302.

A.3.2.1.4 Conclusion on acute oral toxicity related to risk assessment

Not applicable for the CLH report.

A.3.2.2 Acute dermal toxicity

Table A-36: Summary table of animal studies on acute dermal toxicity

Method, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Surface area	Signs of toxicity (nature, onset, duration, severity, reversibility, include concentrations)	Value LD50	Remarks (e.g. major deviations)	Reference
OECD TG 402 **GLP** **Reliability: 2** **Key study** **Statistical value(s)not mentioned**	Wistar rats Males/Females 5 rats/sex/group	Dazomet 98.5% 2000 mg/kg bw TS in 0.5 % aqueous Tylose; Application to ca. 50 cm^2 on the dorsal flank under semi occlusive conditions for 24 hours	There were no relevant findings.	LD50 >2000 mg/kg bw	-	[redacted] (1992) IUCLID: A8.7.3-001
OECD TG 402 **GLP** **Reliability: 2** **Key study** **Chi^2 value for homogeneity-test was 2.12.** **Chi^2 probability 65.37%**	Wistar rats Males/Females 5 rats/sex/group	MITC 98 % 215, 1000, 1470, 2150 mg/kg bw TS in olive oil; Application to ca. 50 cm^2 on the dorsal flank under semi occlusive conditions for 24 hours	No systemic reactions were seen in the dose level group of 215 mg/kg. Males showed dyspnoea, apathy, staggering and poor general state on day one at dose level 1000 mg/kg bw and additionally on day 2 at dose level 1470 mg/kg bw.	LD50 = 1290 mg/kg bw	-	[redacted] (1987b) IUCLID: A8.7.3-002

			Females showed the same symptoms at dose level 1000 mg/higher (tremors only at dose level group 1470 mg/kg bw. Local clinical signs (erythema and oedema) were registered in all groups. Females showed additional scaling at dose level group 2150 mg/kg bw.			

Table A-37: Summary table of human data on acute dermal toxicity

No human data is available.

Table A-38: Summary table of other studies relevant for acute dermal toxicity

No other studies are available.

A.3.2.2.1 Short summary and overall relevance of the provided information on acute dermal toxicity

Dazomet has a low dermal toxicity in rats, with no systemic effects/mortalities noted at the limit dose of 2000 mg/kg bw tested ([redacted] 1992, A8.7.3-001). There was also no local reaction. MITC can be regarded to be moderately toxic in rats via this route of administration (LD50 values ranging from 1000 - 2800 mg/kg bw; [redacted] 1987b, A8.7.3-002). Local skin irritation was observed. Male rats were more sensitive than females.

A.3.2.2.2 Comparison with the CLP criteria

Dazomet: >2000 mg/kg bw (males and females)

MITC: 1000 mg/kg bw < LD50 = 1290 mg/kg bw (m) < 2000 mg/kg bw (acute tox. 4)

A.3.2.2.3 Conclusion on classification and labelling for acute dermal toxicity

For dazomet the data is conclusive but not sufficient for classification.
For MITC taking into account that the ATE is between 1000 and 2000 mg/kg bw, it should be classified “Harmful in contact with skin” (Acute Tox. 4, H312) but in the context of the CLH dossier of dazomet the MITC classification doesn’t change anything (MITC was tested in pure form, the level of MITC generated form the metabolization/hydrolysation of dazomet is much lower which may explain this difference in toxicological effects) on the classification derived from the data provided for Dazomet.

That’s why the conclusion of the classification of Dazomet for acute toxicity previously proposed remain valid.

Value used in the Risk Assessment – Acute dermal toxicity	
Value	Dazomet: Not classified for acute dermal toxicity
Justification for the selected value	Taking into account that the study generated on dazomet is not conclusive at 2000 mg/kg bw no LD50 has been derived because the LD50 should be >2000 mg/kg bw.

A.3.2.2.4 Conclusion on acute dermal toxicity related to risk assessment

Not applicable for the CLH report.

A.3.2.3 Acute inhalation toxicity

Table A-39: Summary table of animal studies on acute inhalation toxicity

Method, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), form (gas, vapour, dust, mist) and particle size (MMAD) Actual and nominal concentration, Type of administration (nose only / whole body/ head only)	Signs of toxicity (nature, onset, duration, severity, reversibility, include concentrations)	Value LC50	Remarks (e.g. major deviations)	Reference
OECD TG 403 **Reliability: 2 (with restriction)** **Key study** **GLP** **Statical value(s) not mentioned**	Wistar rats Males/Females 10 rats/sex/group	Dazomet 98.2 % 3.83, 5.11, 8.4 mg/L tested substance (TS). Administration via dust aerosols (air) with head- nose exposure for 4 hours Particle size (50 %) = 5.42-8.14 µm	During exposure, animals showed attempt to escape. Diminished pain reflex was observed at the top dose. After exposure, animals exhibited piloerection, squatting posture, paresis (dragging hindlimbs, only top-dose) trembling gait, bloody nasal discharge/crusts, hematuria, anemia and abdominal fur with yellow smear.	LC50 ca. 8.4 mg/L/4h	LC50 (m) >8.4 LC50(f) = 7.29 See CLH annex I	[redacted] (1986) IUCLID: A8.7.2-001
No guideline (BASF test)	Rats, strain unspecified	Dazomet Purity not reported	No toxic symptoms were observed.	Neither mortality nor	Inhalation Hazard Test (IHT)	[redacted] (1975) IUCLID:

Supportive study **Reliability: 4 (documentation insufficient for assessment)** **No study conducted prior to the implementation of GLP** **Statical value(s) not mentioned**	Males/Females 3 rats/sex/group	Air stream saturated with the volatile components of TS; Vapors, generated by bubbling 200 l/h air through a substance column of about 5 cm above a fritted glass disc in a glass cylinder for different time periods (e.g. 3 min, 10 min, 1, 3 or 7 or 8 hours).		clinical signs of toxicity	See CLH annex I	A8.7.2-002
Similar to OECD TG 403 **Reliability: 2 (with restriction)** **Key study** **GLP** **Statical value(s) not mentioned**	CD rats Males/Females 5 rats/sex/group	MITC 98 % 0,282, 0.496, 0.570, 0.628, 0.786, 1.640 mg/L TS; Exposure to vapors by whole body exposure over a period of 4 hours		LC50= 0.54 mg/L/4h	See CLH annex I	[redacted] (1981) IUCLID: A8.7.2-003

Table A-40: Summary table of human data on acute inhalation toxicity

No human data is available.

Table A-41: Summary table of other studies relevant for acute inhalation toxicity

No other studies are available.

A.3.2.3.1 Short summary and overall relevance of the provided information on acute inhalation toxicity

Inhalable dust aerosols of Dazomet have a low acute inhalative toxicity in rats after 4 hours nose only exposure (LC_{50} = 7.3 mg/L for females, > 8 mg/L for males; [redacted]. 1986, A8.7.2-001). The inhalation risk test in this species confirms these findings as volatile parts did not lead to clinical symptoms/mortalities even when inhaled as a saturated vapor for 8 hours at 20°C ([redacted] 1975, A8.7.2-002). MITC is considerably more toxic when inhaled by rats (LC_{50} = 0.54 mg/L/4h; [redacted] 1981, A8.7.2-003). This could be explained by the fact that the vapor pressure of MITC is much higher than that of dazomet, which means that MITC is mainly found in vapor form, while MITC seems to act locally and has a significant corrosive effect, which could explain the difference in toxicity observed.

A.3.2.3.2 Comparison with the CLP criteria

LC50 cut-off value for dust aerosols to trigger classification for acute inhalation toxicity is > 5 mg/L. Thus, no classification is warranted.

Regarding MITC according to the CLP regulation taking into that the LC50 is comprise between 0.5 and 2 mg/L, it should be classified as Acute Tox. 2 (H330). We will discuss this further in the sections on STOT SE effects, MITC has toxicological effects mainly by local actions (e.g. corrosive) at the first site of contact in this case by inhalation.

Taking into account the high volatility of MITC and the rapid degradation of dazomet to MITC a risk of exposure by inhalation route cannot be excluded, we can observe that the acute toxicity for the major metabolite of dazomet is higher (for whom no classification cannot be assigned). This can be explained by the fact that MITC was tested in its pure form, while dazomet must undergo successive phases of hydrolysis to lead to the formation of MITC and therefore animals will never be exposed to an acute dose of MITC, which may explain the difference in effect observed.

That's why the conclusion of the classification of Dazomet for acute toxicity previously proposed remain valid.

A.3.2.3.3 Conclusion on classification and labelling for acute inhalation toxicity

Value used in the Risk Assessment – Acute inhalation toxicity	
Value	Dazomet: Not classified for acute inhalation toxicity (Respiratory irritation is discussed under A.3.2.5, STOT SE 3)
Justification for the selected value	Inhalable dust aerosols of Dazomet have an acute inhalative toxicity in rats after 4 hours nose only exposure with LC_{50} = 7.3 mg/L for females and > 8 mg/L for males. According to the CLP regulation, these LC_{50} values are greater than the trigger value set at 5 mg/L (Acute Tox. 4) therefore they do not meet the criteria for classification of the substance.

A.3.2.3.4 Conclusion on acute inhalation toxicity related to risk assessment

Not applicable for the CLH report.

A.3.2.4 Specific target organ toxicity – single exposure Category 1 and 2 (STOT SE 1 and 2)

Table A-42: Summary table of animal studies on Specific Target Organ Toxicity STOT SE 1 and 2

Method, Duration of study, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	Results (including target organ and the effect levels)	Remarks (e.g. major deviations)	Reference
Acute oral neurotoxicity study **Refer to A3.12** **Key study** **U.S. EPA Guidelines Ref. No. 81-8** **GLP** **Reliability: 2** **P≤0.05 (Anova + Kruskal Wallis)** **P≤0.01 (Dunnett)**	Wistar rats Males/Females 10 rats/sex/group	Dazomet > 96.3 % A.S. 0, 50, 130, 450 (males), 0, 13, 50, 130 (females) mg/kg bw, in CMC; Single gavage followed by an observation period of 14 days	No treatment-related neuropathological effects. All other findings did not indicate a neurotoxic effect, but reflected an impairment of the general state of health Neurotoxicity NOAEL= 392 mg/kg bw/day (highest dose tested) NOAEL (females) < 13 mg/kg bw based on decreased motor activity at 13 mg/kg bw	Regarding gross pathology, no substance-related findings were obtained in neither macroscopic, nor histopathological examinations in the central or peripheral nervous system. A spontaneous internal hydrocephalus (congenital hydrocephalus) was seen in one high dose male and a spontaneous single axonal degeneration of minimal degree in the proximal sciatic nerve was noted in two control males in one high dose male. However, these findings were assessed as being incidental and not	[redacted] (1994a) IUCLID: A8.7.1-002

				substance-related. Regarding body weight, the gain was dose-dependently decreased. Animals receiving higher dosages of Dazomet gained considerably less during experimental period than those receiving lower dosages. On day 0, half closure of eyelids was seen in 8 males and all females of the highest dose groups each, 7 males and 3 females of the mid dose groups and 1 male animal of the lowest dose group. Abnormal signs were only detected on day 0. Changes in fur was seen in some females of the highest dose group and one mid-dose female. Salivation, lacrimation and impairment of activity was registered with a dose-dependent relationship in all dose groups, excluding low-dose females.	

Acute oral toxicity **Refer to A.3.2.1** **Key study** **Reliability: 2** **No GLP** **Chi² value for homogeneity-test was 0.09.** **A 95% confidence limit was taken into consideration.**	Sprague-Dawley rats Males/Females 10 rats/sex/group	Dazomet 98 % 147, 215, 316, 464, 562, 681 mg/kg bw TS in 0.5 % aqueous CMC; Single gavage followed by an observation period of 14 days	Target organ: Gastrointestinal tract/stomach (Most likely secondary to corrosive properties of MITC) LD50= 519 mg/kg bw	-	[redacted] (1983) IUCLID: A8.7.1-001
Acute oral toxicity **Refer to A.3.2.1** **Reliability: 2 (with restriction)** **Key study** **GLP** **Statistical value(s) not mentioned**	Wistar rats Males/Females 5 rats/sex/group	MITC > 96.3 % 68.1, 100, 147, 215 mg/kg bw TS in olive oil; Single gavage followed by an observation period of 14 days	Target organ: Gastrointestinal tract/stomach LD50 ca. 147 mg/kg bw	-	[redacted] (1986c) IUCLID: A8.7.1-003
Acute oral toxicity **Refer to A.3.2.1** **Key study** **Reliability: 2**	NMRI mice Males/Females 5 rats/sex/group	MITC > 94.7 % 50, 100, 200 mg/kg bw TS in olive oil;	Target organ: Gastrointestinal tract/stomach LD50 ca 114 mg/kg bw	-	[redacted] (1987a) IUCLID: A8.7.1-004

(with restriction) **Key study** **GLP** **Statistical value(s)not mentioned**		Single gavage followed by an observation period of 14 days			
Acute dermal toxicity **Refer to A.3.2.2** **GLP** **Reliability: 2** **Key study** **Statistical value(s)not mentioned**	Wistar rats Males/Females 5 rats/sex/group	Dazomet 98.5 % 2000 mg/kg bw TS in 0.5 % aqueous Tylose; Application to ca. 50 cm² on the dorsal flank under semi occlusive conditions for 24 hours	Target organ: Not identified; no abnormalities found	-	[redacted] (1992) IUCLID: A8.7.3-001
Acute dermal toxicity **Refer to A.3.2.2** **Key study** **Reliability: 2** **Key study** **Statistical value(s)not mentioned**	Wistar rats Males/Females 5 rats/sex/group	MITC 98 % 215, 1000, 1470, 2150 mg/kg bw TS in olive oil; Application to ca. 50 cm² on the dorsal flank under semi occlusive conditions for 24 hours	No systemic reactions were seen in the dose level group of 215 mg/kg bw. Males showed dyspnoea, apathy, staggering and poor general state on day one at dose level 1000 mg/kg and additionally on day 2 at dose level 1470 mg/kg bw. Females showed the same symptoms at dose level 1000 mg/higher (tremors only at dose level	-	[redacted] (1987b) IUCLID: A8.7.3-002

			group 1470 mg/kg bw. Local clinical signs (erythema and oedema) were registered in all groups. Females showed additional scaling at dose level group 2150 mg/kg. LD50= 1290		
Acute inhalation toxicity **Refer to A.3.2.3** **Reliability: 2 (with restriction)** **Key study** **GLP** **Statical value(s) not mentioned**	Wistar rats Males/Females 10 rats/sex/group	Dazomet 98.2 % 3.83, 5.11, 8.4 mg/L TS; Administration via dust aerosols (air) with head- nose exposure for 4 hours	Target organ: Not identified; LC50 ca. 8.4 mg/L/4h	After exposure, animals exhibited piloerection*, squatting posture, paresis (dragging hindlimbs*, only top-dose) trembling gait, bloody nasal discharge/crusts, haematuria*, anaemia and abdominal fur with yellow smear*. (*signs observed until termination in top-dose animals)	[redacted] (1986) IUCLID: A8.7.2-001
Acute inhalation toxicity **Refer to A.3.2.3** **Reliability: 4** **Key study** **No GLP**	Rats, strain unspecified Males/Females 3 rats/sex/group	Dazomet Purity not reported Air stream saturated with the volatile components of TS; Vapours, generated by bubbling 200 l/h air through a substance column of	Target organ: Not identified; no mortality; no abnormalities found	-	[redacted]. (1975) IUCLID: A8.7.2-002

Statical value(s) not mentioned		about 5 cm above a fritted glass disc in a glass cylinder for different time periods (e.g. 3 min, 10 min, 1, 3 or 7 or 8 hours).			
Acute inhalation toxicity **Refer to A.3.2.3** **Key study** **Reliability: 2 (with restriction)** **GLP**	CD rats Males/Females 5 rats/sex/group	MITC 98 % 0,282, 0.496, 0.570, 0.628, 0.786, 1.640 mg/L TS; Exposure to vapours by whole body exposure over a period of 4 hours	Target organ: respiratory tract (oedema, bronchiolitis, pneumonitis), lung (weight increase) LC50= 0.54 mg/L/4h	-	[redacted]. (1981) IUCLID: A8.7.2-003
Acute skin irritation / corrosivity **EPA OPP 81-5 (Acute Dermal Irritation)** **Refer to A.3.3** **Key study** **Reliability: 1**	Rabbit, New Zealand White, Males 6/group	Dazomet 98.5 % 0.5 g (moistened) 4 hours semi occlusive vehicle: Distilled water	Target organ: Not identified; no abnormalities found Dazomet is considered not irritating to the skin	-	[redacted]. (1992) A8.1.1-001
Acute skin irritation / corrosivity **Refer to A.3.3** **Key study**	Rabbit, White Vienna, Males and Females 3/group	MITC 98 % 0.5 mL 4 hours, semi occlusive vehicle: Olive oil DAB 8	Target organ: Skin (necrosis) MITC is considered to be corrosive to the skin.	-	[redacted] (1986a) A8.1.1-002

Table A-43: Summary table of human data on Specific Target Organ Toxicity STOT SE 1 or 2

No human data is available.

Table A-44: Summary table of other studies relevant for Specific Target Organ Toxicity STOT SE 1 and 2

Type of data / report Reliability, Key / supportive study	**Test substance (including purity), Vehicle**	**Relevant information about the study**	**Main effects, Observations**	**Reference**
28 day repeated dose inhalation study (OECD TG 412) **Reliability: 1** **GLP** **P < 0.01** **Please refer to A3.7.1.3** **Key study**	MITC 96.9 % Vehicle: Nitrogen air	Wistar rats Males/Females 5/sex/group (total: 40 animals) 0, 5, 20, 100 mg/m³ Five days/week 6 hours/day	Target organ: Respiratory tract At 100 mg/m³ mucosal and respiratory irritation, changes in breathing pattern, reddish nasal and eye discharge, increased absolute lung weights, bronchopneumonia, epithelial proliferation in bronchi, bronchioles and trachea, single cell necrosis in trachea, catarrhal-purulent rhinitis in nasal cavity, atrophy of olfactory epithelium, focal squamous metaplasia of respiratory epithelium.	[redacted] (1987) IUCLID: A8.9.5.2-002

A.3.2.4.1 Short summary and overall relevance of the provided information on STOT SE 1 and 2

For the assessment on STOT SE 1 and 2 classification, acute oral, dermal, inhalation and neurotoxicity studies in rat and mouse were taken into consideration. Regarding short-term repeated dose inhalation studies, although effects were observed on the respiratory tract following exposure to MITC, these data are not usable for an assessment of STOT SE 1 and 2 effects. The reason being that the effects were reported after 28 days of exposure without specifying whether they were already observable during the first days of exposure. Studies with MITC have been considered here since MITC is the main metabolite of Dazomet and it will contribute to the toxicological profile (especially toxicological local effect) of Dazomet. Furthermore, the results of the skin irritation/corrosion study of Dazomet were used for further assessment.

In the context of CLH dossier of Dazomet, no classification proposal is provided for MITC.

For the active substance Dazomet, there were no studies with acutely toxic effects relevant for classification for STOT SE. Neither animal studies nor human information. No effects in neuropathological parameters were observed.

For the major metabolite MITC there is evidence from animal studies and human cases that exposure to MITC affect the lung, eyes and the respiratory tract. These effects were considered to be related to the corrosive properties of MITC.

In the acute inhalation toxicity study with MITC, additional effects in the liver (focal necrosis) were observed in the decedents. In the animals sacrificed at terminal sacrifice occasional foci of mononuclear cells was observed in a low incidence, uniformly distributed in control and treated groups. The effect on the liver was considered a secondary effect of the corrosive/general toxic properties of MITC. In the acute oral and dermal toxicity studies the gastrointestinal tract/stomach has been the target organ, which was also considered to be due to the corrosive properties of MITC.

A.3.2.4.2 Comparison with the CLP criteria

Substances are to be classified for STOT SE if they cause specific, non-lethal target organ toxicities resulting from single exposures to the substance. In cases where a single exposure to a substance causes lethality, that effect should result in classification for acute toxicity, not for STOT SE.

Classification into STOT SE, Category 1 or 2, might be appropriate if a substance is presumed to produce significant and/or severe target organ toxicity in humans following single exposure, on the basis of observations in humans or evidence from animal studies or is presumed to have the potential to cause harm to human health following single exposure.

No target organ toxicity was observed after acute exposure (oral, dermal, inhalation) to Dazomet. Furthermore, there was no human evidence for target organ toxicity of Dazomet. Thus, a classification with STOT SE category 1 or 2 is not warranted.

No treatment-related neurotoxic effects were induced by Dazomet. Changes of functional parameters/behaviour were clearly linked to the general health conditions of the animals. No

histopathological indication of neurotoxicity was observed. Furthermore, no neurotoxic effects were observed in any of the available animal studies. Thus, no classification of Dazomet for neurotoxicity is proposed.
Effects on the liver (focal necrosis) were only observed in rats of the acute inhalation study dying before the end of the study. Therefore, these effects are considered to be covered by the classification for acute toxicity taking into account lethality.

A.3.2.4.3 Conclusion on classification and labelling for STOT SE 1 and 2

Not classified - Conclusive but not sufficient data available for classification.

A.3.2.5 Specific target organ toxicity – single exposure Category 3 (STOT SE 3)

Table A-45: Summary table of animal studies on STOT SE 3

Method, Duration of study, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	Results (including type of effect; respiratory tract irritation or narcotic effects)	Remarks (e.g. major deviations)	Reference
Acute oral neurotoxicity study **Reliability: 2** **Refer to A3.12** **P ≤ 0.05 (Anova and Mann-Whitney-U)** **P ≤ 0.01 (Dunnett)** **Key study**	Wistar rats Males/Females 10 rats/sex/group	Dazomet > 96.3 % 0, 50, 130, 450 (males), 0, 13, 50, 130 (females) mg/kg bw, in CMC (0.5 %); Single gavage followed by an observation period of 14 days	No treatment-related neuropathological effects. All other findings did not indicate a neurotoxic effect, but reflected an impairment of the general state of health Neurotoxicity NOAEL= 392 mg/kg bw/day (highest dose tested) NOAEL (females) < 13 mg/kg bw/day based on decreased motor activity at 13 mg/kg bw/day	Regarding gross pathology, no substance-related findings were obtained in neither macroscopic, nor histopathological examinations in the central or peripheral nervous system. A spontaneous internal hydrocephalus (congenital hydrocephalus) was seen in one high dose male and a spontaneous single axonal degeneration of minimal degree in the proximal sciatic nerve was noted in two control males in one high dose male. However, these findings were assessed as being incidental and not	[redacted]. (1994a) IUCLID: A8.7.1-002

				substance-related. Regarding body weight, the gain was dose-dependently decreased. Animals receiving higher dosages of Dazomet gained considerably less during experimental period than those receiving lower dosages. On day 0, half closure of eyelids was seen in 8 males and all females of the highest dose groups each, 7 males and 3 females of the mid dose groups and 1 male animal of the lowest dose group. Abnormal signs were only detected on day 0. Changes in fur was seen in some females of the highest dose group and one mid-dose female. Salivation, lacrimation and impairment of activity was registered with a dose-dependent relationship in all dose groups, excluding low-dose females.	

Acute inhalation toxicity **Refer to A.3.2.3** **Reliability: 2 (with restriction)** **Key study** **GLP** **Statical value(s) not mentioned**	Wistar rats Males/Females 10 rats/sex/group	Dazomet 98.2 % 3.83, 5.11, 8.4 mg/L TS; Administration via dust aerosols (air) with head- nose exposure for 4 hours	Target organ: Not identified LC50 ca. 8.4 mg/L/4h	After exposure, animals exhibited piloerection*, squatting posture, paresis (dragging hindlimbs*, only top-dose) trembling gait, bloody nasal discharge/crusts, haematuria*, anaemia and abdominal fur with yellow smear*. (*signs observed until termination in top-dose animals)	[redacted] (1986) IUCLID: A8.7.2-001
Acute inhalation toxicity **Refer to A.3.2.3** **Reliability: 4 (documentation insufficient for assessment)** **No study conducted prior to the implementation of GLP** **Statical value(s) not mentioned** **Supportive document**	Rats, strain unspecified	Dazomet Purity not reported Air stream saturated with the volatile components of TS; Exposure period: 8 hours 20 °C	Target organ: Not identified; no mortality; no abnormalities found	-	[redacted] (1975) IUCLID: A8.7.2-002

Acute inhalation toxicity **Refer to A.3.2.3** **Reliability: 2 (with restriction)** **Key study** **GLP** **Statical value(s) not mentioned**	CD rats Males/Females 5rats/sex/group	MITC 98 % 0,282, 0.496, 0.570, 0.628, 0.786, 1.640 mg/L TS; Vehicle not reported Exposure to vapors by whole body exposure over a period of 4 hours	Target organ: respiratory tract (oedema, bronchiolitis, pneumonitis), lung (weight increase) Respiratory noise LC50 = 0.54 mg/L/4h	-	[redacted]. (1981) IUCLID: A8.7.2-003

Table A-46: Summary table of human data on STOT SE 3

Type of data / report, Route of exposure, Reliability, Key / supportive study**	**Test substance (including purity)**	**Relevant information about the study**	**Main effects, Observations**	**Reference**
Retrospective, observational case series of metam sodium exposure **Supportive study** **Reliability: 4**	MITC (degradation product of Metam sodium) Purity and vehicle not reported	The study summarizes cases of unintentional exposure to metam sodium via different routes. Number of persons: 106 cases Exposure: Oral route, Respiratory route, Cutaneous route *Oral route: two farmers who unsuspectingly*	Non-persistent irritant cough and dyspnoea with a sensation of chest oppression occurred in four cases, irritant-induced asthma or persistent exacerbation of asthma was observed. *The most common route of exposure was inhalation (n 96). In 79 cases, the patients were people living near fi elds where metam sodium had recently been*	[redacted] (2011) IUCLID: A8.12.4-005

		ingested one or two mouthfuls of the dilute product from an irrigation pipe. *Respiratory route: People living in houses near the treated fi elds were thus exposed to the agent applied by a neighbouring farmer.* *Cutaneous route: application of metam sodium to the soil, spillage of concentrated liquid metam sodium onto his shoes during its preparation, pillage of ready-to-use (and thus dilute) product.* The study shows limitations with respect to data collection and verification and details of data.	*applied. Most of the reported symptoms involved irritation of the eyes (n 76), throat and nose (n 65), attributable to MITC. Cough and dyspnoea occurred in four cases but no persistent, irritant-induced asthma or persistent exacerbation of asthma was observed. Sixteen patients at two different sites of pollution were exposed to emanations from the drainage system in their homes following the illicit discharge of metam sodium into the sewers. Most presented with nausea and headaches, but only four experienced eye or throat irritation.* *The only lethal case recorded was a truck driver who was found dead of acute lung injury after falling into a tank that had previously contained metam sodium.*	

Table A-47: Summary table of other studies relevant for STOT SE 3

Type of data / report, Reliability, Key / supportive study	Test substance (including purity), Vehicle	Relevant information about the study	Main effects, Observations	Reference
28 day repeated dose inhalation study **Please refer to A3.7.1.3** **Key study**	MITC Purity: 96.9 % Vehicle: Nitrogen air	Wistar rats Males/ Females 5/sex/group 0, 5, 20, 100 mg/m³ Five days/week 6 hours/day	Target organ: Respiratory tract At 100 mg/m³ mucosal and respiratory irritation, changes in breathing pattern, reddish nasal and eye discharge, increased absolute lung weights, bronchopneumonia, epithelial proliferation in bronchi, bronchioles and trachea, single cell necrosis in trachea, catarrhal-purulent rhinitis in nasal cavity, atrophy of olfactory epithelium, focal squamous metaplasia of respiratory epithelium (considered secondary to corrosive properties of MITC)	[redacted]. (1987) IUCLID: A8.9.5.2 - 002

A.3.2.5.1 Short summary and overall relevance of the provided information on STOT SE 3

For the assessment on STOT SE 3 classification, acute inhalation and acute oral neurotoxicity studies as well as short-term repeated dose inhalation studies in rat were taken into consideration. In addition, also studies with MITC have been considered here since MITC as the main metabolite of Dazomet might (based on the local effect by inhalation route which can be observed in epidemiological studies, please refer to the section: "*A.3.15 Further Human data*") contribute to the toxicological profile of Dazomet.

No classification proposal is provided for MITC in the context of the Dazomet CLH dossier.

For the active substance Dazomet, there were no studies with acutely toxic effects relevant for classification for STOT SE 3. Neither animal studies nor human information. No effects in neuropathological parameters were observed.

For the major metabolite, MITC, there is evidence from human case reports that exposure to MITC transiently affect the lung, eyes and the respiratory tract after accidental exposure to MITC gas. In a study summarizing several cases of inhalation exposure to metam sodium (MITC was considered to be the active agent), The symptoms most frequently described were irritant, affecting the eyes (with or without conjunctivitis), nose and throat or causing skin erythema, vomiting, nausea and headaches. Much less common were a few cases of respiratory disorders with cough or mild dyspnoea. One case concerned a woman who was 18 weeks pregnant after *in vitro* fertilisation and presented with oropharyngeal irritation.

For the inhalation route, the application methods almost exclude any exposure to an aerosol of metam sodium itself. It is mainly exposure to gaseous MITC, which is rapidly released after soil application, which causes the symptoms. During the application of metam sodium on soil, inhalation of the fumigant by the user or neighbours usually causes only mild symptoms. The respiratory complaints observed in our study were uncommon and limited to a short-lived irritant cough, with a sensation of chest oppression in a few cases.

Acute and short-term inhalation studies support the MITC effects on the lung, eyes and the respiratory tract.

A.3.2.5.2 Comparison with the CLP criteria

Substances are to be classified for STOT SE if they cause specific, non-lethal target organ toxicities resulting from single exposures to the substance. In cases where a single exposure to a substance causes lethality, that effect should result in classification for acute toxicity, not for STOT SE.

If a study shows clear evidence for transient narcotic effects or respiratory tract irritation at any dose level then this could support classification with Category 3. These are target organ effects for which a substance does not meet the criteria to be classified in Categories1 or 2 indicated above. These are effects which adversely alter human function for a short duration after exposure and from which humans may recover in a reasonable period without leaving significant alteration of structure or function.

There were no effects in animal studies after both acute and repeated inhalation of Dazomet

that would justify classification in Category 3. No human cases are described for Dazomet inducing respiratory tract irritation. However, it cannot be ruled out that during exposure to Dazomet its major metabolite MITC is produced, which is known to irritate the respiratory tract. In addition to evidence in animal studies with MITC, there are also many described cases of respiratory tract irritation in humans after accidental exposure to MITC gas.

Thus, classification of Dazomet in Category 3 might be warranted based on human evidence of irritating properties of the main metabolite MITC. No indications of narcotic effects were observed after exposure to Dazomet via inhalation.

A.3.2.5.3 Conclusion on classification and labelling for STOT SE 3

Dazomet: classified as upper airway irritant in humans (case studies) - STOT SE 3; H335

A.3.2.5.4 Overall conclusion on acute toxicity related to risk assessment

Not applicable for the CLH report.

A.3.3 Skin corrosion and irritation

A full set of acute toxicity studies (acute toxicity via the oral, dermal or inhalation route, skin or eye irritation or skin sensitization) for the active substance Dazomet and its active metabolite MITC were provided for the Annex II inclusion and thus peer reviewed by European competent authorities and eCA Belgium.

During the last years, most of the guidelines for repeated dose toxicity testing have been reviewed and adapted to the state of science, a re-evaluation of existing studies was conducted to check for deviations which are no longer compatible with the current evaluation criteria.

For acute toxicity testing, almost all test guidelines changed fundamentally. Mainly, due to the intended reduction of the number of test organisms to be used, for animal welfare reasons and, to the adaptation of the test design with regard to its future suitability for the revised GHS classification criteria. Due to these differences, a comparison of the old studies with the current guidelines would inevitably lead to the identification of a large number of inherent deviations, which would only be of limited informative value and could give a distorted picture of its contemporary reliability. When compared to the guideline in place at the time of study conduction, the applicant follows the assessment by the previous evaluator and considers the study reliable with restrictions. In any case, the study is also considered for animal welfare reasons and the provided results are relied on and used for completion of the toxicological risk characterization.

New information

No new data was submitted for Dazomet and MITC with respect to acute toxicity via the oral, dermal or inhalation route, skin or eye irritation or skin sensitization. Nor have any new studies been found during the open literature search that would provide new data and/or question the results of the existing GLP studies. Even though the submitted studies no longer fully meet the standard of the current test guidelines, they do not deviate in such an extent that would justify

the performance of new vertebrate tests. Thus, the evaluation in Dazomet Assessment Report (Belgium, 2010) remains valid.

Table A-48: Summary table of *in vitro* studies on skin corrosion/irritation

No *in vitro* data is available.

Table A-49: Summary table of animal studies on skin corrosion/irritation

Method, Guideline, GLP status, Reliability, Key/supportive study	Test substance (including purity), Vehicle, Doses	Relevant information about the study	Average score 24, 48, 72 h Erythema (R), Edema (ED)			Results	Reference
			24 h	48 h	72 h		
OECD TG 404 **Key study** **GLP** **Reliability: 1**	Dazomet 98.5 % Distilled water 0.5 g patch test (semi occlusive) Rabbit Number of animals: 6 Duration of treatment: 4 hours	The test substance resulted in a primary irritation index of 0, indicating that Dazomet was not irritating to the intact skin of rabbit.	R/ED: 0/0	R/ED: 0/0	R/ED: 0/0	Reversibility: Yes Not irritating	[redacted] (1992) IUCLID: A8.1.1-001
			Average score (24, 48 and 72 h): 0				
OECD TG 404 **Key study** **GLP** **Reliability: 1**	MITC 98 % Olive oil DAB 0.5 g patch test (semi occlusive) Rabbit Number of animals: male: 3 female: 3 Duration of treatment: 4 hours	After application, severe sign of irritation were observed which persisted up to 72 hours. At this time superficial necrosis were seen in all animals. As reversibility could not be expected the study was finalised after 72 hours.	R/ED: 4/2.83	R/ED: 4/2.33	R/ED: 4/2.33	Reversibility: No Severely irritating	[redacted]. (1986a) IUCLID: A8.1.1-002
			Average score (24, 48 and 72 h): 2.55				

Dazomet:

Observation time	Rabbit n°3597 Erythema	Rabbit n°3597 Oedema	Rabbit n°3598 Erythema	Rabbit n°3598 Oedema	Rabbit n° 3599 Erythema	Rabbit n° 3599 Oedema
24 hours	0	0	0	0	0	0
48 hours	0	0	0	0	0	0
72 hours	0	0	0	0	0	0
Mean Value	0	0	0	0	0	0

Observation time	Rabbit n°3600 Erythema	Rabbit n°3600 Oedema	Rabbit n°3601 Erythema	Rabbit n°3601 Oedema	Rabbit n° 3607 Erythema	Rabbit n° 3607 Oedema
24 hours	0	0	0	0	0	0
48 hours	0	0	0	0	0	0
72 hours	0	0	0	0	0	0
Mean Value	0	0	0	0	0	0

MITC:

Observation time	Animals	Erythema	Oedema	Symptoms
4 H	1	4	4	Hemorrhage/Oedema#
	2	4	4	Hemorrhage/Oedema#
	3	4	4	Hemorrhage/Oedema#

	4	4	4	Hemorrhage/Oedema#
	5	4	4	Hemorrhage/Oedema#
	6	4	4	Hemorrhage/Oedema#
24 H	1	4	4	Hemorrhage/Oedema#
	2	4	3	Hemorrhage/Oedema#
	3	4	2	Hemorrhage/Oedema#
	4	4	2	Hemorrhage/Oedema#
	5	4	3	Hemorrhage/Oedema#
	6	4	3	Hemorrhage/Oedema#
48 H	1	4	3	Hemorrhage/Oedema#
	2	4	2	Hemorrhage/Oedema#
	3	4	2	Hemorrhage/Oedema#
	4	4	2	Hemorrhage/Oedema#
	5	4	3	Hemorrhage/Oedema#
	6	4	2	Hemorrhage/Oedema#
72 H	1	4	3	Necrosis*/+/Oedema
	2	4	2	Necrosis*/+/Oedema
	3	4	2	Necrosis*/+/Oedema
	4	4	2	Necrosis*/+/Oedema
	5	4	3	Necrosis*/+/Oedema
	6	4	2	Necrosis*/+/Oedema
Mean	1	4.0	3.3	-
Mean	2	4.0	2.3	-
Mean	3	4.0	2.0	-
Mean	4	4.0	2.0	-
Mean	5	4.0	3.0	-
Mean	6	4.0	2.3	-
Total (mean)	-	4.0	2.5	-

Table A-50: Summary table of human data on skin corrosion/irritation

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Medical surveillance on manufacturing	Dazomet	Cases of poisoning at the plant production site	Dazomet can cause skin and eye irritation in exposed manufacturing plant personnel, only 17 cases of human irritation to skin and eyes were reported over a period of at least 10 years. In fact, human Dazomet irritation under work place conditions in industry is low, due to appropriate protective measures.	[redacted] (2000b) IUCLID: A8.12.1-001
Clinical cases and poisoning incidents	MITC generated from Dazomet	Cases of poisoning following use of plant product	MITC generating compounds such as Dazomet were reported by Richter G for MITC. The author described the case of poisoning of a 24-year-old woman who did not notice that some Dazomet hat got into her rubber boot, which she wore for about 24 hours. After 24 hours a first to second degree acid burn developed and during the following days a bullous eruption spread over one foot/leg to about 5 % of the body surface.	[redacted] (1980) IUCLID: A8.12.1-002
Clinical cases and poisoning incidents	MITC/Dazomet	Cases of poisoning following use of plant product Testing and analyses	A 67-year-old male farmer presented with an acute onset of itchy bullae and erythema on his feet (Ohata, 2013, IUCLID A8.12.2-003). He had a history of diabetes mellitus. On physical examination, multiple bullae and erythema on the left sole, foot, and lower leg were observed, as well as erythema on the right foot. Additional bullae developed on the right sole 2 days later. To resolve the severe pruritus and extensive bullae formation prednisolone 20 mg/day was administered for 3 days, followed by 10	[redacted] (2013) IUCLID: A8.12.2-003

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			mg/day for 10 days. Diflorasone diacetate was used as topical steroid. During the 3 months after steroid cessation, bullae with pruritus occasionally developed on the patient's feet. Frequent interviews and several laboratory examinations, including skin biopsy, skin cultures, and blood tests, did not reveal the cause. Eventually, the patient's occupation and the lesion sites led doctors to suspect his rubber boots. Patch tests were performed on the patient's boots. Thin square pieces (5 × 5 mm) of the outer surface, inner surface, inner insole, and bottom insole of the boots were applied, avoiding pressure effects with an adhesive bandage, for 48 h. Results were obtained after 2 and 3 days of patch test application on the basis of the scoring system by the International Contact Dermatitis Research Group. Positive results were obtained for the outer surface (D2+/D3+), inner surface (D2+/D3+), inner insole (D2++/D3++), and bottom insole (D2++/D3++). Since contact dermatitis was suspected, patch tests with the constituents of the boots, which were rubber chemicals and matrices of the boot material provided by the manufacturer, were subsequently performed. However, all results were negative. Patch tests performed with new but identical boots were also negative. Therefore, it was hypothesized that some	

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			material absorbed by the rubber boots was the cause of his condition. The patient recalled spraying Dazomet in his fields 17 days before the onset of his first symptoms. One week after spraying Dazomet, he cultivated the fields wearing his boots. The patient also recalled wearing the boots while spraying other fields 4 days before the onset of symptoms and while working in the fields the following day. Although he washed the boots after each working day, he had worn them for more than 10 h a day before symptom onset and for a few hours a day after cessation of systemic steroids. Gas chromatography analysis of the outer and inner surfaces and the inner and bottom insoles of the boots revealed MITC concentrations of 0.7, 15.6, 16.0, and 11.6 ppm, respectively. These concentrations were equivalent to those of Dazomet, i.e., 2, 35, 36 and 26 ppm, respectively. Although the patient had previously used Dazomet once every 5 years, this was the first episode of skin eruptions.	
Observations on exposure of the general population	Dazomet	Case of a paper mill worker	Warin A reported the case of a paper mill worker with a 3-month history of sore itching upper and lower eyelids, with erythema and scaling. The reaction occurred at least 4 hours after finishing work and lasted for more than 24 hours. It could be found out that the occurrence of these reactions was closely related to introduction in the paper mill	[redacted] (1992) IUCLID: A8.12.1-009

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			of a new biocide, Busan 1058, containing 24% Dazomet as active ingredient. Patch testing with this product was positive.	
Observations on exposure of the general population	Dazomet	Worker in a hardboard factory Glasshouse tomato grower	Black H from the skin clinic of the Auckland hospital in New Zealand reported two cases of bullous dermatitis related to Dazomet. The first case was a worker in a hardboard factory who came accidentally in contact with Dazomet (right forearm) while diluting a concentrated solution of the substance in water prior to flushing it through water pipes to prevent the growth of algae. The worker immediately washed his forearm, however, a few days later he became an acute itching dermatitis. Patch testing with a 0.25% aqueous solution of Dazomet gave a positive reaction. The second case was a glasshouse tomato grower with a case history: an acute dermatitis, which he developed one year earlier during handling of a formalin solution. This man came accidentally in contact with Basamid, a granulated form of Dazomet, while he was spreading the granules by hand prior to hoed them in the soil. Some granules accidentally fell into his gumboots. The man developed a severed dermatitis. Patch tests as well as an open test were positive.	[redacted] (1973) IUCLID: A8.12.1-011
Observations on exposure of the general population	MITC	Cases of poisoning following use of plant product	The case of local reaction and systemic poisoning already mentioned above, Richter G from the Department of	[redacted] (1980) IUCLID: A8.12.2-

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			Dermatology, Academy of Medicine, Dresden reported on 9 cases of occupational dermatoses related to MITC which he was asked to give expert opinion within a time frame of 2 years. The patients have been handling MITC generating soil disinfectants like Dazomet, Metham sodium used in agriculture and horticulture, especially garden nurseries. The patients were all reporting several cases of similar skin reaction in colleagues who have not seeked dermatological advice. Although the patients were only exposed to MITC and MITC generating biocides for a short time (few hours to few days) 8 out of 9 showed a strong positive reaction (++ or +++) to Vapam® even when the test was repeated 1 year later. According to the author the workers were handling a 10% aqueous Vapam® or Nematin® formulation containing 32.7 or 29.5% MITC. The tests further showed that no cross-reaction between MITC and benzene isothoiocyanate (BIT) was evident. It can be concluded that MITC can cause strong skin irritation.	001
Observations on exposure of the general population	Dazomet	Hardboard factory worker Cases of poisoning following use of plant product	Black H reported bullous dermatitis in a hardboard factory worker and in a farmer following use of Dazomet or of Dazomet and Chloropicron, respectively was reported by. Patch testing showed a positive reaction to Dazomet (0.25 % in aq.) in the hardboard factory worker and to Dazomet (0.125, 0.25 and 0.5 % in aq.) and	[redacted] (1973) IUCLID: A8.12.1-011

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			Chloropicron (0.5 % in aq.) in the farmer. It appears that use of Dazomet can cause skin irritations.	
Observations on exposure of the general population	Dazomet	Cases of poisoning following use of plant product	Seven cases (all male agricultural workers) of contact dermatitis due to the exposure to Dazomet were reported by Garnier R et al. The primary lesions (mainly bullous skin reactions) that were observed were reversible and healing process lasted for a few days to 3 weeks. Only one of the 7 patients was subjected to an epicutaneous test using aqueous solutions of Dazomet ranging from 0.01% to 0.2%. Even at the lowest concentration of 0.01% Dazomet, an irritant response was observed which was characterized by a bullous skin reaction with sensation of burning.	[redacted] (1993) IUCLID : A8.12.1-008

A.3.3.1 Short summary and overall relevance of the provided information on skin corrosion/irritation

Dazomet is not an irritant to rabbit skin ([redacted]. (1992, A8.1.1-001)) whereas MITC causes severe irritation. However, without full thickness necrosis in this species ([redacted] (1986a, A8.1.1-002)).

A.3.3.2 Comparison with the CLP criteria

The in-vivo study performed on Dazomet ([redacted]. (1992, A8.1.1-001)), not irritant effect has been proven on the other hand of the study performed on MITC ([redacted] (1986a, A8.1.1-002)) which clearly proves significant corrosive effect. However numerous epidemiological data proves irritant effects following to Dazomet.
According to the CLP regulation an active substance is defined like irritant if they exist human data, single or repeated exposure. Which is the case here. Based on weight of evidence the:

- Dazomet: Classified as skin irritant in humans (case studies) – H315

Negative animals' findings overruled by human case-studies in the open literature

- MITC: Classified as skin corrosive based on *in vivo* testing (rabbit) – H314

A.3.3.3 Conclusion on classification and labelling for skin corrosion / irritation

Dazomet: Classified as skin irritant in humans (case studies) – H315

Negative animals' findings overruled by human case-studies in the open literature

MITC: Classified as skin corrosive based on *in vivo* testing (rabbit) – H314

For Dazomet the difference observed between the absence effect on rabbit study and the presence on clear effect detected on humans (epidemiological study) could be explained by the fact that the lab study has been performed on olive oil solution. Indeed the MITC is generated following the hydrolysis of Dazomet, which could explain this difference in results.

A.3.3.4 Overall conclusion on skin irritation and corrosivity related to risk assessment

Not applicable for the CLH report.

A.3.4 Serious eye damage and Eye irritation

A full set of acute toxicity studies (acute toxicity via the oral, dermal or inhalation route, skin or eye irritation or skin sensitization) for the active substance Dazomet and its active metabolite MITC were provided for the Annex II inclusion and thus peer reviewed by European competent authorities and eCA Belgium.

During the last years, most of the guidelines for repeated dose toxicity testing have been reviewed and adapted to the state of science, a re-evaluation of existing studies was conducted to check for deviations which are no longer compatible with the current evaluation criteria.

For acute toxicity testing, almost all test guidelines changed fundamentally mainly due to the intended reduction of the number of test organisms to be used for animal welfare reasons and to the adaptation of the test design with regard to its future suitability for the revised GHS classification criteria. Due to these differences, a comparison of the old studies with the current guidelines would inevitably lead to the identification of a large number of inherent deviations, which would only be of limited informative value and could give a distorted picture of its contemporary reliability. When compared to the guideline in place at the time of study conduction, the applicant follows the assessment by the previous evaluator and considers the study reliable with restrictions. In any case, the study is also considered for animal welfare reasons and the provided results are relied on and used for completion of the toxicological risk characterization.

New information

No new data was submitted for Dazomet and MITC with respect to acute toxicity via the oral, dermal or inhalation route, skin or eye irritation or skin sensitization. Nor have any new studies been found during the open literature search that would provide new data and/or question the results of the existing GLP studies. Even though the submitted studies no longer fully meet the standard of the current test guidelines, they do not deviate in such an extent that would justify

the performance of new vertebrate tests. Thus, the evaluation in Dazomet Assessment Report (Belgium, 2010) remains valid.

Table A-51: Summary table of *in vitro* studies on serious eye damage and eye irritation

No *in vitro* data is available.

Table A-52: Summary table of animal studies on serious eye damage and eye irritation

Method, Duration of study, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	Average score for corneal opacity, iritis, conjunctival redness and conjunctival oedema (24, 48, 72 h) per animal, observations and time point of onset, reversibility				Results	Reference
			Cornea	Iris	Conjunctiva			
					Redness	Chemosis		
OECD TG 405 **Key study** **Reliability: 1** **GLP**	Rabbit (Vienna white) Number of animals: female: 4 Male: 2	Dazomet 98.2 % 0.1 mL bulk volume (about 39 mg of the comminuted test substance) Observation: 1, 24, 48 and 72 hours after application Vehicle: probably mixed with drinking water.	0	0	0.6	0	Reversibility: Yes Not irritating	[redacted]. (1985a) IUCLID: A8.2.1-001

Dazomet:

Observation time	Animal	Cornea (Opacity)	Iris	Conjunctiva		Symptoms
				Redness	Chemosis	
1 H	1	0	0	2	1	Pupil contracted
	2	0	0	2	1	Pupil contracted
	3	0	0	2	1	Pupil contracted
	4	0	0	2	1	Pupil contracted
	5	0	0	2	1	Pupil contracted
	6	0	0	2	2	Pupil contracted
24 H	1	0	0	2	0	-
	2	0	0	1	0	-
	3	0	0	1	0	-
	4	0	0	2	0	-
	5	0	0	2	0	-
	6	0	0	1	0	-
48 H	1	0	0	0	0	-
	2	0	0	0	0	-
	3	0	0	0	0	-
	4	0	0	0	0	-
	5	0	0	1	0	-
	6	0	0	0	0	-
72 H	1	0	0	0	0	-
	2	0	0	0	0	-
	3	0	0	0	0	-
	4	0	0	0	0	-

	5	0	0	0	0	-
	6	0	0	0	0	-
Mean	1	0.0	0.0	0.7	0.0	-
	2	0.0	0.0	0.3	0.0	-
	3	0.0	0.0	0.3	0.0	-
	4	0.0	0.0	0.7	0.0	-
	5	0.0	0.0	1.0	0.0	-
	6	0.0	0.0	0.3	0.0	-
Mean	**-**	**0.0**	**0.0**	**0.6**	**0.0**	-

Table A-53: Summary table of human data on serious eye damage and eye irritation

Type of data/report	**Test substance,**	**Relevant information about the study (as applicable)**	**Observations**	**Reference**
Medical surveillance on manufacturing	Dazomet	Cases of poisoning at the plant production site	Dazomet can cause skin and eye irritation in exposed manufacturing plant personnel, only 17 cases of human irritation to skin and eyes were reported over a period of at least 10 years. In fact, human Dazomet irritation under work place conditions in industry is low, due to appropriate protective measures.	[redacted], (2000b) IUCLID: A8.12.1-001
Observations on exposure of the general population	MITC from the degradation of Metam sodium	Train tanker car derailment containing Metam sodium	As a consequence of the spill of Metham sodium (33 % aqueous solution) that resulted from the train tanker car derailment mentioned above, MITC was subsequently released into the air as a result of chemical break down under the environmental conditions present at that	[redacted] (1994) IUCLID : A8.12.1-003 Kreutzer RA et al. (1994) IUCLID : A8.12.1-003

			time . In the nearby township of Dunsmuir measured MITC levels ranged from 0.2 to 37 ppb and estimated peak levels ranged from 140 to 1600 ppb. 2129 inhabitants were exposed to MITC vapours and complained of burning eyes, nasal and throat irritation, shortness of breath and non-specific neurological complaints such as dizziness and headache. All these symptoms were consistent with MITC exposure. The onset of symptoms was as early as 12 hours after the spill but generally the day after.	
Epidemiological study	MITC from the degradation of Metam sodium	People living near fields where metam sodium had been applied. Exposed to emanations from the drainage system in their homes.	The toxicity of poisoning by metam sodium, a dithiocarbamate fumigant, the breakdown products of which is, besides others, methyl isothiocyanate (MITC) was evaluated by means of a retrospective, observational case series of metam sodium exposure cases reported to the Angers Poison and Toxicovigilance Centre from 1992 through 2009, which served as the data source of the study reported by Deguigne MB. A total of 106 cases of metam sodium exposure were recorded and 102 cases were included in this study. All cases of exposure were unintentional. Occupational poisoning occurred in eight cases. The most common route of exposure was inhalation (n= 96). In 79 cases, the patients were people living near fields where metam sodium had recently been applied. Most of the reported symptoms involved irritation of the eyes (n= 76), throat and nose (n= 65), attributable to MITC. Cough and dyspnoea occurred in four cases but no persistent,	[redacted] (2011) IUCLID: A8.12.4-005

			irritant-induced asthma or persistent exacerbation of asthma was observed. Sixteen patients at two different sites of pollution were exposed to emanations from the drainage system in their homes following the illicit discharge of metam sodium into the sewers. Most presented with nausea and headaches, but only four experienced eye or throat irritation.	

A.3.4.1 Short summary and overall relevance of the provided information on serious eye damage / eye irritation

Dazomet is also not an irritant to the eyes in rabbits ([redacted] (1985a, A8.2.1-001). For MITC a severe effect on mucous membranes was observed in the acute inhalation study in rats and a marked skin reaction in rabbits suggests that MITC is likely to be a severe irritant to the eye.

A.3.4.2 Comparison with the CLP criteria

The in-vivo study performed on Dazomet ([redacted] (1985a, A8.2.1-001), not irritant effect has been proven. However numerous epidemiological data proves irritant effects following to Dazomet exposure.
According to the CLP regulation an active substance is defined like irritant if they exist human data, single or repeated exposure. Which is the case here. Based on weight of evidence the:

Dazomet: classified as eye irritant in humans (case studies, please refer to the above table for more information) – H319

A.3.4.3 Conclusion on classification and labelling for serious eye damage / eye irritation

Dazomet: Classified as eye irritant in humans (case studies, please refer to the above table for more information) – H319
Negative animals' findings overruled by human case-studies in the open literature

MITC: Classified as skin corrosive based on *in vivo* testing (rabbit) – H314, therefore this substance is also classified as corrosive for eyes

A.3.4.4 Overall conclusion on eye irritation and corrosivity related to risk assessment

Not applicable for the CLH report.

A.3.5 Skin sensitisation

A full set of acute toxicity studies (acute toxicity via the oral, dermal or inhalation route, skin or eye irritation or skin sensitization) for the active substance Dazomet and its active metabolite MITC were provided for the Annex II inclusion and thus peer reviewed by European competent authorities and eCA Belgium.

During the last years, most of the guidelines for repeated dose toxicity testing have been reviewed and adapted to the state of science, a re-evaluation of existing studies was conducted to check for deviations which are no longer compatible with the current evaluation criteria.

For acute toxicity testing, almost all test guidelines changed fundamentally mainly due to the intended reduction of the number of test organisms to be used for animal welfare reasons and to the adaptation of the test design with regard to its future suitability for the revised GHS classification criteria. Due to these differences, a comparison of the old studies with the current guidelines would inevitably lead to the identification of a large number of inherent deviations, which would only be of limited informative value and could give a distorted picture of its contemporary reliability. When compared to the guideline in place at the time of study

conduction, the applicant follows the assessment by the previous evaluator and considers the study reliable with restrictions. In any case, the study is also considered for animal welfare reasons and the provided results are relied on and used for completion of the toxicological risk characterization.

New information

No new data was submitted for Dazomet and MITC with respect to acute toxicity via the oral, dermal or inhalation route, skin or eye irritation or skin sensitization. Nor have any new studies been found during the open literature search that would provide new data and/or question the results of the existing GLP studies. Even though the submitted studies no longer fully meet the standard of the current test guidelines, they do not deviate in such an extent that would justify the performance of new vertebrate tests. Thus, the evaluation in Dazomet Assessment Report (Belgium, 2010) remains valid.

Table A-54: Summary table of animal studies on skin sensitisation

Method, Duration of study, Route of exposure (e.g. topical/intradermal, induction/challenge if relevant), Guideline, GLP status, Reliability, Key/supportive study	**Species, Strain, Sex, No/Group**	**Test substance (including purity), Vehicle, Dose levels, Duration of exposure**	**Results (e.g. EC3-value or amount of sensitised animals at induction dose)**	**Remarks (e.g. major deviations)**	**Reference**
OECD TG 406 **GLP** **Reliability: 1** **Key study**	Guinea Pig 98.2 % Vehicle: olive oil DAB (Dunkin-Hartley) Female Number of animals per control group: 10 Number of	Dazomet Percutaneous 0.3g test substance Carried out 1 week after intradermal induction. Duration of exposure: 48 hours Selection was made on the basis of a pre-test.	Dazomet 60 % in olive oil, 1st challenge: 0/17 (The study was performed with 20 animals/group, though 1 animal was sacrificed on day 9 after intradermal induction because of suspicion of pneumonia. Another 2 animals died from pulmonary emphysema or peritonitis 12 and 14 days after intradermal induction) Dazomet 60 % in olive oil, 2nd challenge: 0/14 (3 further animals died from	-	[redacted] (1985b) [redacted] (1986) Amendment IUCLID: A8.3.1-001

	animals per test group: 20		pneumonia 23, 26 and 27 days after intradermal induction). Therefore not sensitizing effect. No erythema or oedema has been observed on the completion of the study. No skin findings were seen after 48 hours following the first and the second challenge.		
OECD TG 406 **GLP** **Reliability: 1** **Key study**	Guinea Pig (Dunkin-Hartley) Female Number of animals per control group: 10 Number of animals per test group: 20	MITC 98 % Vehicle: olive oil DAB Percutaneous 0.3 g test substance Carried out 1 week after intradermal induction. Duration of exposure: 48 hours Selection was made on the basis of a pre-test.	MITC 0.5 % in olive oil, 1st challenge: 12/20 MITC 0.5 % in olive oil, 2nd challenge: 13/20 After the first challenge 7/20 test group animals showed slight erythema, 4/20 distinct erythema in addition to slight edema and 1/20 distinct erythema. There was no indication of a skin reaction in the control group 1. After the second challenge 7/20 test group animals showed slight erythema, 2/20 distinct erythema in addition to slight edema and 4/20 distinct erythema. There was no skin reaction in control group 1 and 2. To conclude this substance is considered as sensitizing.	-	[redacted] (1986b) IUCLID: A8.3.1-002

Table A-55: Summary table of human data on skin sensitisation

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Observations on exposure of the general population	Dazomet	Worker in a hardboard factory Glasshouse tomato grower	Black H from the skin clinic of the Auckland hospital in New Zealand reported two cases of bullous dermatitis related to Dazomet. The first case was a worker in a hardboard factory who came accidentally in contact with Dazomet (right forearm) while diluting a concentrated solution of the substance in water prior to flushing it through water pipes to prevent the growth of algae. The worker immediately washed his forearm, however, a few days later he became an acute itching dermatitis. Patch testing with a 0.25% aqueous solution of Dazomet gave a positive reaction. The second case was a glasshouse tomato grower with a case history: an acute dermatitis, which he developed one year earlier during handling of a formalin solution. This man came accidentally in contact with Basamid, a granulated form of Dazomet, while he was spreading the granules by hand prior to hoed them in the soil. Some granules accidentally fell into his gumboots. The man developed a severed dermatitis. Patch tests as well as an open test were positive. According to these findings, Dazomet appeared to be a strong sensitiser, a primary irritant and possibly a vesicant, and may cause contact dermatitis in occupational exposure. Black H reported bullous dermatitis in a hardboard factory worker and in a farmer following use of Dazomet or of Dazomet and Chloropicron, respectively was reported by. Patch testing showed a positive reaction to Dazomet (0.25 % in aq.) in the hardboard factory worker and to Dazomet (0.125, 0.25 and 0.5 % in aq.) and Chloropicron	[redacted] (1973) IUCLID: A8.12.1-011

Type of data / report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			(0.5 % in aq.) in the farmer. It appears that use of Dazomet can cause skin irritations and sensitisation.	
Observations on exposure of the general population	Dazomet	Worker in agricultural sector Patch test	Lisi P *et al.* tested 36 substances with 652 subjects from different areas (males and females; agricultural workers, ex agricultural workers, other) to establish the optimal test concentrations and the frequencies of irritant and allergic reactions. Dazomet was tested at concentrations of 0.25 % or 0.1 % in petrolatum. MITC was not tested in this study. The frequency of skin irritation and sensitisation was low. There was no skin reaction in agricultural workers. Allergenic responses were noted in ex-agricultural workers at 0.25 % (1 out of 32) and 0.1 % (1 out of 37). In the other 'non-agricultural' collective an irritant response was noted at 0.25 (1 out of 191) and 0.1 % (1 out of 198). These results show that Dazomet has a low irritant and sensitizing potential in this study and there is no indication that agricultural workers are more at risk. However it should be noted, that Dazomet was tested in petrolatum which might have prevented the generation of the potent allergen MITC, and MITC has also not been tested in this study.	[redacted] (1986, 1987) IUCLID : A8.12.1-007
Observations on exposure of the general population	Dazomet	Worker in agricultural sector Patch test	Seven cases (all male agricultural workers) of contact dermatitis due to the exposure to Dazomet were reported by . The primary lesions (mainly bullous skin reactions) that were observed were reversible and healing process lasted for a few days to 3 weeks. Only one of the 7 patients was subjected to an epicutaneous test using aqueous solutions of Dazomet ranging from 0.01 % to 0,2 %. Even at the lowest concentration of 0.01 %	[redacted] (1993) IUCLID : A8.12.1-008

Type of data / report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			Dazomet, an irritant response was observed which was characterized by a bullous skin reaction with sensation of burning. Comparing the results of the present study (positive skin reaction) to those of the study of Lisi P and coworkers (negative skin reaction; see above), the difference between the respectively obtained results was explained by the fact that in the study of Lisi *et al.* and in contrast to the study of Garnier et al., Dazomet was tested in petrolatum instead of water: Dazomet is not dissociated in organic solvents. Nevertheless the authors would not rule out a sensitising effect of Dazomet due to its degradation to the known allergen MITC.	
Observations on exposure of the general population	Dazomet	Patch test	In an older study a total of 19 out of 200 volunteers (10 %) reacted positive with respect to skin sensitisation when 1 % Dazomet was applied dry to the test persons (Patch test). An aqueous solution of 0.01 % Dazomet however was negative.	[redacted] (1966) IUCLID : A8.12.1-015
Observations on exposure of the general population	Dazomet	Cases of poisoning following use of plant product Patch test	In a case report of pruritus and papulous reaction after handling various pesticides Vilaplana J. *et al*., the potential contact to Dazomet was reported to result in no skin reaction. The Patch-test reaction to Dazomet (0.1 % in pet.) was negative.	Vilaplana [redacted] 1993, IUCLID : A8.12.1-010
Observations on exposure of the general population	MITC generated form the degradation of Dazomet	Patch test	Wuerbach G *et al.* reported that the dermatological department of the University of Erfurt/Germany performed human patch tests in patients sensitized to Afugin® a local human antimycotic drug (3,5-Dibenzylperhydro-1,3,5-thiadiazin-2-thion), closely related to Dazomet (3,5-Dimethylperhydro-1,3,5-	[redacted] (1982) IUCLID : A8.12.1-006

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			thiadiazin-2-thion) and related compounds releasing either benzene-isothiacyanate like Afugin® or beta-phenylethyl-isothiacyanate. In addition patients sensitised to Nematin® (Sodium methyl-dithiocarbamate) were tested to closely related structures including methylisothiacyanade (MITC) a known metabolite of Nematin® and Dazomet. The patients were tested under occlusive conditions for 24 hours (Gothatest ®) at specified concentrations who varied from test substance to test substance. All skin reactions 24, 38 and 72 hours after the test were evaluated as positive. Patients sensitized to Afugin® reacted positive to the benzene-derivates but not phenylethyl-derivates, indicating that the side chain might influence the result of the test. Patients sensitised to the known MITC generator Nematin® (0.01 % aqueous preparation) reacted positive (4 out of 4 patients) and also 1 patient tested for MITC (0.01 % in petrolatum) reacted positive. Dazomet was also tested (1 % in petrolatum) and only 1 out of 4 patients sensitized to Nematin® reacted positive. The authors suggested that the methyl moiety of MITC would be the relevant allergens structure while the isothiocyanate group would be responsible for the haptene conjugation due to its high affinity to proteins. MITC has been identified as a strong allergen to humans also the exposure under practical use conditions in the described cases came from Nematin® an agricultural nematicide generating MITC when farmers handling treated potatoes with their hand and MITC was formed under acidic conditions of the exposed skin. Dazomet reacted to a much lower degree (1 out of 4 patients). The	

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			formation of MITC under dermatological test conditions might have been impaired as Dazomet was applied in petrolatum stabilizing the molecule. It is noteworthy that Dazomet is not a skin sensitizer in the Guinea Pig Maximisation Test (GPMT) when petrolatum has also been used as vehicle. MITC itself is a strong skin sensitizer in the GPMT.	
	MITC generated form the degradation of Meta sodium	Cases of professional dermatoses following use of ppp or biocidal product	Richter G from the Department of Dermatology, Academy of Medicine, Dresden reported on 9 cases of occupational dermatoses related to MITC which he was asked to give expert opinion within a time frame of 2 years. The patients have been handling MITC generating soil disinfectants like Dazomet, Metham sodium used in agriculture and horticulture, especially garden nurseries. The patients were all reporting several cases of similar skin reaction in colleagues who have not seeked dermatological advice. Although the patients were only exposed to MITC and MITC generating biocides for a short time (few hours to few days) 8 out of 9 showed a strong positive reaction (++ or +++) to Vapam® even when the test was repeated 1 year later. According to the author the workers were handling a 10 % aqueous Vapam® or Nematin® formulation containing 32.7 or 29.5 % MITC. The tests further showed that no cross-reaction between MITC and benzene isothoiocyanate (BIT) was evident. It can be concluded that MITC can cause strong skin irritation as well as sensitisation. Based on the exposure information given by the patients, MITC must be regarded as a potent skin sensitizer.	[redacted] (1980) IUCLID: A8.12.2-001

Type of data/report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Observations on exposure of the general population	MITC generated form the degradation of Meta sodium	Cases of professional dermatoses following use of ppp	In 1970, Jung H-D and Wolf F reported on 16 cases indicative of a contact dermatitis due to the compound Vapam, an MITC generating nematicide based on Metham sodium, in agricultural workers handling Vapam-treated potatoes. The authors observed bullous skin reactions. Seven of these 16 cases were subjected to the patch test. The concentrations of the Vapam formulation ranged from 1.5 to 10 % and airborn aerosols from a 10 % preparation also were tested. All 7 patients reacted to the applied concentrations and the authors concluded that the reactions seen were not only toxic reactions but also of the allergic type. Even airborne vapours in a room did cause such reactions. While under practical field conditions the skin reaction in a female agricultural worker was noted 3 weeks after start of exposure, skin findings as soon as two days after re-exposure were noted one year later. MITC generation was assumed to play an important role in the development of the dermatitis (toxic and allergic). It is presumed that MITC generated from Nematin (Vapam) was responsible for toxic and allergic contact dermatitis in agricultural workers. Even vapours in a closed room were sufficient to cause skin reactions in sensitised persons (airborne contact dermatitis).	[redacted] (1970) IUCLID: A8.12.1-012
Observations on exposure of the general population	MITC generated form the degradation of Meta sodium	Cases of professional dermatoses following use of ppp. Patch test	Schubert H noticed that such cases of dermatitis still were seen in 1978 following use of Metham sodium in agriculture (airborn aerosols), almost under hot, moist weather conditions. The primary cause for such dermatitis is therefore explained by the formation of MITC by hydrolysis of the parent compound Metham sodium under acid conditions when the compound is in contact with sweating wet skin. In order to find out whether	[redacted] (1978) IUCLID: A8.12.1-014

Type of data / report	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
			Metham sodium as such or one of its degradation products was the actual allergen, a series of patch tests in patients were undertaken for Metham sodium (trade name Nematin) as well as for further chemically related substances including 2-thion-3, 5-dimethyl-3, 5-thiadiazine (Dazomet 1 %, vehicle not given) and MITC (0.1 % aqueous). The author reported that older solutions of Nematin always produce stronger allergic patch test reactions than fresh ones. Furthermore an aq. 0.5 % Nematin solution corresponding to 0.15 % Metham sodium causes toxic bullous reactions. Within the series of chemically related substances, Dazomet and MITC were reported to result in positive skin reactions with no further information given.	

Table A-56: Summary table of other studies relevant for skin sensitisation

No other studies are available.

A.3.5.1 Short summary and overall relevance of the provided information on skin sensitisation

Dazomet is not a skin sensitiser in the Guinea Pig Maximization Test ([redacted] (1985b, A8.3.1-001) and [redacted] (1986, A8.3.1-001, Amendment)). However, the human data shows cases of skin sensitization of workers following the use of products containing Dazomet. These allergic reactions are undoubtedly due to the hydrolysis of dazomet into MITC which is known to induce an allergic reaction. This inconsistency between animal study and human data may be due to the fact that the tested substance (dazomet) on animal was carried out in olive oil (no dissociation of dazomet into MITC in organic solvents).

In contrast, MITC was found to be positive in this test system ([redacted] (1986b, A8.3.1-002)). This observation is also confirmed by the human data.

A.3.5.2 Comparison with the CLP criteria

No skin reactions in control and test group animals were reported, indicating that Dazomet is not sensitizing to the skin of guinea pig. But classified as sensitizer in humans (case studies, please refer to the above table) – H317.

MITC was a skin sensitizer (H317) in the Guinea Pig Maximisation Test under the test conditions chosen.

A.3.5.3 Conclusion on classification and labelling for skin sensitisation

No skin reactions in control and test group animals were reported, indicating that Dazomet is not sensitizing to the skin of guinea pig. But classified as sensitizer in humans (case studies) skin sens. 1 – H317.

MITC was a skin sensitizer (H317) in the Guinea Pig Maximisation Test under the test conditions chosen.

A.3.5.4 Overall conclusion on skin sensitisation related to risk assessment

Not applicable for the CLH report.

A.3.6 Respiratory sensitisation

Table A-57: Summary table of animal data on respiratory sensitisation

No animal data is available.

Table A-58: Summary table of human data on respiratory sensitisation

No human data is available.

Table A-59: Summary table of other studies relevant for respiratory sensitisation

Method, Guideline, GLP status, Reliability, Key/supportive study	Test substance (including purity), Doses, Vehicle	Relevant information about the study	Results	Remarks	Reference
Profiling for structural alerts for respiratory sensitization by the OECD QSAR Toolbox[2] profiler for respiratory sensitization[3] **Supportive study**	Dazomet	Experimental data on respiratory sensitization can be found in two of the OECD QSAR Toolbox databases Skin sensitization ECETOC4 ECHA REACH	No alert found for both substances. No experimental data found for both substances.	In silico approach	[redacted] (2021a) IUCLID: A8.3.2-001

[2] https://qsartoolbox.org/
[3] Respiratory sensitisation profiler, developed by Liverpool John Moores University, UK; Version 1.1/April 2017
[4] ECETOC 1999. Skin and Respiratory Sensitisers: Reference Chemicals Data Bank. Technical report No. 77. ISSN-0773-8072-77

Profiling for structural alerts for respiratory sensitization by the OECD QSAR Toolbox[5] profiler for respiratory sensitization[6] **Supportive study**	MITC	Experimental data on respiratory sensitization can be found in two of the OECD QSAR Toolbox databases Skin sensitization ECETOC ECHA REACH	No alert found. No experimental data found.	In silico approach	[redacted](2021b) IUCLID: A8.3.2-002
Information from Danish EPA (Q)SAR Databases[7] **Supportive study**	Dazomet	Details about the mode of operation are given on the website of the database	Prediction results for respiratory sensitization negative but out of applicability domain	In silico approach	[redacted](2021c) IUCLID: A8.3.2-003
Information from Danish EPA (Q)SAR Databases **Supportive study**	MITC	Details about the mode of operation are given on the website of the database	Prediction results for respiratory sensitization negative but out of applicability domain	In silico approach	[redacted](2021d) IUCLID: A8.3.2-004
Prediction of respiratory sensitization by Danish EPA (Q)SAR models[8] **Supportive study**	Dazomet	Details about the mode of operation are given on the website of the models	Prediction results for respiratory sensitization negative but out of applicability domain	In silico approach	[redacted](2021e) IUCLID: A8.3.2-005

[5] https://qsartoolbox.org/
[6] Respiratory sensitisation profiler, developed by Liverpool John Moores University, UK; Version 1.1/April 2017
[7] http://qsar.food.dtu.dk/
[8] https://qsarmodels.food.dtu.dk/index.html

A.3.6.1 Short summary and overall relevance of the provided information on respiratory sensitisation

Regarding Dazomet and MITC, LMW chemicals (those less than 500 Da) are not of sufficient size to engage effectively with the immune system in order to provoke an immune response; chemicals must be inherently electrophilic or must be transformed *in vivo* to an electrophilic species. Next, they should form a stable association with a protein to trigger an immune response and cause allergic sensitization ([redacted] 2011).

Therefore, the QSAR approach which is based on the structural analysis of substances is not sufficient on its own to conclude that no sensitization effect by inhalation route is expected.

For information, regarding the substances that are sensitive via the respiratory tract, there is still uncertainty regarding the exact mechanisms leading to respiratory sensitization. Based on the current knowledge, the induction of respiratory sensitization can occur via inhalation or dermal exposure to the sensitizing substance ([redacted] 2010; [redacted]., 2015). The current hypothesis is that the mechanism favors Th2-type immune responses (skin sensitization favors Th1-type response), which is characterized by the production of cytokines, such as IL-4 and IL-5,and IgE antibodies. This is supported by studies performed in rodents and by human evidence ([redacted].,2012; [redacted], 2014b; [redacted]., 2015). Recently, it has been hypothesized that Th17 cells would also play a crucial role in respiratory sensitization via secretion of IL-17 ([redacted], 2013).The role of IgE may be the greatest reason for uncertainty, as there are patients who display serum IgE antibodies of the appropriate specificity, whereas in other instances (and particularly with respect to the isocyanates) there are symptomatic subjects in whom it is not possible to detect these IgE antibodies. It has been hypothesized that either there may be a mechanism leading to respiratory sensitization that is IgE-independent, or this is linked to technical difficulties in the accurate measurements of hapten-specific IgE-antibodies ([redacted], 2015).

In addition, an Adverse Outcome Pathway (AOP) for respiratory sensitization to low molecular weight substances is currently under development at the OECD. The proposed Key Events for respiratory sensitization are:

1. Key Event 1:Covalent binding of substances to proteins (note: based on current knowledge, there seems to be a greater selectivity of respiratory sensitizers lysine reactivity than for cysteine, whereas skin sensitizers bind both to cysteine and lysine ([redacted]., 2013a));
2. Key Event 2:Cellular danger signals (activation of inflammatory cytokines and chemokines and cytoprotective gene pathways (Th2));
3. Key Event 3:Dendritic cell activation and migration (Th2 skewed);
4. Key Event 4 ([redacted] 2014 and [redacted] 2015):Activation and proliferation of T-cells (Th2)

That's why it is difficult at the moment to define an harmonized experimental protocol.
In order to conclude, taking into account of data lacking (epidemiological data) on isocyanate(s) (MITC, derived from the degradation of dazomet, is a member of the isocyanate family) in particular. It is impossible to know if the asthma following exposure to Dazomet/MITC is only consequence of the significant irritation of the respiratory tract and/or to these sensitizing property.

A.3.6.2 Comparison with the CLP criteria

Taking into account that dazomet and MITC are sensitisers for skin, these substances could be sensitisers for respiratory tract. However due to data lacking and harmonized approach to assess the potential of respiratory sensitizer of the LMW chemicals it is not possible to conclude on the basis of current knowledge.

Conclusion on classification and labelling for respiratory sensitisation: not classified at the moment.

Therefore, on the basis of the information provided we cannot conclude. We propose not to derive a classification, we will wait for the next renewal of the dazomet to require if necessary further data (if in the future harmonised standards would be published to assess this type of effects for low molecular weight substances).

A.3.6.4 Overall conclusion on respiratory sensitisation related to risk assessment

Not applicable for the CLH report.

A.3.7 Repeated dose toxicity / STOT RE

A full set of repeated dose toxicity studies for the active substance Dazomet and its active metabolite MITC were provided for the Annex II inclusion and thus peer reviewed by European competent authorities and eCA Belgium.

During the last years, most of the guidelines for repeated dose toxicity testing have been reviewed and adapted to the state of science Also, a re-evaluation of existing studies was conducted to check for deviations which are no longer compatible with the current evaluation criteria.

During the reliability check it was recognized that the effects observed within the 90-day dog study should be considered to be only of limited reliability and a new study was recommended by the authorities Bulgaria and The Netherlands in the framework of the European Plant Protection Product active substance renewal occurring concurrently with the biocides active substance renewal. For further explanation please see below under “new information”.

New information

A new 90-day toxicity study in dogs with the test substance Dazomet has been conducted. The main reason for considering the old study only to be of limited reliability is the fact that a major part of the animals on study showed parasitic infestations, i.e., lung worms, which in some cases have caused severe lung symptoms like pneumonia. It could not be ruled out that some observed effects were not substance-induced effects, but are rather caused by the poor general condition of the animals.

Furthermore, there were some reporting shortcomings in the study. All in all, the study is of low reliability due to the weak statistical power arising from the limited number of animals within this kind of studies (4 animals per dose group). As there were some pivotal organs affected, especially with respect to the endocrine system, the authorities Bulgaria and The Netherlands in the framework of the European Plant Protection Product active substance

renewal (occurring concurrently with the biocides active substance renewal) recommended a new 90-day study performed in dogs for the evaluation of endocrine effects. The study has been provided and for more information please refer to the “A.3.7.2 Sub-chronic repeated dose toxicity” section (IUCLID: A8.9.5.1-010).

A.3.7.1 Short term repeated dose toxicity

A.3.7.1.1 Short-term oral toxicity

Dazomet CAR Section 2.4.1.1. (Belgium, March 2010):

Active substance Dazomet

The short-term oral toxicity of Dazomet was studied in rats, mice and dogs. In the subchronic rodent studies, the blood and the liver were detected as the target tissue/organ. In the rat, fatty hepatocyte degeneration was observed. In the mouse, spleen haemosiderin deposits confirmed the haematological disorders. The dog showed the same toxicological profile, supplemented with methaemoglobinemia, increased alkaline phosphatase and alanine aminotransferase activities, and extramedullary haematopoiesis in the 90 days study. In the 1-year study, at the top dose some animals exhibited moderate to severe hepatitis or cirrhosis. The rat and dog were found to be the most sensitive species. The lowest NOAEL was established in the 90 days rat and dog study, i.e. 1.5 mg/kg bw/d, based upon the liver toxicity (increased liver weight, fatty liver degeneration) observed at 4.5 mg/kg bw/d.

NOAEL short-term = NOAEL (90-days, oral, rat or dog) = 1.5 mg/kg bw/d.

Degradation product/metabolite MITC

Considering the short-term oral and long-term oral and dermal toxicity of MITC, only summarized information is made available. Validation of these summarised studies is not possible.

Table A-60: Summary table of oral short-term animal studies (usually 28-day studies)

Method, Duration of study, Route of exposure (gavage, in diet, other), Guideline, GLP status, Reliability, Key/supportive study	**Species, Strain, Sex, No/Group**	**Test substance (including purity), Vehicle, Dose levels, Duration of exposure**	**NOAEL, LOAEL**	**Results[9] (all dose levels including severity and magnitude of all effects, including also target organs)**	**Remarks (e.g. major deviations)**	**Reference**
OECD TG 407 **Reliability:1** **Key study** **Oral feed study** **GLP (including QA statment)** **P < 0.05 and P < 0.01 (Anova + Dunnett's)** **S ≥ 95% or S ≥ 99% (Chi²)**	Rat (Wistar) Number of animals per test group: 5/sex Total number of tested animals: 10/group	Dazomet (purity 97 %) Vehicle: Food 28 days (sub-acute) Dose: 0, 20, 60, 180, 540 ppm	LOAEL: 180 ppm (15 mg/kg bw/d) NOAEL: 60 ppm (5 mg/kg bw/d)	No test substance-related mortalities. **<u>20 and 60 ppm:</u>** No test substance-related changes **<u>180 ppm:</u>** Reduction in body weight gain, uncoordinated swimming movements (one case), increased relative liver weights (m). Fatty degeneration in the livers **<u>540 ppm:</u>** Motor disturbances including paresis, delayed and uncoordinated swimming movements (swimming	-	[redacted] (1989d) IUCLID: A8.9.5.1 -001

[9] The results mentioned are all statistically significant in which case a note would appear in the remarks column. For more information about significance levels please refer to the Annex I (Confidential data).

				test), Body weights reduction (f¸ 26 % lower than controls), increased absolute liver weight (m), increased relative liver weights, fatty liver degeneration		
No guideline **Reliability: 4** **Key study** **The test substance was added and mixed thoroughly with FRL solid diet 2C.** **No GLP** **No statistical value(s)**	Sherman other species, as well: mice, guinea pigs, New Zealand albino rabbits Rat Number of animals per test group: 5/sex Total number of tested animals: 10	Dazomet Purity not reported Vehicle: Food 30 days (sub-acute) Dose: 30, 120, 500, 2000 ppm	LOAEL: 120 ppm (10 mg/kg bw/d) NOAEL: 30 ppm (2.5 mg/kg bw/d)	No test substance-related mortalities. **30 ppm:** No test substance-related changes **120 ppm:** Reduction in body weight gain **500 ppm**: Reduction in body weight gain, increase in relative kidney and liver weights. **2000 ppm:** Reduction in food consumption, weight loss, increase in relative kidney and liver weights, pathological	-	[redacted] (1966) IUCLID: A8.9.5.1 -002

Table A-61: Summary table of human data on short-term oral toxicity

No human data is available.

A.3.7.1.2 Short-term dermal toxicity

Dazomet CAR Section 2.4.1.1. (Belgium, March 2010):

Active substance Dazomet

The short-term dermal toxicity of Dazomet was studied in a 21-day dermal toxicity study in rabbits. No local effects were observed at a dose level of 1000 mg/kg bw/d. Apart from one mortality at the highest dose, no substantial systemic effects were observed. Therefore, the NOAEL for systemic effects was set at 100 mg/kg bw/d.

Degradation product/metabolite MITC

Considering the short-term oral and long-term oral and dermal toxicity of MITC, only summarized information is made available. Validation of these summarised studies is not possible.

Table A-62: Summary table of dermal short-term animal studies (usually 28-day studies)

Method, Duration of study, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Surface area, Duration of exposure	NOAEL, LOAEL	Results (all dose levels including severity and magnitude of all effects, including target organs)	Remarks (e.g. major deviations)	Reference
EPA 82-2 **Dermal route**	New Zealand white rabbits 34 males/ 36 females	Dazomet Purity: 99 % 10 % of the total	100 mg/kg bw/d	There were no substance related mortalities or clinical signs of toxicity in the		[redacted] (1987) IUCLID: A8.9.5.3-001

Key study **P < 0.05 and P < 0.01 (Anova + Dunnett's)** **S ≥ 95 % or S ≥ 99 % (Chi²)** **Reliability: 2**	10 animal/sex/group (low dose or vehicle) 5 animal/sex/group (mid or hight dose)	body area Vehicle: CMC 3 weeks (sub-acute) 0, 10, 100, 1000 mg/kg bw/d TS Five days/week, 6 hours/day		treatment groups. Body weight and food consumption were not affected. Clinical-chemical and haematological examinations did not reveal test substance-related changes. Gross macroscopic observations, organ weight determination and histopathological examinations did not show any treatment related effects. There were no signs of skin irritation in any of the animals.		
No guideline **Dermal route** **Supportive study** **No GLP** **No statistical value(s)** **Reliability: 4**	Sprague- Dawley rats	MITC Purity and vehicle not reported 1 month (sub-acute) 120, 240 and 480 mg/kg bw/d	No determination of the systemic NOAEL was possible	Dermal irritation was observed at all dose levels. Further treatment-related changes were noted in the respiratory tract and were characterized by enlargement of the peribronchial lymphnodes		[redacted] (1990) IUCLID: A8.9.5.3-002

Table A-63: Summary table of human data on short-term dermal toxicity

No human data is available.

A.3.7.1.3 Short-term inhalation toxicity

Dazomet CAR Section 2.4.1.1. (Belgium, March 2010):

Degradation product/metabolite MITC

Short-term inhalation toxicity. The subacute 4-week inhalation study with MITC in rats was characterized by severe respiratory irritation and inflammation consistmg of bronchopneumonia, epithelial proliferation, single cell necrosis and pathological changes in the nasal cavity. The $NOAEL_{systemic}$ = 5 mg/m^3 (1.2 mg/kg bw/d) is based on decreased body weight (gain), clinical signs, increased non-focal atrophy of the olfactory epithelium, and increased neutrophils still observed at 20 mg/m^3. The $LOAEL_{local}$ = 5 mg/m^3 is based on focal atrophy of the olfactory epithelium observed at 5 mg/m^3.

NOAEL short-term= NOAEL (4-week, inhalation, rat) = 1.2 mg/kg bw/d.

Table A-64: Summary table of inhalation short-term animal studies (usually 28-day studies)

Method, Duration of study, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Form (gas, vapour, dust, mist) and particle size (MMAD), Actual and nominal concentration, Type of administration (nose only / whole body/ head only), Duration of exposure	NOAEL, LOAEL	Results (all dose levels including severity and magnitude of all effects, including target organs)	Remarks (e.g. major deviations)	Reference
No guideline **Key study** **Reliability: 2** **No GLP** **P < 0.01**	Wistar rats Males/Females 5/sex/group (control group) 10 animals/sex/group (in total: 40 animals)	Dazomet Purity: 98 % Vehicle: Air Inhalation (dust) 3 weeks 33 µg/m³ Five days/week 6 hours/day	NOAEL: 0.033 mg/m³	Neither clinical signs of intoxication nor impairments of body weight were reported. Food and water consumption were inconspicuous. Ophthalmological examination revealed no treatment-related abnormalities. The hematological and clinical-chemical parameters as well as the urinalysis revealed no treatment-related changes. Necropsy revealed abnormalities (*a pale subpleural area which was seen on the right lungs of 1 control (middle lobe, 1 mm diam) and 1 female rat (posterior lobe, 4 mm diam)*).	-	[redacted] (1976) IUCLID: A8.9.5.2-001

OECD TG 412 **Key study** **Reliability:1** **No GLP** **P < 0.01**	Wistar rats Males/Females 10/sex/group (in total: 40 animals)	MITC Purity: 96.9 % Vehicle: Nitrogen air 28 days (sub-acute) 0, 5, 20, 100 mg/m³ Five days/week 6 hours/day	NOEAL: 5 mg/m³ LOAEL: 20 mg/m³	No test substance-related mortalities 5 mg/m³: No test substance-related changes 20 mg/m³: Eyelid closure, somnolence, ruffled fur (all reversible) 100 mg/m³: Mucosal and respiratory irritation, changes in breathing pattern, reddish nasal and eye discharge, salivation, reduction in body weight, decreased values for clinical chemical parameters (e.g., urea), increased values for white blood cell parameters (e.g., leucocytes), increased absolute lung weights, bronchopneumonia, epithelial proliferation in bronchi, bronchioles and trachea, single cell necrosis in trachea, catarrhal-purulent rhinitis in nasal cavity, atrophy of olfactory epithelium, focal squamous metaplasia of respiratory epithelium	-	[redacted] (1987) IUCLID: A8.9.5.2-002

Table A-65: Summary table of human data on short-term inhalation toxicity

No human data is available.

A.3.7.1.4 Overall conclusion on short-term repeated dose toxicity related risk assessment

Not applicable for the CLH report.

A.3.7.2 Sub-chronic repeated dose toxicity

Dazomet CAR Section 2.4.1.1. (Belgium, March 2010):

Active substance Dazomet

The short-term oral toxicity of Dazomet was studied in rats, mice and dogs. In the subchronic rodent studies, the blood and the liver were detected as the target tissue/organ. In the rat, fatty hepatocyte degeneration was observed. In the mouse, spleen haemosiderin deposits confirmed the haematological disorders. The dog showed the same toxicological profile, supplemented with methaemoglobinemia, increased alkaline phosphatase and alanine aminotransferase activities, and extramedullary haematopoiesis in the 90 days study. In the 1-year study, at the top dose some animals exhibited moderate to severe hepatitis or cirrhosis. The rat was found to be the most sensitive species. The lowest NOAEL was established in the 90 days rat or dog study, i.e. 1.5 mg/kg bw/d, based upon the liver toxicity (increased liver weight, fatty liver degeneration) observed at 4.5 mg/kg bw/d.
NOAEL short-term = NOAEL (90-days, oral, rat) = 1.5 mg/kg bw/d.

Degradation product/metabolite MITC

Considering the short-term oral and long-term oral and dermal toxicity of MITC, only summarized information is made available. Validation of these summarised studies is not possible.

A.3.7.2.1 Sub-chronic oral toxicity

Table A-66: Summary table of oral sub-chronic animal studies (usually 90-day studies)

Method, Duration of study, Route of exposure (gavage, in diet, other), Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	NOAEL, LOAEL	Results[10] (all dose levels including severity and magnitude of all effects, including also target organs)	Remarks (e.g. major deviations)	Reference
OECD TG 408 **Oral feed,** **Key study** **90 days** **Reliability:1** **GLP** **P ≥ 0.01 (Dunnett)** **P≥0.05 (Anova)**	Wistar rats Males/Females 20 (10/sex/group)	Dazomet Purity ≥ 97% Vehicle: mixed with food 0, 20, 60, 180, 360 ppm; Daily	<u>NOAEL:</u> Males: 20 ppm (1.5 mg/kg bw/d) Females: 60 ppm (5.4 mg/kg bw/d) <u>LOAEL:</u> 60 ppm in males (corresponding to 4.6 mg/kg bw/d) 180 ppm in females (corresponding to 15.4 mg/kg bw/d)	No mortality or clinical signs of toxicity occurred in the study at any dose level **20 ppm:** No test substance related changes **60 ppm:** Increased absolute and relative liver weights, fatty liver degeneration (m, histopathology) **180 ppm:** Total protein decrease (m), increased absolute and relative liver weights, fatty liver degeneration (histopathology)	-	[redacted] (1987a) IUCLID: A8.9.5.1-003

[10] The results mentioned are all statistically significant in which case a note would appear in the remarks column. For more information about significance levels please refer to the Annex I.

				360 ppm: Slightly reduced food consumption (f), affected food efficiency, affected body weight/ body weight gain, decrease in haematological and clinical-chemical parameters (e.g., haemoglobin, total protein), increased absolute and relative liver weights, fatty liver degeneration (histopathology)		
EPA 82-7 **Oral feed,** **Supportive study** **90 days** **Reliability: 1** **GLP** **P ≥ 0.05 (Anova and Kruskal Wallis)**	Wistar rats Males/ Females 10/sex/group	Dazomet Purity≥ 96.3% Vehicle: mixed with food 0, 50, 200, 400 (females only), 450 (males only) ppm; Daily	LOAEL: Males= 50 ppm (corresponding to 4 mg/kg bw/d) Females= 200 ppm (corresponding to 16 mg/kg bw/d) NOAEL: Males < 50 ppm (corresponding to < 4 mg/kg bw/d) Females = 50 ppm (corresponding to 4 mg/kg bw/d)	No mortality or clinical signs of toxicity occurred at any dose level **50 ppm:** Fatty change in the liver (m) **200 ppm:** Increased relative liver weights, fatty change in the liver (histopathology) **400 ppm (females):** Body weight/body weight gain affected, increased relative liver weights, fatty change in the liver (histopathology)	-	[redacted] (1994b) IUCLID: A8.9.5.1-004 (also see neurotoxicity)

				450 ppm (males): body weight/body weight gain affected, fatty change in the liver (histopathology)		
OECD TG 407 **Oral feed** **Key study** **Reliability: 1** **The test substance was first administrated during 4 weeks. Since no effects were observed during this period of treatment, the test period was prolonged to 91 days** **P < 0.05, P < 0.01 (Anova, Dunnett test)** **S ≥ 95 %, S ≥ 99 % (t-test)**	B6C3F1 mice Males/Females 5/sex/group	Dazomet Purity ≥ 97 % Vehicle: mixed with food 0, 20, 60, 180, 360, 540 ppm; Daily	LO(A)EL: 360 ppm in males (corresponding to 68.9 mg/kg bw/d) 360 ppm in females (corresponding to 109.2 mg/kg bw/d) NO(A)EL: 180 ppm in males (corresponding to 37.5 mg/kg bw/d) 180 ppm in females (corresponding to 50.3 mg/kg bw/d)	No mortality or clinical signs of toxicity occurred at any dose level. No effect on body weight or body weight gain in any of the groups for both sexes. **20 & 60 ppm:** No test substance related changes **180 ppm:** Increase in absolute and relative liver weight (m) **360 ppm:** Reduced food consumption (m), decrease of the clinical-chemical and haematological parameters (e.g., haemoglobin), increase in absolute and relative liver weight, histopathology demonstrated increased occurrence of haemosiderin	60 ppm = 13.3 mg/kg bw/d based on increased number of reticulocytes and increased liver weight at 180 ppm (37.5 mg/kg bw/d (males))	[redacted] (1989a) IUCLID: A8.9.5.1-005

				deposits in the spleen (f) **540 ppm:** Reduced food consumption (m), Decrease of the clinical-chemical and haematological parameters (e.g., haemoglobin), increase in absolute and relative liver weight, histopathology demonstrated an increased occurrence of haemosiderin deposits in the spleen		
OECD TG 409 **Oral feed** **Key study** **90 days** **Reliability:2** **P < 0.05, P < 0.01 (KW, WMW test)** **S ≥ 95%, S ≥ 99% (t-test)**	Beagle dogs Males/Females 4/sex/group	Dazomet Purity≥ 98.2 % Vehicle: mixed with food 0, 25, 100, 400 (reduced to 200 at day 23) ppm; Daily	<u>LO(A)EL:</u> 200 ppm in males (corresponding to 5.7 mg/kg bw/d) 200 ppm in females (corresponding to 5.2 mg/kg bw/d) <u>NO(A)EL:</u> 100 ppm in males (corresponding to 2.5 mg/kg bw/d) 100 ppm in females (corresponding to 2.3 mg/kg bw/d)	No mortality occurred at any dose level. **25 ppm:** No test substance-related changes **100 ppm:** Sporadical lack of appetite (one f), increased relative liver weights (m) **400 (reduced to 200 at day 23) ppm:** Vomiting, lack of	-	[redacted] (1987b) IUCLID: A8.9.5.1-006

S ≥ 95%, S ≥ 99% (Chi²)			Other A concentration of 400 ppm was shown to be too high based on decreased food consumption and body weight. At 400/200 ppm, Dazomet caused a hemolytic anemia associated with increased haemosiderin deposits in the spleen. Relative liver weights were increased without pathological changes.	appetite, weight loss (f), decrease of the clinical-chemical and haematological parameters (e.g., haemoglobin), increased relative liver weights, slightly increased occurrence of haemosiderin deposits in the spleen (histopathology)		
OECD TG 409 **Oral capsule** **GLP compliant** **Reliability: 1** **90 days** **P < 0.05, P (Bartlett, Anova, KW , Dunnett test)**	Beagle dogs Males/Females 4/sex/group	Dazomet Purity: 98.3 % Vehicle: gelatin capsule (*gastrosoluble*) Daily (after feeding) dose level of 0, 1.5, 4.5, 13.5/9 mg/kg bw/d	1.5 mg/kg bw/d based on reduced RBC parameters, increased spleen hemosiderosis and haematopoiesis at 4.5 ppm	<u>13.5/9 mg/kg bw/d</u> ↓body weight *Haematology:* ↓Hb, RBC, Hct; ↑platelets, APTT *Clinical chemistry:* ↓proteins, albumin , ↑liver weight ↑ kidney weight Histopathology reveal hemosiderosis (spleen) haematopoiesis (spleen) (f)	The dose was changed from 13.5 mg/kg bw/d to 9 mg/kg bw/d at week 11. Temporal discontinuation of the treatment was applied for two females [Animal no. 33 at weeks 13 and 14 (from day 91 to 94) and Animal no. 35 at	[redacted] (2020) IUCLID: A8.9.5.1-010

				brown pigment deposition in Kupffer cell (liver) <u>4.5 mg/kg bw</u> *Haematology:* ↑platelets , APTT Hytopathology reveal hemosiderosis (spleen) (f)	week 9 (from day 58 to 63)].	
Gavage (drinking water), **Supportive study** **No guideline** **90 days** **Reliability: 4**	Mouse common rodent species Males/Females	MITC 1, 5, 20 mg/kg bw/d; Daily	LO(A)EL:1 mg/kg bw/day NO(A)EL: < 1 mg/kg bw/day	The administration of 20 mg/kg bw/d MITC resulted in thickening of the forestomach lining, small cell infiltration in liver tissues and slight disturbance of spermatogenesis with edema of interstitial cells. These effects were occasionally noted at 5 mg/kg bw/d and also occurred at a slight incidence at 1 mg/kg bw/d. Both the absolute and relative ovary weights showed a significant decrease, but there were no microscopic changes associated with this finding even at 20 mg/kg bw/d.	-	[redacted](1990) IUCLID: A8.9.5.1-008

Table A-67: Summary table of human data on sub-chronic oral toxicity

No human data is available.

A.3.7.2.2 Sub-chronic dermal toxicity

Dazomet CAR Section 2.4.1.1. (Belgium, March 2010)

Active substance Dazomet:

The short-term dermal toxicity of Dazomet was studied in a 21-day dermal toxicity study in rabbits. No local effects were observed at a dose level of 1000 mg/kg bw/d. Apart from one mortality at the highest dose, no substantial systemic effects were observed. Therefore, the NOAEL for systemic effects was set at 100 mg/kg bw/d.

Degradation product/metabolite MITC

Considering the short-term oral and long-term oral and dermal toxicity of MITC, only summarized information is made available. Validation of these summarised studies is not possible.

Table A-68: Summary table of dermal sub-chronic animal studies (usually 90-day studies)

No animal data is available.

Table A-69: Summary table of human data on sub-chronic dermal toxicity

Type of data/report	Test substance	Route of exposure Relevant information about the study (as applicable)	Observations	Reference
Clinical cases and poisoning incidents	MITC generated from Dazomet	Cases of poisoning following use of plant product	MITC generating compounds such as Dazomet were reported by Richter G for MITC. The author described the case of poisoning of a 24-year-old woman who did not notice that some Dazomet hat got into her rubber boot, which she wore for about 24 hours. After 24 hours a first to second degree acid burn developed and during the following days a bullous eruption spread over one foot/leg to about 5 % of the body surface. A liver biopsy showed a hypersensitivity hepatitis of non-specific type and the transaminases (GOT, GPT) were clearly increased. According to the author, the reversible damage of the liver parenchyma was conditioned by the oral contraceptiva the patient took, but caused by percutaneously uptake of MITC. A second liver biopsy did not show any adverse effects, and liver enzymes had returned to normal. One year after the exposure, the patch test to a 0.05 % aqueous solution of Vapam (soil disinfectant based on metam sodium and acting in the same way as Dazomet, by hydrolytic release of MITC) was performed and was still found to be strongly positive. It can be concluded that if MITC generating compounds like Dazomet are exposed to a larger area of the body and not removed immediately, systemic poisoning (transient, reversible liver damage) can occur.	[redacted] (1980) IUCLID: A8.12.1-002

A.3.7.2.3 Sub-chronic inhalation toxicity

Dazomet CAR Section 2.4.1.1. (Belgium, March 2010)

Degradation product/metabolite MITC:
Short-term inhalation toxicity. The subacute 4-week inhalation study with MITC in rats was characterized by severe respiratory alteration and inflammation consisting of bronchopneumonia, epithelial proliferation, single cell necrosis and pathological changes in the nasal cavity. The $NOAEL_{systemic}$ = 5 mg/m^3 (1.2 mg/kg bw/d) is based on decreased body weight (gain), clinical signs, increased non-focal atrophy of the olfactory epithelium, and increased neutrophils still observed at 20 mg/m^3. The $LOAEL_{local}$ = 5 mg/m^3 is based on focal atrophy of the olfactory epithelium observed at 5 mg/m^3.

NOAEL short-term= NOAEL (4-week, inhalation, rat) = 1.2 mg/kg bw/d.

Table A-70: Summary table of inhalatory sub-chronic animal studies (usually 90-day studies)

Method, Duration of study, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Form (gas, vapour, dust, mist) and particle size (MMAD), Actual and nominal concentration, Type of administration (nose only / whole body/ head only), Duration of exposure	NOAEL, LOAEL	Results (all dose levels including severity and magnitude of all effects, including also target organs)	Remarks (e.g. major deviations)	Reference
No guideline **Reliability: 4** **No GLP** **90 days Head-nose chamber** **Supportive study**	Wistar rats Males/ Females	MITC Concentrations of 1, 10 and 45 ppm 4 hours/ day, 5 days/ week	LO(A)EL: 45 ppm NO(A)EL: 10 ppm (30.67 mg/m³), corresponding to 2.9 mg/kg bw/d	**1 ppm:** No effects reported **10 ppm:** No effects reported **45 ppm:** Increased salivation and nasal discharge during exposure, apathy, reduced food consumption and reduced body weight gain	Secondary literature, a reliability score is not clearly assignable as the data were provided within the publication in summarized form. Nevertheless, these data were retained as no more recent data on the sub-chronic inhalation toxicity of MITC in rat exist.	[redacted] (1990) IUCLID: A8.9.5.2-003

Table A-71: Summary table of human data on sub-chronic inhalation toxicity

No human data is available.

A.3.7.2.4 Overall conclusion on sub-chronic repeated dose toxicity related risk assessment

Not applicable for the CLH report.

A.3.7.3 Long-term repeated dose toxicity

A.3.7.3.1 Long-term oral toxicity

Dazomet CAR Section 2.4.1.1. (Belgium, March 2010):

Active substance Dazomet

The long-term oral toxicity of Dazomet was studied in rats. The effects were in line with those observed in the short-term studies. The liver was detected as the target organ. Hepatotoxicity (increased weight, increased liver enzymes, decreased protein) was confirmed by centrilobular fatty degeneration. The long-term NOAEL was established at 0.9 mg/kg bw/d, based on the decrease in haematological and clinical-chemical parameters found at 5.3 mg/kg bw/d in females in the 2-year rat study. Chronic dermal and inhalation toxicity was not investigated.

NOAEL long-term = NOAEL (2-year, oral, rat) = 0.9 mg/kg bw/d.

Degradation product/metabolite MITC

Considering the short-term oral and long-term oral and dermal toxicity of MITC, only summarized information is made available. Given the low level of reliability of animal studies generated on the MITC, the results obtained will only be taken into account as an indication (supportive information) in deriving a classification of dazomet.

Table A-72: Summary table of oral long-term animal studies

Method, Duration of study, Route of exposure (gavage, in diet, other), Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	NOAEL, LOAEL	Results[11] (all dose levels including severity and magnitude of all effects, including target organs)	Remarks (e.g. major deviations)	Reference
OECD TG 452 **Oral feed** **Key study** **Reliability: 1** **24 months** **GLP (including QA support)** **P < 0.05, P< 0.01 (Anova + Dunnett's)** **S ≥ 95 % or S ≥ 99% (chi²)**	Wistar rats Males/Females 40 per group (20/sex/group)	Dazomet Purity 98.2 % 0, 5, 20, 80, 320 ppm; Daily	LO(A)EL Males: 320 ppm (equivalent to 18 mg/kg bw/d) Females: 80 ppm (equivalent to 5.3 mg/kg bw/d) NOAEL: Males: 80 ppm (3.6 mg/kg bw/d) Females: 20 ppm (0.9 mg/kg	No test substance related mortalities or signs of clinical toxicity in any of the treatment groups **5 and 20 ppm:** No test substance related effects at 20 and 5 ppm. **80 ppm:** Decrease of some haematological and clinical chemical parameters (f) excepted for platelets (increased) **320 ppm:** Reduced body weight, decreased haematological and	-	[redacted] (1989a) IUCLID: A8.9.5.1-011 [redacted] (1989) (Amendement) IUCLID: A8.9.5.1-011 [redacted] (1989), (Pathology report) IUCLID: A8.9.5.1-011

[11] The results mentioned are all statistically significant in which case a note would appear in the remarks column. For more information about significance levels please refer to the Annex I (Confidential data).

			bw/d)	clinical chemical parameters (f) excepted for platelets and bilirubin (increased), increased relative and absolute liver weight (m), slightly increased incidence and severity of hepatocellular fat deposition (f), partly associated with hepatocellular vacuolation		
No guideline (oral feed) **Key study** **Reliability: 4** **24 months** **No GLP** **P < 0.05 (t-test)**	Wistar rats Males/Females 40 per group (20/sex/group)	Dazomet 10, 40, 160, 640 ppm; Daily	<u>NO(A)EL:</u> 10 ppm (equivalent to 0.5 mg/kg bw/d)	No test substance-related mortalities in any of the treatment groups **10 ppm:** No substance-related effects **40 ppm:** Diffuse cloudy swelling (liver) was considered an adverse effect at dose levels of 40 ppm **160 ppm:** Decreased food consumption, diffuse cloudy swelling (liver) **640 ppm:** Reduced body weight gain, decreased food	-	[redacted]. (1966) IUCLID: A8.9.5.1-012 [redacted] (1960) IUCLID: A8.9.5.1-012

				consumption, increased relative liver weight, increased relative kidney weights (m), focal necrosis with central fatty metamorphosis and diffuse cloudy swelling of hepatocyte cords in liver, glomerular nephritis with frank necrosis of some cells of the proximal convoluted tubules in the kidney		
No guideline **Oral feed** **Key study** **Reliability: 2** **12 months** **GLP (including QA support)** **P < 0.05, P < 0.02, P < 0.002 (Kruskal Wallis or Wilcoxon Mann-Whitney)** **S ≥ 95 % or** **S ≥ 99 % (Chi²)**	Beagle dogs Males/ Females 12 per group (6/sex/group)	Dazomet Purity: 98.2 % a.s. Vehicle: mixed with food 0, 15, 50, 150 ppm; Daily	LO(A)EL: 150 ppm (corresponding to 4.8 mg/kg bw/d) NO(A)EL: 50 ppm (corresponding to 1.6 mg/kg bw/d)	No test substance-related mortalities in any of the treatment groups **15 ppm:** No substance related effects **50 ppm:** Increased severity of iron positive pigmentation in the liver (f) **150 ppm:** A single case of emaciation with a marginal impairment of food consumption (f), slight reduced body weight gain, changes in	-	[redacted] (1989c) IUCLID: A8.9.5.1-013 [redacted] (1989a) (Pathology report) IUCLID: A8.9.5.1-013

				some clinical-chemical parameters (e.g., increase in alkaline phosphatase and aspartate aminotransferase, decrease in albumin), increased relative liver weight (m), Histopathology reveal focal / diffuse discoloration of the liver (2 f), chronic liver lesions (2 f, 1 m), slight to moderate atrophy of the testes (2 m), marked atrophy of the prostate gland (1 m), increased severity of iron positive pigmentation in the liver.		
Drinking water, **Supportive study** **Reliability: 4 (not assignable)** **104 weeks** **No GLP** **No statistical value(s)**	CD-1 rats Males/ Females	MITC Purity: 20 % Vehicle: drinking water 0, 2, 10, 50 ppm; Daily	<u>NO(A)EL:</u> Males: 10 ppm (equivalent to 0.514 mg/kg bw/d) Females: 10 ppm (equivalent to 0.746 mg/kg bw/d)	**2 & 10 ppm:** No substance-related effects reported **50 ppm:** Consistent reduction in water intake, reduced body weight gain (m)	-	[redacted] (1990) IUCLID: A8.9.5.1-014

Drinking water, **Supportive study** **Reliability: 4 (not assignable)** **106 weeks** **No GLP** **No statistical value(s)**	ICR mice, Males/ Females	MITC Purity: 20 % Vehicle: Drinking water 5, 20, 80, 200 ppm; Daily	<u>LO(A)EL:</u> 80 ppm <u>NO(A)EL:</u> Males: 20 ppm (equivalent to 3.30 mg/kg bw/d) Females: 20 ppm (equivalent to 3.66 mg/kg bw/d)	No effects on mortality, general behavior, food consumption and efficiency, as well as ophthalmoscopic findings in any of the treatment groups. **5 & 20 ppm:** No substance-related effects reported **80 ppm:** Reduced body weight gain, slight changes in absolute and relative organ weights **200 ppm:** Reduced body weight gain, slight changes in absolute and relative organ weights	-	[redacted] (1990) IUCLID: A8.9.5.1-015

Table A-73: Summary table of human data on long-term oral toxicity

No human data is available.

A.3.7.3.2 Long-term dermal toxicity

Dazomet CAR Section 2.4.1.1. (Belgium, March 2010):

Active substance Dazomet
Chronic dermal and inhalation toxicity was not investigated.

Degradation product/metabolite MITC
Considering the short-term oral and long-term oral and dermal toxicity of MITC, only summarized information is made available. Validation of these summarised studies is not possible

Table A-74: Summary table of dermal long-term animal studies

No animal data is available.

Table A-75: Summary table of human data on long-term dermal toxicity

No human data is available.

A.3.7.3.3 Long-term inhalation toxicity

Dazomet CAR Section 2.4.1.1. (Belgium, March 2010):

Active substance Dazomet
Chronic dermal and inhalation toxicity was not investigated.

Table A-76: Summary table of inhalation long-term animal studies

No animal data is available.

Table A-77: Summary table of human data on long-term inhalation toxicity

No human data is available.

A.3.7.3.4 Overall conclusion on long-term repeated dose toxicity related risk assessment

Not applicable for the CLH report.

A.3.7.4 Specific target organ toxicity – repeated exposure (STOT RE)

A.3.7.4.1 Short summary and overall relevance of the provided information on STOT RE

The 4-week short term oral toxicity of Dazomet was investigated in rats:

The high dose level (540 ppm) resulted in clinical signs of toxicity, including paresis in females. Food consumption and body weight gain were severely reduced in females resulting in a reduction of body weight of these animals of 26 %. At 180 ppm body weight gain was still reduced in females. The target organ was the liver with weight increases at 540 ppm (both sexes) and 180 ppm males. The NOAEL was determined to be 60 ppm.

The 90-day oral toxicity of Dazomet was studied in rats, mice and dogs:

In rats at the high dose level (320 ppm) body weight gain was reduced. There was also a reduction of haemoglobin and changes in clinical chemistry. Total protein was also reduced in 180 ppm males. As in the 4-week study, the target organ was the liver. There were increased absolute and relative liver weights at 180 and 320 ppm as well as in 60 ppm males. At these doses foci of fatty degeneration in the liver were observed. The NOAEL was 20 ppm in males (1.5 mg/kg bw/d) and 60 ppm (1.8 mg/kg bw/d) in females.

In mice, reduced food consumption was noted in males at 540 and 320 ppm, without an apparent effect on body weight. At these dose levels a haemolytic anaemia and compensatory bone marrow reaction was seen for both sexes. The haemosiderin deposits in the spleen at 540 ppm (both sexes) and in 320 ppm females are also related to the haemolytic anaemia. However, the anaemia could be considered as marginal. Increased absolute and relative liver weights were seen at 540 ppm (both sexes) and in 320 ppm males, however, in contrast to the observations in the rat, without pathological changes. The NOAEL was 180 ppm i.e., 37.5 mg/kg bw/d in males and 50.3 mg/kg bw/d in females.

In dogs, toxicity at the initial high dose level (400 ppm) was clearly above the maximum tolerated dose level. Clinical signs of toxicity, vomiting and marked reduction of food consumption resulting in body weight loss, were observed at this dose. A reduction of the high dose to 200 ppm resulted in a clear improvement of food consumption and body weight gain, although over the entire study period these remained below control level. At the high dose level, reduced red blood cell parameters, indicating anaemia and altered clinical chemistry were noted. The haemosiderin deposits in the spleen are also indicative of the anaemic effect of Dazomet. Moreover, increased relative liver weights at the high dose level, however, without pathological changes were observed. The NOAEL was established at 100 ppm (2.5 mg/kg bw/d males, 2.3 mg/kg bw/d females). A new 90 days dogs study (Ito, T.) has been performed in 2020, the results showed one lethal effect for one female during the 13.5 mg/kg bw/day treatment period. Vomiting of feed, low food consumption and body weight, and the effect on the kidney were detected in males at 13.5 mg/kg bw/day and females at 13.5/9 mg/kg bw/day.

Low Ht, Hb, and RBC and high PLT were detected in males at 13.5 mg/kg/day.

The effects on the liver of both sexes and spleen of females were detected at 4.5 mg/kg/day (LOAEL) or more. Finally, any toxicological significance effects were observed in either sex at 1.5 mg/kg bw/d (NOAEL).

Overall, the short-term oral toxicity of Dazomet is characterized by clinical signs of toxicity in rat and dogs at dose levels of 540 - 400 ppm respectively. These doses were clearly above the MTD. A moderate reduction in the dietary dose levels (320 - 200 ppm) was sufficient to reduce the elicited toxicity significantly, indicating a steep dose response relationship. Similar effects were not seen in mice at a dose of 540 ppm.

In rats the target organ was the liver with weight increases and fatty degeneration. In dogs and mice liver weight increases were in Table A-78: Effects and corresponding guidance values to assist classification for STOT RE also seen.

In mice and dogs Dazomet induces hemolytic anemia, with a clear compensatory response by the bone marrow in mice. In both species increased deposits of haemosiderin in the spleen are also related to the induced hemolytic anemia. In rats, similar changes were not observed, the only related effect was a reduction of haemoglobin at the high dose level in the 3-month study.

The long-term oral toxicity of Dazomet was investigated in rats, mice and dogs:
In a chronic toxicity study in rats the high dose level (320 ppm) resulted in decreased body weight gain. At 320 ppm (both sexes) and 80 ppm (females) some red blood cell parameters were reduced. The target organ was the liver in which weight increases as well as histopathological changes (increased fat deposition and vacuolation) were observed. The clinical-chemical changes (reduced protein synthesis) are also indicative for liver toxicity.

The NOAEL in this study was 80 ppm (3.6 mg/kg bw) for males and 20 ppm for females (0.9 mg/kg bw).

In an older chronic toxicity study (of clearly limited reliability), reduced body weight gain was noted at 640 ppm and food consumption was reduced at 160 and 640 ppm. The target organs were the liver and the kidneys. At the high dose level increased organ weight was noted for both organs. The histopathological changes in the liver were focal necrosis, fatty metamorphosis and diffuse cloudy swelling. The changes in the kidneys (glomerular nephritis) have not been observed in any of the more recent studies.
The NOAEL in this study was 10 ppm (ca. 0.5 mg/kg bw) based on diffuse cloudy swelling in the liver at dose of 40 ppm and higher.

In a carcinogenicity study in rats, the only test substance related effects were noted during the histopathological examination of the liver. In high dose (80 ppm) males a slightly increased incidence and severity of diffuse hepato-cellular fat deposition and hepato-cellular vacuolization were observed. In high dose females there was a slightly increased incidence of mixed cell and basophilic foci in the liver. Also, the combined incidence of all altered liver cell foci was slightly increased in high dose females. The NOAEL in this study was 20 ppm (0.9 mg/kg bw).

Dazomet

A mouse carcinogenicity study with Dazomet resulted in increased liver weights and increased numbers of basophilic foci indicating a proliferative effect of the test substance on female mouse liver. Dazomet at the high dose level (320 ppm) induced toxicity consisting of body weight reduction in males, and an apparent anemic effect indicated by increased haemosiderin deposits in the spleen and extramedullary haematopoiesis. The target organ was the liver, in which toxic (increased liver weights and fat deposit) as well as proliferative changes were observed. The proliferative effect on the liver was indicated by an increased incidence of basophilic foci. Dazomet was considered to be not carcinogenic in mice.

In the 12-month study in dogs, Dazomet was shown to be hepatotoxic at a dose level of 150 ppm. The NOAEL in this study was 50 ppm, which is equivalent to 1 mg/kg bw/d.

In an older 12-month dog study (of clearly limited reliability), no test substance related effects were found at a dose of 45 ppm (presumably 0.8 mg/kg bw/d).

The short-term dermal toxicity of Dazomet was investigated in rabbits:
In the 21-day dermal study in rabbits no systemic toxicity nor signs of local irritation were observed at a dose level of 1000 mg/kg bw/d, indicating the very low toxic potential of Dazomet after dermal exposure.

The short-term inhalation toxicity of Dazomet was investigated in rats:
After 3 weeks exposure via inhalation, neither clinical signs of intoxication nor impairments of body weight due to the treatment were reported. Food and water consumption were inconspicuous and the ophthalmological examination revealed no treatment-related abnormalities. The hematological and clinical-chemical parameters as well as the urinalysis revealed no treatment-related changes. Necropsy (organ weights, pathology) revealed no treatment-related abnormalities. However, since only one concentration was tested the study is of limited reliability and was not considered for evaluation of STOT RE via inhalation.

Repeated dose neurotoxicity was investigated in rats:
No mortality or clinical signs of toxicity occurred in the study at any dose level. Body weight and body weight gain were affected in high dose males and females. At the end of the administration period, animals of these groups weighed 92 % (males) and 90 % of the respective control groups. Body weight gain was reduced by 12 % in males and 24 % in females. Relative liver weights were increased in 400 ppm and 200 ppm females. Fatty change in the liver was observed in mid and high dose males and females, as well as in 3 out of 5 low dose males. The NOAEL in this study for systemic toxicity was 50 ppm or 4 mg/kg bw/d for female rats and < 50 ppm (4 mg/kg bw/d for male rats). There were no signs of neurotoxicity at any dose level (please refer to A3.12).

Immunotoxicity after repeated dose exposure was investigated in rats, mice and dogs:
Since there is no specific study on immunotoxicity available, a weight of evidence evaluation was performed considering all available repeated dose toxicity studies with a special focus set on effects on the function and/or the organs of the immune system. Details and results of the evaluation can be found under A3.13. It was shown that exposure to Dazomet did not impair the immunological function in all tested species. However it’s appear that MITC has an impact on immunotoxicity modulation (high dose level).

Clinical cases and poisoning incidents (BPR Annex II 8.12.2) related to MITC generating compounds such as Dazomet were reported by [redacted] (1980, A8.12.1-002) for MITC. The author described the case of poisoning of a 24-year-old woman who did not notice that some Dazomet hat got into her rubber boot, which she wore for about 24 hours. After 24 hours a first to second degree acid burn developed and during the following days a bullous eruption spread over one foot/leg to about 5 % of the body surface. A liver biopsy showed a hypersensitivity hepatitis of non-specific type and the transaminases (GOT, GPT) were clearly increased. According to the author, the reversible damage of the liver parenchyma was conditioned by the oral contraceptiva the patient took, but caused by percutaneously uptake of MITC. A second liver biopsy did not show any adverse effects, and liver enzymes had returned to normal. One year after the exposure, the patch test to a 0.05% aqueous solution of Vapam (soil disinfectant based on metam sodium and acting in the same way as Dazomet, by hydrolytic release of MITC) was performed and was still found to be strongly positive. It can be concluded that if MITC generating compounds like Dazomet are exposed to a larger area of the body and not removed immediately, systemic poisoning (transient, reversible liver damage) can occur.

Table A-79: Effects and corresponding guidance values to assist classification for STOT RE

Study reference	Target organ effect(s) (all significant health effects that can impair function, both reversible and irreversible, immediate and/or delayed)	Effective dose (mg/kg bw/d)	Length of exposure	Guidance value/extrapolated guidance value for an exposure duration other than 90 days	Classification supported by the study (Cat 1, Cat 2, NC)
[redacted] **(1989a)** **IUCLID: A8.9.5.1 -005** **Oral, rat** **Key study**	<u>540 ppm</u> ↓food consumption (f) ↓body weight (f) ↓body weight gain *Haematology:* ↓Hb (m), Hct (m), RBC (m); ↑platelets (f) *Clinical chemistry:* ↓AST (f), ALT (f), creatinine, cholesterol (f), ↑triglyceride (f), ↓AChE (plasma) (f), ↓AChE (brain) (f) ↑liver weight ↑fatty degeneration (liver) <u>180 ppm</u> ↓food consumption (f) ↓body weight (f) ↓body weight gain (f) *Haematology:* ↑platelets (f) *Clinical chemistry:*	15 mg/kg bw/d	28 days	30 mg/kg bw/day	STOT RE cat. 1

	↓AST (f), ALT (f), ↑triglyceride (f) ↑liver weight ↑fatty degeneration (liver) <u>60 ppm</u> *Clinical chemistry:* ↓ALT (f), ↑triglyceride (f) NOAEL = 60 ppm = 5 mg/kg bw/day LOAEL based on decreased body weight (gain), increased liver weight and fatty hepatocyte degeneration at **180 ppm (15 mg/kg bw/day)**				
[redacted] **(1987)** **IUCLID: A8.9.5.3-001** **Dermal, rabbit** **Key study**	<u>1000 mg/kg bw/day</u> One moribund animal was sacrificed following a history of hypoactivity, mucoid diarrhoea, bloated abdomen an anorexia. No treatment-related findings at other doses NOAEL (systemic) = 100 mg/kg bw/day LOAEL based on the mortality and clinical signs at **1000 mg/kg bw/day.**	1000 mg/kg bw/day	21 days	600 mg/kg bw/day	Classification not supported
[redacted] **(1976)** **IUCLID:**	No abnormalities found at the tested nominal concentration of 0.033 mg/m³	Not applicable	21 days	Not applicable	Not applicable

A8.9.5.2-001 Inhalation rat **Supportive study**					
[redacted] **(1989)** **IUCLID: A8.9.5.1-005** **Oral, rat** **Key study**	<u>360 ppm</u> ↓food consumption (f) ↓body weight ↓body weight gain *Haematology:* ↓Hb; ↑MCV (f), platelets (m), WBC (m) *Clinical chemistry:* ↓ALT (m), AST (m), total protein, albumin (f), creatinine (f), triglycerides (m), cholesterol (f), potassium (f), phosphor (m) ↑chloride (f) ↑liver weight ↑fatty degeneration of liver <u>180 ppm</u> ↓body weight gain (f) *Haematology:* ↑platelets (m), WBC (m) *Clinical chemistry:* ↓total protein, albumin (f), phosphor (m); ↑chloride (f) ↑liver weight ↑fatty degeneration of liver <u>60 ppm</u> *Haematology:*	13.3 mg/kg bw/day	90 days	100 mg/kg bw/day	STOT RE, Cat. 2

	↑ platelets (m) *Clinical chemistry:* ↓total protein (f), albumin (f), ↑liver weight (m) ↑fatty degeneration of liver <u>20 ppm</u> *Clinical chemistry:* ↓total protein (f), albumin (f), NOAEL = 20 ppm = 1.5 mg/kg bw/day LOAEL based on increased liver weight and fatty degeneration at **60 ppm (13.3 mg/kg bw/d)**				
[redacted] **(1989)** **IUCLID: A8.9.5.1-005** **Oral, mice** **Key study**	<u>540 ppm</u> ↓food consumption (m) ↓bw gain (m) *Haematology:* ↓RBC, Hb, Hct, MCHC, WBC ↑MCV, reticulocytes ↑Heinz bodies ↑Liver weight ↑Hemosiderosis (spleen) Inflammatory reaction in liver <u>360 ppm</u> ↓food consumption (m) *Haematology:* ↓RBC, Hb, Hct (m) ↑MCV, reticulocytes ↑Heinz bodies	37.5 mg/kg bw/day	90 days	100 mg/kg bw/day	Classification not supported Dazomet induced only a slight haemolytic anaemia at top dose; there is no histopathological explanation for liver weight increase

	↑Liver weight ↑Hemosiderosis (spleen) <u>180 ppm</u> Haematology: ↑ reticulocytes ↑Heinz bodies ↑Liver weight <u>60 ppm</u> *Haematology:* ↑ reticulocytes NOAEL = 60 ppm = 13.3 mg/kg bw/day LOAEL based on increased number of reticulocytes and increased liver weight at **180 ppm (37.5 mg/kg bw/day).**				
[redacted] **(1987b)** **and** [redacted] **(2005) (Addendum)** **IUCLID: A8.9.5.1-006** **Oral, dogs** **Supportive study**	<u>400/200 ppm</u> ↓food consumption ↓body weight ↓body weight change ↓feed efficiency (f) ↑emesis *Haematology:* ↓Hb, RBC, Hct; ↑platelets, Met-Hb, PT (f), APTT *Clinical chemistry:* ↓proteins, albumin (f), cholesterol (m), Calcium levels, ALT; ↑Cl (f), P (f) ↑liver weight	5.7 mg/kg bw/day	90 days	10 mg/kg bw/day	Classification not supported. Only a slight anaemia (observed in both sexes, as well as a loss of weight and appetite) was suspected at the top dose which was in line with hemosiderosis and slight haematopoiesis in the spleen. Other minor gross and histopathological

	↓testes weight Hemosiderosis (spleen) Haematopoiesis (spleen) (f) Thymus involution (f) <u>100 ppm</u> *Haematology:* ↑platelets (m), Met-Hb (f), PT (m), APTT (m) *Clinical chemistry:* ↓Calcium levels (m), ALT (m) ↑liver weight (m) ↓testes weight Hemosiderosis (spleen) NOAEL = 100 ppm = 2.3 mg/kg bw/day LOAEL based on clinical signs, reduced RBC parameters, increased spleen hemosiderosis (could be due to the increased decomposition of erythrocytes as shown by the haematological parameters like reduction in haemoglobin, haematocrit and erythrocytes count) and haematopoiesis at **200/400 ppm (5.7 mg/kg bw).**				effects might be contributed to the general poor health state of the animals, since a major part of the animals on study showed parasitic infestations
[redacted] **(2020)** **IUCLID: A8.9.5.1-010** **OECD TG 409** **Oral capsule**	<u>13.5/9 mg/kg bw</u> ↓body weight *Haematology:* ↓Hb, RBC, Hct; ↑platelets, APTT	4.5 mg/kg bw/d	90 days	10 mg/kg bw/day	STOT RE.1

GLP compliant **90 days** **Beagle dogs** **Key study**	*Clinical chemistry:* ↓proteins, albumin , ↑liver weight ↑ kidney weight Hemosiderosis (spleen) Haematopoiesis (spleen) (f) brown pigment deposition in Kupffer cell (liver) 4.5 mg/kg bw *Haematology:* ↑platelets , APTT Hemosiderosis (spleen) (f) **NOAEL = 1.5 mg/kg bw/d**, but the lowest adverse effect level to which of the effects on the liver of both sexes and spleen of females were detected at **4.5 mg/kg/day** or more				
[redacted] **(1989a)** **and** [redacted] **(1989a)** **IUCLID A8.9.5.1 - 011** **Wistar rat** **Oral**	**<u>Non-neoplastic findings</u>** <u>320 ppm</u> ↓body weight (slight) ↓body weight gain (slight) *Haematology:* ↓Hb (f), Hct (f), RBC (f), PT (m); ↑platelets (f), reticulocytes Polychromasia (m), anisocytosis (m) *Clinical chemistry:* ↓AP (m), AChE (plasma), creatinine, triglyceride (f), globulin (f), albumin (f), total protein (f),	3.6 mg/kg bw/day (slight anaemia) 18 mg/kg bw/day (liver effects)	24 months	1.25 mg/kg bw/day (10 mg/kg bw/day /8) 12.5 mg/kg bw/day (100 mg/kg bw/day /8)	Classification not supported. Liver weight increases in combination with histopathological effects in the liver have only been observed at the highest dose Only marginal anaemia as no increase in reticulocytes has

	↑total bilirubin (f), cholesterol ↑P (m) ↓K (m) ↓kidney weight (abs.) ↑liver weight (rel.) ↑liver – fatty deposition, vacuolation (f), altered cell foci (f) <u>80 ppm</u> *Haematology:* ↓Hct (f), RBC (f); ↑platelets (f), Polychromasia (m), anisocytosis (m) *Clinical chemistry:* ↓AP (m), AChE (plasma, f), creatinine (m), triglyceride (f), globulin (f), albumin (f), total protein (f), ↑cholesterol (m) ↓K (m) <u>20 ppm</u> *Haematology:* ↑platelets (f), NOAEL = 20 ppm = 0.9 mg/kg bw/day LOAEL based on decreased RBC, Hct and proteins (f) at **80 ppm (3.6 mg/kg bw/d)** and decreased body weight **320 ppm (18 mg/kg bw/d)**				been found

[redacted] **(1989a)** **and** [redacted]. **(1989a)** **and** [redacted] **(1989b)** **IUCLID:** **A8.11-001** **Wistar** **rat** **Oral**	**Non-neoplastic findings** 80 ppm ↑liver weight (abs. + rel.(f)) ↑liver – fatty deposition (m), vacuolation (m), altered cell foci (f), basophilic cell foci (f) ↑stomach – epithelial hyperplasia (m) 20 ppm No relevant findings Toxicity NOAEL = 20 ppm = 0.9 mg/kg bw/day LOAEL based on increased liver weight, altered liver cell foci, liver fatty vacuolation and stomach epithelial hyperplasia at **80 ppm (3.6 mg/kg bw/d).**	3.6 mg/kg bw/day	24 months	1.25 mg/kg bw/day (10 mg/kg bw/day /8) 12.5 mg/kg bw/day (100 mg/kg bw/day /8)	STOT RE, Cat. 2
[redacted] **(1989c)** **and** [redacted] **(1990)** **IUCLID:** **A8.11-002** **B6C3F1** **Mouse** **Oral**	**Non-neoplastic findings** 320 ppm ↓body weight (m) ↓body weight gain (m) *Haematology:* Extramedullary haematopoiesis in spleen ↑liver weight (abs. + rel.) ↓kidney weight (abs. + rel.) (m) ↑liver – lipid deposition, single cell necrosis, basophilic foci ↑spleen – haemosiderosis (m), haematopoiesis ↑urinary bladder – mucosal	16 mg/kg bw/day	78 weeks	1.67 mg/kg bw/day (10 mg/kg bw/day /6) 16.7 mg/kg bw/day (100 mg/kg bw/day /6)	STOT RE, Cat. 2

	lipofuscin (f) ↑ovaries – follicular cysts ↓lipid deposition in kidney tubules <u>80 ppm</u> ↑liver weight (abs. + rel.(f)) ↓kidney weight (abs. + rel.) (m) ↑liver – lipid deposition (f), single cell necrosis (f), basophilic foci (f) ↑spleen – haemosiderosis (m) ↑urinary bladder – mucosal lipofuscin (f) ↑ovaries – follicular cysts ↓lipid deposition in kidney tubules <u>20 ppm</u> ↓kidney weight (abs.) (m) Toxicity NOAEL = 20 ppm = 4 mg/kg bw/day LOAEL based on increased liver weight, basophilic liver cell foci, hepatocyte lipidosis, liver adenoma, urinary bladder lipofuscin deposits, spleen hemosiderosis and ovary cysts at **80 ppm (16 mg/kg bw/d).**				
[redacted] **(1987b)** **A8.9.5.1 -006** **Oral, dogs** **Key study**	<u>150 ppm</u> ↓body weight change ↓feed efficiency *Haematology:* ↑platelets (f),	3.1 mg/kg bw/day	1 year	2.5 mg/kg bw/day (10 mg/kg bw/day /4) 25 mg/kg bw/day	STOT RE, Cat. 2

	Clinical chemistry: ↓albumin (m, severely affected) ↑globulin (m, severely affected) ↑total bilirubin ↑ALT, AP (m, severely affected), *Urinalysis:* ↑urobilinogen, bilirubin (m) ↑liver weight (m) ↑thyroid weight (f) ↓testes weight *Liver:* ↑hemosiderosis ↑fatty change ↑hypertrophy ↑necrosis (m) ↑hepatitis (f) ↑cirrhosis (m) ↑oesophagus - round cell infiltration (f) ↑stomach – congestion (f) ↑stomach – erosion (m) ↑ileum – haemorrhage (f) ↑prostate - alveolar distension and atrophy ↑testes - tubular atrophy ↑thyroid - round cell infiltration ↑parathyroid - ductal remnants ↑zygomatic salivary gland - round cell infiltration (f) and sialoliths ↑mammary glands - ductal dilation (f)			(100 mg/kg bw/day /4)	

	<u>50 ppm</u> *Haematology:* ↑platelets (f), ↑liver weight (f) *Liver:* ↑hemosiderosis ↑necrosis (f) ↑stomach – congestion (f) ↑parathyroid - ductal remnants ↑zygomatic salivary gland - round cell infiltration (f) and sialoliths ↑mammary glands - ductal dilation (f) <u>15 ppm</u> No treatment related findings NOAEL = 50 ppm = 1.0 mg/kg bw/day LOAEL based on clinical chemistry parameters, increased serum and urine bilirubin, increased liver weight with necrotic and cirrhotic findings at **150 ppm (3.1 mg/kg bw/day).**				
[redacted] **(1994b)** **A8.9.5.1-004** **Oral, rats** **Supportive study**	450/400 ppm (34 mg/kg bw/day) ↓body weight ↑liver weight ↑liver – fatty chances	4 mg/kg bw/day	90 days	10 mg/kg bw/day	STOT RE, Cat. 1

	FOB: No relevant findings ↓foot-splay at landing (questionable tox relevance, f) Figure eight-maze: No relevant findings 200 mg/kg bw/day ↑liver weight ↑liver – fatty chances FOB: No relevant findings Figure eight-maze: No relevant findings 50 mg/kg bw/day ↑liver – fatty chances FOB: No relevant findings Figure eight-maze: No relevant findings No relevant neuropathological findings Liver weights: the absolute liver weights were increased in the 450 ppm males , the 400 ppm females and the males of the 200 ppm group. The relative liver weights were statistically significantly increased in the females of the				

	200 ppm (p <= 0.05, ca. 12% compared to control) and the 400 ppm (p<= 0.01, ca. 26% compared to control) groups. Increased relative liver weights were also reported for the males of the 450 and the 200 ppm groups. This effect was considered to be test substance-related. Gross lesions: no test substance-related gross lesions were reported. Histopathology: light microscopy revealed fatty degeneration in the livers of the 450 ppm males, the 400 ppm females, both, males and females of the 200 ppm group, and in the males of the 50 ppm **(4 mg/kg bw)** group. This effect was considered to be test substance-related.				

A.3.7.4.2 Comparison with the CLP criteria

The repeated-dose toxicity of Dazomet by the oral route has been investigated in 28-day, 90-day and chronic studies in rats, mice and dogs, and by a 3-week inhalation study in rats. Although the reproduction studies are also repeated dose toxicity studies, they were not considered for an assessment of STOT RE here. The studies lack histopathological examination of the dams and, organ weights and necropsy were also limited. Taken together that extrapolation of effective doses using Haber's law can lead to large uncertainties, especially in studies with short exposure durations, and the toxicological gain is limited by the study design it appeared reasonable not to include this study type for STOT RE evaluation.

The liver could be identified as the target organ after oral administration in all three test species after short-term, sub-chronic and long-term exposure. In most of the studies liver weight increase and fatty changes in liver tissue have been observed as the main toxicological effects. Furthermore, cirrhosis, necrosis and inflammation could be observed.

However, significance and severity of liver effects varied considerably across the studies. In the 28-day study in rats and in one 90-day neurotoxicity study, also in rats, the effects already occurred at comparable low doses which would trigger classification in category 1, whereas in another 90-day study and nearly all long-term studies the liver effects occurred at moderate doses which would trigger classification in category 2 except for the additional 90-day dog studies performed on 2020, that triggers classification in category 1. In 90-day study in mice and dogs, in one long-term study in rats and in the dermal toxicity study, liver effects occurred at high doses which do not trigger any classification.

All studies have been performed under GLP conditions; however, the reliability of the dog studies is somewhat limited since the animals suffered from parasitic infestations with the consequence of a generally reduced health state of the animals. That's why a new 90-days dog studies ([redacted] 2020) has been performed, this test showed that liver effects occurred at low doses which should triggered classification as STOT RE 1.

The 90-day study in mice was initiated as a 4-week range finder study and expanded to a 90-day exposure. Therefore, the statistics of the test is based on only 5 animals compared to the other 90-day studies with 10 animals. The same applies for the 28-day oral study in rats which was also designed as a range finding study.

Since two of three studies with effects at doses triggering no classification (90-day mice and 90-day dog) were of limited reliability compared to the other available studies, a classification as STOT RE appears to be reasonable.

There were three 90-day studies (relevant) and three long-term studies of comparable quality left for the decision whether category 1 or category 2 is the most suitable representing the hazard of Dazomet after repeated exposure.

According to guidance on the application of the CLP criteria[12], for a 90-day oral study in the rat, the guidance cut-off value for category 2 is ≤ 100 mg/kg bw/day and for category 1, the guidance cut-off value for an oral 90-day study in rats is ≤ 10 mg/kg bw/day. To account for the different exposure durations, the effective doses (ED) have been extrapolated according to

[12] ECHA-17-G-21-EN; 10.2823/124801

Haber's rule (i.e., the extrapolated 90-day ED corresponds to 8x ED of 24-month exposure).

Comparing the 90-day studies, the repeated dose neurotoxicity study would trigger classification in cat 1 (ED = 4 mg/kg bw/day) whereas the 90-day repeated dose toxicity study would trigger classification in cat. 2 (ED = 13.3 mg/kg bw/day) if compared to the guidance values given above. From the long-term studies, two studies would trigger classification in cat. 2 (rat: extrapolated ED = 29 mg/kg bw/day; mice: extrapolated ED = 97 mg/kg bw/day) and one study would trigger no classification (effects in rat livers only at the highest dose; extrapolated ED = 144 mg/kg bw/day). Generally, it can be said that studies of longer duration give more substantial information compared to shorter duration studies. Furthermore, it was clearly demonstrated within the long-term studies, that the observed liver effects were not live threatening to the animals since there was no significant mortality/morbidity observed with the liver effects being of the same quality as described in the 90-day studies.

However, 90 day-dog study ([redacted].; 2020) has shown that a dose level of 4.5 mg/kg/day for males caused an increase in relative liver weight. One female showed diffuse hepatocellular single cell necrosis, infiltration of mononuclear cell, centrilobular haemorrhage, brown pigment deposition in Kupffer cell, and hepatocellular degeneration in the liver. Regarding haematology, both sexes, at 4.5 mg/kg/day or more, showed increased APTT. Since many globulins and coagulation factors are synthesized in the liver, the decreased Glob and TP and increased A/G and APTT might be associated with the treatment effects on the liver.

According to guidance on the application of the CLP criteria, for a 90-day oral study, the guidance cut-off value for category 1 is ≤ 10 mg/kg bw/day. Therefore, the triggered classification should be STOT RE.1.

Therefore, considering the weight of evidence, Dazomet should be classified in <u>category 1</u> considering the hazard of repeated dose exposure with respect to liver effects. Regardless of studies above 90 days of exposure suggesting an adaptive process without impairment of animals' life quality, indicating that the liver effects are of significance but less severe (no significant mortality/morbidity).

This conclusion is confirmed by clinical cases and poisoning incidents (BPR Annex II 8.12.2) related to MITC generating compounds such as Dazomet were reported by [redacted] (1980, A8.12.1-002) for MITC. Indeed, a liver biopsy showed a hypersensitivity hepatitis of non-specific type and the transaminases (GOT, GPT) were clearly increased. According to the author, the reversible damage of the liver parenchyma was exacerbated by the oral contraceptiva the patient took, caused by percutaneously uptake of MITC. A second liver biopsy did not show any adverse effects, and liver enzymes had returned to normal. One year after the exposure, the patch test to a 0.05% aqueous solution of Vapam (soil disinfectant based on metam sodium and acting in the same way as Dazomet, by hydrolytic release of MITC) was performed and was still found to be strongly positive. It can be concluded that if MITC generating compounds like Dazomet are exposed to a larger area of the body and not removed immediately, systemic poisoning (transient, reversible liver damage) occur.

Within the repeated dose neurotoxicity study in rats, no treatment-related neurotoxic effects were induced by Dazomet. No histopathological indication of neurotoxicity was observed. Furthermore, no neurotoxic effects were observed in any of the available animal studies. Thus,

no classification of Dazomet for neurotoxicity is proposed.

The immunological function of the test animals was not impaired in any of the available studies. Thus, no classification of Dazomet for immunotoxicity is proposed.

A.3.7.4.3 Conclusion on classification and labelling for STOT RE

Classified - STOT RE, Category 1 (H372: Causes damage to liver)

A.3.8 Genotoxicity / Germ cell mutagenicity

A full set of genotoxicity studies for the active substance Dazomet and its active metabolite MITC has been provided for the Annex II inclusion and thus peer reviewed by European competent authorities and eCA Belgium.
Since the Annex II inclusion of Dazomet, the data requirements and also the European evaluation criteria for genotoxicity have changed fundamentally, therefore additional studies with Dazomet and MITC have been performed.

During the last years, most of the guidelines for genotoxicity testing have been reviewed and adapted to the state of science, a re-evaluation of existing studies was conducted to check for deviations which are no longer compatible with the current evaluation criteria.
In those cases where the study reliability was no longer given leading to data gaps with respect to the current European testing requirements for genotoxicity, new studies have been initiated to address all the mutagenic endpoints as required.

Dazomet CAR Section 2.4.1.1. (Belgium, March 2010):

Active substance Dazomet
No evidence was found that Dazomet is genotoxic. *In vitro*: In bacterial cells Dazomet was negative for the induction of mutagenic changes. In contrast, in eukaryotic cells, results of different tests revealed a mutagenic and clastogenic potential for Dazomet which was observed generally in absence of metabolic activation. Endoreduplication and/or polyploidisation occurred in 2 assays (mouse lymphoma, human lymphocytes) at doses where mitotic indices were not suppressed. *In vivo*: Micronuclei were weakly induced in mouse bone-marrow when Dazomet was administered intraperitoneally. However, the majority of the data (including a UDS study, a mouse micronucleus test with oral administration, and higher-tier germ cells assays: the spermatogonia chromosome aberration test and the SLRL Drosophila assay) indicate that Dazomet in not genotoxic. In conclusion, the global weight-of-evidence suggests that Dazomet should not be considered a genotoxicant.

Degradation product/metabolite MITC
No evidence was found that MITC is genotoxic. *In vitro*: MITC tested negative in bacteria and in the *in vitro* chromosome aberration test. In contrast, the open literature pointed to a possible positive outcome in a single cell gel assay in HepG2 cells, a weak positive result was obtained in an *in vitro* micronucleus assay, and DNA-comets were present in the Comet-assay. *In vivo*: MITC showed no evidence of mutagenic potential in mouse bone marrow when administered by gavage in an *in vivo* micronucleus test as discussed in the 91/414 DAR of Metam-Na and Dazomet. In conclusion, the global weight-of-evidence suggests that MITC should not be considered a genotoxicant.

A.3.8.1 In vitro

Table A-80: Summary table of *in vitro* genotoxicity studies

Method, Guideline, GLP status, Reliability, Key/supportive study	Organism/ strain(s)	Test substance (including purity), Vehicle, Doses	Relevant information about the study (e.g. organism (e.g. bacteria), cell type, strains)	Results (including cytotoxicity and +/- S9 mix) +: mutation effect -: no mutation effect +/-: equivocal mutation effect (+)mutation effect with caution		Remarks (e.g. major deviations)	Reference
				+ S9	- S9		
Ames test / Standard Test similar to OECD TG 471 **Reliability: 1** **Supportive study**	Salmonella typhimurium: TA 98, TA 100, TA 1535, TA 1537	Dazomet Purity : 100 % (assumed) DMSO	3.7 - 300 µg/plate without S9 mix 3.7 - 1000 µg/plate with S9 mix	-	-	Cytotoxic concentration ≥ 300 µg/plate in all experiments	[redacted] (1980a) IUCLID: A8.5.4-001
				The results for the test with S-9 mix gained from Phenobarbital-induced liver of rat as well as the results of both tests performed with S-9 gained from mouse (Aroclor and Phenobarbital-induced liver) were similar to the results without S9 also showed that the numbers of colonies counted for Dazomet were within the negative and DMSO control range, and clearly below			

				the values obtained with the positive controls.			
Ames test / Standard Test similar to OECD TG 471 **Reliability: 1** **Supportive study**	Salmonella typhimurium: TA 100, TA 98, TA 1535, TA 1537, TA 1538	MITC Purity: 98 % DMSO	20 - 5000 µg/plate (with and without S9 mix)	-	-	Cytotoxic concentration > 500 µg/plate depending on strain and experiment	[redacted] (1986) IUCLID: A8.5.4-002
				The results for the test with S-9 mix were similar to the results without S9 and also showed that the numbers of colonies counted for MITC were within the negative and DMSO control range, and clearly below the values obtained with the positive controls.			
Bacillus subtilis recombination assay / EPA 84-4 **Reliability: 2** **Supportive study**	Bacillus subtilis strains M45 (rec-) and H17 (rec+)	Dazomet Purity: not reported DMSO	1 - 10000 µg/plate (with and without S9 mix)	-	-	Cytotoxic concentration ≥ 10 µg/plate	[redacted] (1987) IUCLID: A8.5.4-003
				The results for the test with S-9 mix were similar to the results without S9 and also showed that the numbers of colonies counted for Dazomet were within the negative and DMSO control range, and clearly below the values obtained with the positive controls.			

Bacillus subtilis recombination assay / EPA 84-4 **Reliability: 2** **Supportive study**	Bacillus subtilis strains M45 (rec-) and H17 (rec+)	MITC Purity: 98 % DMSO	1 – 10000 µg/plate (with and without S9 mix)	-	-	cytotoxic concentration ≥ 5000 µg/plate	[redacted] (1989) IUCLID: A8.5.4-004
				The MITC didn't induce any DNA damage with or without metabolic activation. The levels of inhibition measured (mm, treated with MITC 1-2502 µg/plate) are close to the levels obtained in the group treated only with DMSO. Remark: there are no difference (inhibition zone) between control group without S9 and positive control without S9.			
Bacterial reverse mutation assay (OECD TG 471, 1997) **Reliability: 2** **GLP** **Key study**	Test system: *S. typhimurium* strains TA98, TA100, TA102, TA1535, TA1537 plate incorporation and pre-	Dazomet Purity: 96.64 % DMSO	0 - 2.5 mg/plate (± S9)	-	-	cytotoxic concentration ≥ 1000 µg/plate There is a deviation when comparing to the OECD guideline 471, indeed the 2-amino anthracene (2-	[redacted]. (2008) IULCID: A8.5.4-014

	incubation assay			No substantial increase in revertant colony numbers of any of the five tester strains was observed following treatment with Dazomet TGAI at any concentration level, neither in the presence nor absence of metabolic activation (S9 mix). There was also no tendency of higher mutation rates with increasing concentrations in the range below the generally acknowledged border of biological relevance.	AA) is used like positive control for the test group with metabolic activation S9, however according to the guideline the 2-AA cannot be used as a sole indicator of the effectiveness of the mixture S9. 2 others positives control must also be tested.	

Bacterial reverse mutation assay (Ames, OECD TG 471, 1997) **Reliability: 1** **GLP** **Key study**	*S. typhimurium* strains TA98, TA100, TA1535, TA1537 *E.coli* WP2 uvrA	MITC Purity: 99.6 % DMSO	1.6, 0.50, 0.16, 0.050, 0.016, 0.0050 and 0.0016 mg/mL (500, 158, 50.0, 15.8, 5.00, 1.58, 0.500 and 0.158 µg/plate) (± S9)	-	-	cytotoxic concentration ≥ 0.5 mg/plate Experiment 1, the mean transformed (square root) number of spontaneous revertants for tester strain TA1535 (6.5) was outside the normal characteristic range (3.3-4.9). The genotyping results, as well as the negative and positive control results for TA1535 in Experiment 1 were acceptable. Therefore, this deviation did not adversely affect the outcome of the study or the interpretation of results.	[redacted] (2019a, 2019b, 2019c) IUCLID: A8.5.4-015
				The colony counts per plate for all concentrations of MITC (mean ± SD) were within or below the concurrent negative control range (mean ± SD) for all tester strains and conditions in both experiments with the exception of 0.00050 mg/plate for WP2 uvrA in the presence of S9 in Experiment I. This increase in colony counts was not dose-related or statistically significant. In addition, the mean transformed colony counts for the			

				tester strains treated with MITC were within, close to or lower than the historical negative control range. Therefore, MITC was considered negative under the conditions of the test.			
Photo-bacterial reverse mutation assay **in compliance with OECD TG 471 with modifications for photochemical testing (No specific OECD guidance available)** **Reliability: 2** **GLP** **Key study**	*S. typhimurium* strains TA98, TA100, TA1535, TA1537 *E. coli* strain WP2 *uvrA* plate incorporation	Dazomet Purity: 96.6 % DMSO	0.40, 0.13, 0.044, 0.015, 0.0049 and 0.0016 mg/plate (-S9)	-	-	The present study is a modification of the OECD TG 471, it doesn't integrate the appropriate metabolic activation system. According to this study the use of metabolic activation is not required because S9 and the cofactors (e.g. NADP, glucose-6-phosphate etc.)found in the S9 mix absorb or scatter light in the UV region.	[redacted] (2019a, 2019b) IUCLID: A8.5.4-013
				The colony counts per plate for all concentrations of Dazomet (mean ± SD) were within or below the concurrent negative control range (with irradiation) (mean ± SD) for all tester strains with two exceptions. TA100 treated with Dazomet at 0.0049 and 0.015 mg/plate had 257 ± 13 and 264 ± 10 colonies per plate, respectively,			

				which exceeded the concurrent irradiated negative control with 233 ± 8 colonies per plate. The increases in colony counts were not statistically significant when evaluated by Dunn's test ($p > 0.01$). Historical negative control data with irradiation were not available for comparison, but the mean transformed (square root) numbers of revertant colonies for all concentrations of Dazomet ranged from within to moderately higher (0.3 to 2.5 mean transformed colonies) than the normal characteristic range of the historical negative control data without irradiation. Any increases in the number of colonies over the historical negative control range was the result of irradiation and not the test item.		

Cytogenetic assay / OECD TG 473 **Reliability: 2** **Key study**	Human lymphocytes	Dazomet Purity: 98.2 % DMSO	0.002, 0.01 and 0.05 µg/mL without S9 mix 2.5, 12 and 25 µg/mL with S9 mix	-	-	There was only a slight increase in the frequency of gaps without S-9 mix at the highest dose and with metabolic activation in all three dose groups but without any dose-dependency. The origin and genetic consequences of gaps are rather uncertain and the occurrence of this aberration type in isolation is no suitable criteria for the evaluation of a clastogenic event.	[redacted] (1989) and [redacted] (1989) (Amendement) IUCLID: A8.5.4-005
				Without S9: Untreated control: 12 (6 %) aberrant cells inclu. Gaps and 3 (1.5 %) aberrant cells excl.gaps (2×B';1×F") were found. Sovent control: 20 (10 %) aberrant metaphases incl. gaps and 5 (2.5 %) aberrant metaphases excl.gaps (4×B';1×F") were observed. 27 (13.5 %) chromosomally damaged cells incl. gaps and 6 (3 %) aberrant cells excl. gaps (4×B';1×B";1×F') were detected. 0.01 µg/mL: 16 (8 %) aberrant metaphases incl. gaps and 3 (1.5 %)				

				chromosomally damaged cells excl. gaps (2×B'; 1×B") were observed. 0.002 µg/mL: 24 (12 %) aberrant cells incl. gaps and 5 (2.5 %) aberrant metaphases excl.gaps (2×B'; 2×B"; 1×F") were analyzed. 0.1 µg mitomycin C/mL: With 45 (45 %) aberrant cells incl. gaps and 41 (41 %) aberrant mitosis excl.gaps including 3 multiple aberrant metaphases and 13 cells with exchanges, the positive control substance led to expected increase in the number of chromosomally damaged cells. No differences regarding aneuploidies (hyperploid meta phases) polyploidies between the various dose groups and the negative controls were observed With S9: Untreated control: 15 (7.5 %) aberrant mitosis incl. gaps and 5 (2.5 %) aberrant cells excl. gaps (3×B'; 1×B"; 1×F")		

				were analysed. Solvent control: 11 (5.5 %) aberrant metaphases incl.gaps and 1 (0.5 %) chromosomally damaged cells excl.gaps (1×EX) were found. 25 µg/mL: 31 (15.5 %) chromosomally damaged cells incl.gaps and 6 (3 %) aberrant cells excl. gaps (2×B'; 1×B"; 2×F";1×m.A.) were observed. 12 µg/mL: 22 (11 %) aberrant metaphases incl.gaps and 5 (2.5 %) aberrant cells excl.gaps (2×B'; 1×B"; 2×F') were detected. 2.5 µg/mL: 26 (13 %) chromosomally damaged cells incl. gaps and 4 (2 %) aberrant cells aexcl. Gaps (1×B' ; 2×B" ; 1×Ex) were found. 6 µg cyclophosphamide/mL: With 27 (27 %) aberrant cells incl. gaps and 20 (20 %) aberrant metaphases excl.gaps including 1 cell with an exchange, the positive control substance led to the expected increase in		

				the number of chromosomally damaged cells. When compared to the negative control groups there were no differences regarding aneuploidies (hyperploid metaphases) and polyploidies in the any dose groups. Dazomet did not lead to an increase in the number of aberrant metaphases excl. gaps both with and without the addition of a metabolizing system when compared to the solvent control.			
Cytogenetic assay / OECD TG 473 **Reliability: 2** **Supportive study**	Human lymphocytes	MITC Purity: 98.1% DMSO	0.1, 0.5 and 1.0 µg/mL without S9 mix 0.05, 0.1 and 0.5 µg/mL with S9 mix.	-	-	Cytotoxicity was observed with and without activation at the highest concentration tested (0.5 and 1.0 µg/mL MITC respectively).	[redacted] (1987) IUCLID: A8.5.4-006
				Without S9: Untreated control: 10 (5.0 %) aberrant cells incl. gaps and 2 (1.0 %) aberrant cells excl. gaps (2×B') were found. Solvent control: 10 (5.0 %) aberrant metaphase incl. gaps and 7 (3.5 %) aberrant metaphases			

				excl. gaps (5×B'; 2×B") were observed. 0.5 µg/mL: 27 (13.5 %) chromosomally damaged cells incl.gaps (95 % statistical significance) and 4 (2.0 %) aberrant cells excl.gaps (3×B'; 1×F') were detected. 0.1 µg/mL: 16 (8.0 %) aberrant metaphases incl.gaps and 7 (3.5 %) chromosomal damaged cells excl.gaps (4×B'; 2×B";1×D') were observed. 0.05 µg/mL: 23 (11.5 %) aberrant cells incl.gaps and 5 (2.5 %) aberrant metaphases excl.gaps (3×B';1×B";1×F") were analyzed. 0.3 µg mitomycin C/mL: With 53 (53 %) aberrant cells incl.gaps and 51 (51 %) aberrant mitosis excl.gaps including 9 multiple aberrant metaphases and 24 cells with exchanges, the positive control substance led to the expected increase in the number of chromosomally damaged cells.		

				With S9: Untreated control: 11 (5.5 %) aberrant mitosis incl.gaps and 2 (1.0 %) aberrant cells excl.gaps (1×B', 1×I') were analyzed. Solvent control: 7 (3.5 %) aberrant metaphases incl.gaps and 1 (0.5 %) chromosomally damaged cell excl.gaps (1×B') were found. 1.0 µg/mL: 29 (14.5 %) chromosomally damaged cells incl.gaps (Fisher Yates Test: statistical significance of 95 % and 99 % against the untreated control and the solvent control respectively) and 7 (3.5 %) aberrant cells excl.gaps (5×B';1×B";1×D") were observed. 0.5 µg/mL: 16 (8.0 %) aberrant metaphases incl. gaps and 4 (2.0 %) aberrant cells excl.gaps (4×B') were detected. 0.1 µg/mL: 20 (10.0 %) chromosomally damaged cells incl. gaps and 6 (3.0 %) aberrant cells excl. gaps (4×B'; 2×B") were found. 6 µg		

				cyclophosphamide/mL: With 23 (23 %) aberrant cells incl.gaps and 15 (15 %) aberrant metaphases excl.gaps including 4 cells with exchanges, the positive control substance led to the expected increase in the number of chromosomally damaged cells. The test substance MITC caused a statistically significant increase in the number of chromosomally damaged cells both in the experimental rats with and without metabolic activation. However, this increase was observed only in the highest dose groups where cytotoxicity was also found (slightly decreased mitotic index, reduced quality of chromosomal structure). Furthermore, there was only an increase in the number of aberrant cells incl.gaps; the aberration frequencies excl.gaps were always in the range of that of the control. Thus, the increase only		

				of gaps in cytotoxic concentrations is not considered to be indicative for a chromosome damaging effect of the test substance, but might rather be a consequence of cytotoxicity. Furthermore, the genetic consequences of gaps are rather uncertain and the occurrence of this aberration type alone is no suitable criteria for the substance for the evaluation of clastogenic event. Therefore, the test substance MITC is considered to have no chromosome-damaging (clastogenic) effect *in vitro* using human lymphocytes.			
L5178Y TK+/- mouse lymphoma mammalian chromosome aberration test / comparable to	L5178Y TK+/- mouse lymphoma	Dazomet (N-521) Purity: not reported DMSO	Solvent: DMSO Concentrations tested: 0.6 – 4 µg/mL (- S9) or 0.8 - 5 µg/mL (- S9)	+	-	-S9: endoreduplication at highest dose	[redacted] (1980b) A8.5.4-007

OECD TG 473 **Reliability: 2** **Key study**			and 4.0 – 20 µg/mL (+ S9) or 6.0 – 30 µg/mL (+ S9)	N-521 was less toxic in the presence of an Aroclor 1254 induced rat liver S-9, and no genetic activity was apparent in any of endpoints in the presence of activation. When assayed directly , N-521 showed a reproducible significant increase in gene mutations at doses of 1 µg/mL or greater in two of the three trials. The first trial results are included for the reference even though the cloning efficiency is unusually high. In the cytogenetic aberrations occurred at a dose level of 4 and 5 µg/mL. At lower doses there were increases in numerical aberrations. No significant increase in sister chromatid exchanges (SCE's) was evident when N-521 was assayed either directly or with activation, but the number of cells available for scoring was reduced in the direct assay. Under the conditions of the standard assay , cells which had not completed		

				two rounds of replication in BrdU in 24 hours would not stain for SCE's. The number of cells transiting the cell circle in the expected time could be reduced by chromosome aberrations of the type we observed and result in fewer cells stained fir SCE's.			
Cytogenetic assay measuring sister chromatic exchange and chromosome aberrations / comparable to OECD TG 473 **Reliability: 3** **Supportive study**	Mouse lymphoma L5178Y cells	Dazomet (N-521) Purity: not reported DMSO	1.56, 3.13, 6.25, 12.5 and 25 ng/mL (with and without S9 mix)	+/-	(+)	**Invalid, too many deviations from guideline** Test substance reported to be weakly clastogenic in the absence of metabolic activation. Results in the presence of metabolic activation are considered to be ambiguous.	[redacted] (1979) IUICLID: A8.5.4-008
				<u>Without S9:</u> N-521 produced an erratic dose response with regard to chromosome aberration frequencies. Only the lowest dose is associated with a significant elevation in the frequency of cells with aberrations, although the middle dose frequency is also			

				quite high (6×solvent control). It is perhaps more significant that several breakage-reunion type aberrations were observed at these two dose levels (1 translocation, 2 triradials and 1 complex rearrangement at 1.56 ng/mL; and, 1 translocation and 1 triradial at 6.25 ng/mL). Such aberrations are relatively rare in negative and solvent controls, and none were observed in the present controls. This it must be concluded that N521 is capable on inducing chromosome aberrations under certain conditions. When used with metabolic activation, the test compound induced statistically significant ($p<0.05$) increase in the frequency of cells with aberrations at 3 dose levels. None of these frequencies were especially high, however, and only two reunion-type aberrations were observed among the 250		

				cells scored from cultures exposed to N521. It is therefore difficult to state unequivocally that this compound is clastogenic but the consistently elevated aberration frequencies (at all dose levels) suggest that it is. SCE frequencies without activation were normal (i.e., not above control range) at all doses but the highest. Thus, there is the suggestion that this compound may induce SCEs, but the evidence is not conclusive. <u>With S9:</u> N521 did not induce SCEs at any of the dose levels employed in this assay. SCE frequencies were generally elevated, but this was clearly due to the activation mixture because control frequencies were also elevated (by approximately 40%) compared to those observed without activation.		

				-	(+)	**Not relied upon, not according to current guidelines** Isolated positive result at the highest concentration tested without metabolic activation.	
Chromosomal aberration test / guideline not specified **Reliability: 4** **Supportive study**	Chinese Hamster V79 cells	MITC Purity: 20 % Vehicle not reported	0.1 - 2.5 µg/mL (with and without S9 mix)	+	+	**Not relied upon, not according to current guidelines** MITC is clastogenic only at cytotoxic doses with and without metabolic activation: 2.5 µg/mL with metabolic activation 1.0 µg/mL without metabolic activation	[redacted] (1990) IUCLID: A8.5.4-009
				Without S9: Chromosomal aberrations, especially breaks and exchanges, were reported following treatment with 1 µg/mL test substance after 28 hours. With S9: Chromosomal aberrations, especially breaks and exchanges,			

				were reported following treatment with 2.5 µg/ml test substance after 28 hours.			
Sister chromatid exchange assay / guideline not specified **Reliability: 4** **Supportive study**	Chinese Hamster V79 cell line	MITC Purity: 20 % Vehicle not reported	0.1 - 5 µg/mL (with and without S9 mix)	-	-	**Not relied upon, not according to current guidelines** MITC clearly reduced the plating efficiency of the V 79 cells at 2.0 µg/mL although the replication index was suppressed only after treatment at the top dose levels (with and without metabolic activation) in both experiments.	[redacted] (1990) IUCLID: A8.5.4-010
				There was no reproducible increase in cells with SCEs at any dose level with or without S9.			

Mammalian cell gene mutation assay / comparable to OECD TG 476 **Reliability: 2** **+Key study**	Chinese hamster ovary cells (HGPRT locus)	Dazomet Purity: 99.3 % DMSO	0.00464-0.1 µg/mL (1st experiment) 0.01 - 0.464 µg/mL (2sd experiment)	+		In the first experiment acceptance criteria for this study type were not fully met due to low cloning efficiency (app. 45 % without and 50 % with S9-mix) in the control. In addition there was no cytotoxic effect observed in the presence of S9 mix. In the second experiment cloning efficiency in the control groups was acceptable and a dose related cytotoxic effect was noted with and without metabolic activation. The data obtained from the second	[redacted] (1986) IUCLID: A8.5.4-011
				A dose-related increase of mutant numbers in the absence of S9-mix was obtained at the two highest concentrations. In the presence of S9-mix a triphasic dose response was observed with small and dose-related increases of mutation rates in the 2 lowest concentrations and, again, an increase at the highest dose level.			

				It is unclear whether the cytotoxicity of S9-mix and the test material may have prevented the expression of mutants in the other dose groups. Dazomet was considered mutagenic in cytotoxic conditions, in the absence of S9, and equivocally positive in the presence of S9.	experiment were not confirmed in an independent experiment since the acceptance criteria in the first experiment were not fulfilled and could not be used for evaluation.	
***In vitro* Mammalian Cell Micronucleus Test (OECD TG 487, 2016)** **GLP** **Reliability: 1** **Key study**	Test system: Chinese hamster ovary (CHO) cells	MITC Purity: 99.6 % DMSO	0.078, 0.12, 0.18, 0.26, 0.39, 0.59, 0.89, 1.3, 2.0 µg/mL (- S9)	+ Only without S9	Because the volatile MITC was positive in the *in vitro* micronucleus test in preliminary study, no additional volatile positive controls were evaluated in this study.	[redacted] (2020b) A8.5.4-017
				4-hour treatment without S9: The degree of cytotoxicity, evaluated by determining the Relative Increase in Cell (Nuclear) Counts (RICC), ranged from non-toxic to toxic (RICC of 136 to 2 %) following treatment with MITC (Table 1). At a non-toxic concentration of 0.59		

				µg/mL MITC (RICC 78 %), increases in %MN (2.03 %) and %HD (1.97 %) were observed that were greater than the tolerance interval, i.e. mean + 3 × SD, of the historical negative controls (0.69 for %MN and 0.22 for %HD) (Appendix V). In addition, an increase in %HD (0.25 %) that was greater than the tolerance interval of the negative controls was observed at 0.39 µg/mL MITC. These increases were not significant when evaluated using the z' statistic (all had z' < 0.6). However, the increases in %MN and %HD were determined to be dose-related ($p < 0.01$) using two trend tests, the Cochran-Armitage trend test and a t-test on the slope of the dose response curve. Therefore, MITC was determined to be positive, i.e. capable of inducing aneuploidy, in the sealing foil version of the *in vitro* micronucleus		

				test		
Unscheduled DNA synthesis / Method complies to a great extent with OECD TG 482 **Reliability: 2** **Supportive study**	Cultured primary rat hepatocytes	Dazomet Purity: 99.3 % Vehicle: Acetone	0.125 - 12.5 µg/mL (without S9 mix)	- only without S9 The UDS assay resulted in a small increase in nuclear labelling (increase in the percentage of nuclei having 6 or more net grains) of primary rat hepatocytes, which was detected in both assays at a moderate cytotoxic dose of 5 µg/mL (survival rate > 75 %). The criteria for a significant increase in the mean net nuclear grain count and for an increase in the percent nuclei having 20 or more net grains were not met in either trial. In contrast the positive control caused a large increase in nuclear labelling indicating that the system is able to detect compounds causing DNA damage and repair in primary rat hepatocytes.	**Not relied upon, not according to current guidelines** cytotoxic concentration ≥ 10 µg/mL	[redacted] (1985) IUCLID: A8.5.4-012

Unscheduled DNA Synthesis / Method complies to a great extent with OECD TG 482 **Reliability: 4** **Supportive study**	Cultured primary rat hepatocytes	MITC Purity: 20 % Vehicle not reported	0.254 - 30.3 µg/mL (without S9 mix)	- only without S9 MITC did not induce significant changes in the nuclear labeling of primary rat h hepatocytes at concentrations ranging from 0.253 to 15.2 µg/ml. The highest tested dose of 30.3 µg/mL MITC was completely lethal.			[redacted] (1990) IUCLID: A8.5.4-018
***In vitro* Mammalian Cell Gene Mutation Tests Using the Thymidine Kinase Gene (OECD TG 490, 2016)** **Reliability: 1** **GLP** **Key study**	Mouse lymphoma L5178Y cells TK locus	MITC Purity: 99.6 % DMSO	1.5, 1.0, 0.67, 0.44, 0.30, 0.20 and 0.13 µg/mL (-S9) 3.8, 2.5, 1.7, 1.1, 0.74 and 0.50, µg/mL (+S9)	-	(+)		[redacted] (2020a) IUCLID: A8.5.4-016
				3-Hour Treatment Without S9: At 1.0 µg/mL, the RTG for MITC was 23 %, which was consistent with, but just outside the target of 20 to 10 % RTG (Relative Total Growth). The next highest dose of MITC (1.5 µg/mL) yielded an RTG that was less than 10% (6 %). For all non-toxic (RTG >			

				10 %) concentrations of MITC, no increases in induced mutant frequency (IMF) over the negative control met the Global Evaluation Factor (GEF) of 126 recommended by the OECD. Although the IMF was > 126 (i.e. 184) for MITC at 1.5 µg/mL, this concentration was cytotoxic with an RTG less than 10 % (6 %). As per OECD guidelines (2), a result is not considered positive if the increase in MF occurs only at or below 10 % RTG. As per the OECD guidelines, there are some circumstances in which additional information can assist in determining that a test item is not mutagenic when there is no culture showing an RTG between 10-20 %, as in this case in the 3 h -S9 condition. The test item is negative if there is no evidence of mutagenicity in a series of data points within 100 to 20 % RTG and there is at least one data point between 20 and 25 % RTG. In the absence of		

				evidence of mutagenicity (no increase in IMF that met the GEF) in a series of data points within 98 to 23 % RTG, including one data point between 20 and 25 % RTG (i.e. 23 %), the test item is considered to be negative for the 3h -S9 condition. 3-Hour Treatment With S9: At 2.5 µg/mL, the RTG for MITC was 16 %, which met the target of 20 to 10 % RTG. An increase in IMF of 302 at 3.8 µg/mL MITC did not meet the criteria for a positive response as it occurred below 10 % RTG (i.e. 2 %). However, at 2.5 µg/mL MITC (RTG 16 %), an increase in IMF over the negative control (i.e. 147) exceeded the GEF of 126 recommended by the OECD. This increase was evaluated and found to be statistically significant (p = 0.00064) for a dose response. In accordance		

				with OECD guidelines, care should be taken when interpreting positive results only found between 20 and 10 % RTG. Therefore, MITC is considered to be positive for the 3h +S9 condition, but these results should be interpreted with caution.		

A.3.8.2 In vivo

Table A-81: Summary table of *in vivo* genotoxicity studies

Method, duration of study, Guideline, GLP status, Reliability, Key / supportive study	Test substance (including purity), Vehicle, Doses	Relevant information about the study (e.g. species and strain, sex, no per group, route, frequency of application, sampling times, duration of exposure)	Main effects, Observations (specify regarding dose and sampling time)	Remarks (e.g. major deviations)	Reference
Mammalian Erythrocyte Micronucleus Test (OECD TG 474, 2016) **GLP**	Dazomet Purity: 96.6 % Vehicle: Corn Oil	Sprague-Dawley Rat Duration of treatment / exposure: 3 days Frequency of treatment: 1/day	Micronucleus assay: Dazomet is neither clastogenic nor aneugenic in the bone marrow of female rats. Mean: 0 mg/kg bw/d: 55.6 % ± 3.1 PCE (polychromatic	-	[redacted] (2020) IUCLID: A8.5.5-008

Oral gavage **Key study** **Reliability: 1**		No. of animals per sex per dose: 5 31.75, 62.5, 125, 250 mg/kg bw/day	erythrocytes) and 0.045 % ± 0.037 MN (Micronuclei)-PCE 31.75 mg/kg bw/d: 56.4 % ± 2.1 PCE and 0.080 % ± 0.065 MN-PCE 62.5 mg/kg bw/d: 56.8 % ± 1.8 PCE and 0.070 % ± 0.021 MN-PCE 125 mg/kg bw/d: 53.6 % ± 3.2 PCE and 0.080 % ± 0.033 MN-PCE 250 mg/kg bw/d: 55.3 % ± 2.5 PCE and 0.088 % ± 0.048 MN-PCE Even though bone marrow cytotoxicity was not apparent (no reduction in % PCE) within the micronucleus study, the exposure to the bone marrow was proven since the main metabolite of Dazomet (M5) was successfully detected in plasma samples collected from the treated and untreated animals. Thus, the negative outcome of the study is valid. Comet assay: Dazomet is not mutagenic in the Comet assay performed in liver and stomach of female rats.		

			Mean: 0 mg/kg bw/d: 2.92¨% ± 0.54 PCE (polychromatic erythrocytes) and 9.81 % ± 3.36 MN-PCE (Number of micronucleated polychromatic erythrocytes) 31.75 mg/kg bw/d: 3.08 % ± 2.10 PCE and 8.56 ± 3.15 MN-PCE 62.5 mg/kg bw/d: 2.95 % ± 1.49 PCE and 9.31 ± 3.06 MN-PCE 125 mg/kg bw/d: 4.27 % ± 1.22 PCE and 10.13 % ± 3.30 MN-PCE 250 mg/kg bw/d: 2.54 % ± 0.83 PCE and 8.00 % ± 1.22 MN-PCE As the specific Dazomet metabolite (M5) was identified in plasma and liver tissue, the exposure to the target organ liver was verified. The exposure of the stomach tissue as the second target tissue is proven in that the stomach as the organ of first contact is always exposed to the test substance after oral administration. Thus, the negative outcome of the study is valid.		

Micronucleus assay / OECD TG 474 **Reliability: 3** **Oral** **Supportive study**	Dazomet Purity: 99.3 % DMSO	NMRI Mouse No. of animals per sex per dose: 5 45, 90,180 mg/kg bw	After the single administration of the highest dose of 180 mg/kg bw, 2.22 ‰ polychromatic erythrocytes containing micronuclei were found after 16 hours, 2.0 ‰ after 4 hours and 1.8 ‰ after 48 hours. In the two lower dose groups rates of micronuclei of about 1.8 ‰ (90 mg/kg group) and 1.2 ‰ (45 mg/kg group) were detected after a sacrifice interval of 24 hours in each case. With 27.1 ‰, however, the positive control substance cyclophosphamide, as expected, led to a very clear increase in the rate of polychromatic erythrocytes containing micronuclei at a dose level of 40 mg/kg body weight. The number of normochromatic erythrocytes containing micronuclei did not differ to any appreciable extent in the negative control (solvent control) or in the various dose groups at any of the sacrifice intervals. The test substance Dazomet	The validity criteria of the negative historical control data are not met (not segregated by sex, and pooled for both oral and i.p. administration, and for various vehicles (water, DMSO or olive oil)). Animals were housed individually during the experiment The age of the animals is not given (but mean body weight) The weight variation of the animals at study start was not given - DMSO as an untypical solvent was used (presumably typical for the time the study was conducted); with the exception of the concurrent negative control, there was no information given to what extent DMSO might influence the results due to its cytotoxic properties One animal died within the 16 h sampling time top-dose group, thus for that group there were only 4 analysable animals (however 16 h sampling time is of less	[redacted] (1985) IUCLID: A8.5.5-002

			thus did not lead to any increase in the rate of micronuclei. The number of normochromatic or polychromatic erythrocytes containing small micronuclei (d < D/4) or large micronuclei (d ≥ D/4) did not deviate from the solvent control values at any sacrifice interval. An inhibition of erythropoiesis induced by the treatment of mice with Dazomet was not detected; the ratio of polychromatic t normochromatic erythrocytes was always in the same range as that of the control values in all dose groups. Dazomet has no chromosome-damaging (clastogenic) effect nor does it lead to any impairment of distribution in the course of mitosis.	relevance since 24 h after administration is the earliest sampling time recommended by current guideline) Only one single treatment regime followed, whereas two or more treatments are recommended by the recent OECD TG 474. The exposure of the bone marrow was not proven (no bone marrow toxicity occurred) but assumed by systemic toxicity Randomization and evaluation procedure of bone marrow slides were not described in detail. An operator bias could not be excluded The criteria for scoring micronucleated cells are not given At least 4000 PCE per animal should be scored for the incidence of micronucleated polychromatic erythrocytes (PCE) according to OECD TG 474 (2016). However, in the current study, only 1000 PCE per animals were scored, since this was required by the	

				previous guideline OECD 474 (1983). Since both sexes of mice were exposed in the present study, the overall number of assessed PCEs (10000) per dose group is only half the number required in the current guideline OECD 474 (therefore, acceptability criteria of study not met) No positive control data base was provided to be in line with the acceptability criteria of OECD TG 474 (2016)	
Mammalian Erythrocyte Micronucleus Test (OECD TG 474, 2016) **Oral** **Reliability: 1** **GLP** **Key study**	MITC Purity: 98.1 % Corn Oil (2.3 % hexane)	Sprague-Dawley Rat <u>Frequency of treatment:</u> twice at 24 hours interval <u>No. of animals per sex per dose:</u> 5 0, 20, 40, 60 mg/kg bw	Micronucleus assay: Substance (dose × number of treatments) Corn oil (0 × 2): 0.230 % ± 0.06 MN-PCE/PCE and 59.0 % ± 9.1 PCE/(PCE+NCE) MITC (20 × 2): 0.155 % ± 0.07 MN-PCE/PCE and 60.0 % ± 3.0 PCE/(PCE+NCE) [^{14}C]MITC (40 × 2): 0.105 % ± 0.07 MN-PCE/PCE and 53.2 % ± 9.1 PCE/(PCE+NCE) MITC (60 × 2): 0.130 % ± 0.03 MN-PCE/PCE and 56.8 % ± 7.4 PCE/(PCE+NCE) Mitomycin C (1.0 × 1): 1.335	Radiolabelled test substance 14-C MITC	[redacted] (2020) IUCLID: A8.5.5-010

			% ± 0.38 MN-PCE/PCE and 68.2 % ± 2.5 PCE/(PCE+NCE) MNPCE : Number of micronucleated polychromatic erythrocytes PCE : Number of polychromatic erythrocytes NCE : Number of normochromatic erythrocytes The mean frequencies of micronucleated polychromatic erythrocytes in the test substance treated groups were 0.105 - 0.155 %, showing no significant increase when compared with the concurrent vehicle control group, in which the mean frequency of micronucleated polychromatic erythrocytes was 0.230 %. In the 40 and 60 mg/kg groups, the micronucleated polychromatic erythrocyte frequencies were statistically lower than that of the vehicle control (p = 0.0418) but the amount of differences was small and there was no dose-relationship. Therefore, this decrease is not considered to have any biological meaning		

			or to be related to administration of MITC. The reason for the statistically significant differences was probably that the concurrent vehicle control (0.230 %) was relatively higher than the historical background data (0.200 %). On the other hand, a statistically significant increase in the frequency of micronucleated polychromatic erythrocytes was noted in the positive control group treated with mitomycin C in which the mean frequency was 1.335 %, indicating the assay to be sensitive. The frequency was also compatible with the historical positive control data. The mean ratios of polychromatic erythrocytes in the test substance treated groups were 53.2 - 60.0 %, showing no significant decrease when compared with the concurrent vehicle control group, in which the mean ratio of polychromatic erythrocytes was 59.0 %. The test substance did not show toxic effects on the bone marrow.		

			It was concluded that MITC (and [14C]MITC) did not induce micronuclei (chromosome aberrations) in bone marrow cells of SD (Crl:CD) rats under the conditions used in this study.		
Micronucleus assay / no guideline specified **Reliability: 4** **Supportive study**	MITC Purity: 20 % Vehicle: not reported	CD-1 Mouse 110 mg/kg bw/day (nominal)	No increase in the number of polychromatic erythrocytes (PCEs) containing micronuclei **24hrs:** The ratio of PCEs to NCEs (normochromatic erythrocytes) in MITC treated mice was comparable to control **48hrs:** The ratio of PCEs to NCEs in MITC treated mice was clearly lower than in control **72hrs:** The ratio of PCEs to NCEs in MITC treated mice was clearly lower than in control	Not relied upon, not according to current guidelines	[redacted] (1990) IUCLID: A8.5.5-001
Cytogenetic assay / Method similar to OECD TG 475	Dazomet Purity: not reported	Sprague-Dawley Rat	Structural chromosomal aberration frequencies were within the normal range in	Not relied upon, many deviations from guideline	[redacted] (1979) IUCLID:

Reliability: 3 (not reliable) **Supportive study (oral)**	Distilled water	No. of animals per sex per dose is equal to 8 6, 20 and 60 mg/kg bw <u>Post exposure period:</u> 6, 24, 48 hrs	the subchronically treated animals at all tested doses. In the acutely treated rats, the frequencies also were quite low; a single case of elevated frequency was reported that was considered as not biologically relevant. All aberrations seen were simple fragments and no doseresponse relationship was evident. The percentage of cells with aberrations was within the negative control range (0.3 to 0.8 % for the acute study and 1.4 % for the subchronic), excepted for one case where a significantly elevated value was obtained because of the absence of aberrations in the concurrent negative control (acute study, 6 mg/kg, 24 hours: 1.8 % of cells with aberrations versus 0 in the corresponding water control). N-521 was not clastogenic, nor did it affect the mitotic process under the conditions of this assay.		A8.5.5-003

Micronucleus assay / no guideline specified **Reliability: 3 (not reliable)** **Supportive study (intraperitoneal)**	Dazomet Purity: 99.9 % Dimethylsulfoxide (DMSO) in olive oil	Swiss mouse <u>Frequency of treatment:</u> 2 <u>Post exposure period:</u> 16 and 24 hrs 50, 70 and 90 mg/kg (32P-DNA Postlabelling Technique) 100 mg/kg (Alkaline Elution Assay) 2 x 50 mg/kg bw (Micronucleus Assay) <u>No. of animals per sex per dose:</u> 3 females (32P-DNA Postlabeling Technique) 4 males (Alkaline Elution Assay) 12 males (Micronucleus Assay)	Very slight but statistically significant ($p < 0.05$) increase in micronuclei frequency in the bone marrow cells of mice treated with 100 mg/kg bw at both sampling intervals	Invalid, too many deviations from guideline (incl. intraperitoneal application)	[redacted] (1998) UICLID : A8.5.5-004
Unscheduled DNA synthesis / method similar to OECD TG 486 **Reliability: 4 (not**	Dazomet Purity : 99.3 % DMSO	Fischer 344 Rat <u>Post exposure period :</u> 4 hrs <u>No. of animals per</u>	Viability of the hepatocytes as measured by trypan blue exclusion method ranged from 72.4 to 90.3 % of the total cells collected in the	Not relied upon, not according to current guidelines An *in vivo* UDS test is	[redacted] (1986) IUCLID : A8.5.5-005

reliable) **GLP: yes** **Supportive study**		sex per dose: 3 37.5, 75, 150, 300 mg/kg	perfusate. The viability of attached cells was very good (90.5 – 96.7%). None of the treatments with the test material samples caused nuclear labeling significantly different from vehicle control. Dazomet was inactive in the *in vivo* rat hepatocyte UDS assay after oral treatment under the test conditions chosen.	not anymore considered a valid follow-up study to a positive *in vitro* gene mutation assays in mammalian cells.	
Mammalian germ cell cytogenetic assay / no guideline specified **Reliability: 2 (reliable with restrictions)** **GLP** **Supportive study**	Dazomet Purity : 99.3 % DMSO	Hamster Chinese No. of animals per group: 10 Test groups: 1 negative control (18 hours) 2 positive controls (18 hours) 6 treated groups (18, 42 and 66 hours) Post exposure period: 18 hours (all groups), 42 and 66 hours (each the highest dose level	In fact, a slight increase in number of cells with aberrations without gaps at the 18 h time point was reported (33 mg/kg bw: 1.4 %; 100 mg/kg bw: 1.8 %). However, these findings were not regarded as expression of mutagenic properties of the test substance, as the values for negative control are known to range between 1 and 2 % of cells with aberrations.	Rationale for reliability incl. deficiencies test procedure in accordance with national standard methods with acceptable restrictions. A number of deviations become apparent when compared to the requirements as set out in the current test guideline, including missing information on laboratory proficiency	[redacted] (1985) IUCLID: A8.5.5-006

		group) 10, 33 and 100 mg/kg	In a second approach, the mean aberration rate of 1.8 % in the 100 mg/kg bw group which was treated additionally and analyzed together with the positive control Doxorubicinhydrochlorid was also below 2 %. Dazomet did not induce chromosomal aberration in germ cells even after oral treatment with toxic doses. A toxic reaction was observed in hamsters, however, no mortality was noted at the high dose level of 100 mg/kg bw.	and historical control data. However, most of these were not in charge at the time of study conduction and the study appears scientifically sound when assessed independently. Thus, with respect to its age and the contemporary requirements, the applicant follows the opinion of the previous evaluator and considers the study reliable, however, with clear restrictions regarding compliance to current requirements.	
Drosophila SLRL test / no guideline specified **GLP** **Supportive study** **Reliability: 4**	Dazomet Purity : not reported Dimethylsulfoxide (DMSO)	Drosophila melanogaster <u>Duration of treatment / exposure:</u> up to 24 hrs <u>No. of animals per sex per dose:</u> 25 0.025 and 0.05	The pooled data from all the broods of the solvent control is 0.19 %. Upon examination of the data score sheets, 4 of the 10 lethals observed in Brood I of the solvent control were found to arise from one male. Since stages which	Rationale for reliability incl. deficiencies documentation insufficient for assessment. The study does not follow an official test protocol, yet it appears well designed and conducted	[redacted] (1979) IUCLID: A8.5.5-007

		mg/mL	were post-meiotic (no longer replicating) at the time of treatment, this cluster was determined to be pre-existing and was counted as 1 event to correct for this. When the correction is made, the pooled frequency becomes 0.18%. This is slightly higher than our historical frequency of 0.13 % for pooled data. The 0.29% in Brood I is high but this number is not improbable in a sample size of 2.453 chromosomes, especially since studies have shown an increased spontaneous frequency in the first sperm sampled in successive brooding sequences. The positive control group was not adjusted for clusters since with a mutation frequency of	according to good scientific practice. However, this type of study is no longer appropriate for regulatory purposes and hence not relied upon. Therefore, it is considered to be supportive information only.	

			nearly 25 %, one would expect more than one independent event occurring in some males. The mutation frequencies of the high dose group remain consistently though not significantly, higher than the control group in Broods II and III which sample spermatids. There is also a slight increase in the frequency of lethals found in Brood III of the low dose group in comparison with the same group of the solvent control. Brood II of the low dose group, 0.025 mg/mL, produced one cluster event of 2 lethals which, since it occurred in a post-meiotically treated sperm cell stage , was determined to be pre-existing and was counted as one event. There were no clusters found in the		

			high dose. Dazomet was inactive in the production of sex-linked recessive lethals in Drosophila melanogaster under the test conditions of this assay.		
***In vivo* Mammalian Alkaline Comet Assay (OECD TG 489 TG, 2016)** **Reliability: 1** **GLP** **Key study**	Dazomet Purity : 96.6 % Vehicle : Corn oil	Sprague-Dawley Rat Female <u>Duration of treatment / exposure:</u> 3 days <u>Frequency of treatment:</u> 1/day <u>No. of animals per sex per dose:</u> 5 <u>Dosing:</u> 0, 31.75, 62.5, 125, 250, 150 mg/kg bw/day	Micronucleus assay: Dazomet is neither clastogenic nor aneugenic in the bone marrow of female rats. Mean: 0 mg/kg bw/d: 55.6 % ± 3.1 PCE (polychromatic erythrocytes) and 0.045 % ± 0.037 MN (Micronuclei)-PCE 31.75 mg/kg bw/d: 56.4 % ± 2.1 PCE and 0.080 % ± 0.065 MN-PCE 62.5 mg/kg bw/d: 56.8 % ± 1.8 PCE and 0.070 % ± 0.021 MN-PCE 125 mg/kg bw/d: 53.6 % ± 3.2 PCE and 0.080 % ± 0.033 MN-PCE 250 mg/kg bw/d: 55.3 % ± 2.5 PCE and 0.088 % ± 0.048 MN-PCE Even though bone marrow cytotoxicity was not apparent (no reduction in % PCE) within the micronucleus		[redacted] (2020) IUCLID: A8.5.5-008

			study, the exposure to the bone marrow was proven since the main metabolite of Dazomet (M5) was successfully detected in plasma samples collected from the treated and untreated animals. Thus, the negative outcome of the study is valid. Comet assay: Dazomet is not mutagenic in the Comet assay performed in liver and stomach of female rats. Mean: 0 mg/kg bw/d: 2.92¨% ± 0.54 PCE (polychromatic erythrocytes) and 9.81 % ± 3.36 MN-PCE (Number of micronucleated polychromatic erythrocytes) 31.75 mg/kg bw/d: 3.08 % ± 2.10 PCE and 8.56 ± 3.15 MN-PCE 62.5 mg/kg bw/d: 2.95 % ± 1.49 PCE and 9.31 ± 3.06 MN-PCE 125 mg/kg bw/d: 4.27 % ± 1.22 PCE and 10.13 % ± 3.30 MN-PCE 250 mg/kg bw/d: 2.54 % ± 0.83 PCE and 8.00 % ± 1.22 MN-PCE		

			As the specific Dazomet metabolite (M5) was identified in plasma and liver tissue, the exposure to the target organ liver was verified. The exposure of the stomach tissue as the second target tissue is proven in that the stomach as the organ of first contact is always exposed to the test substance after oral administration. Thus, the negative outcome of the study is valid.		
***In vivo* Mammalian Alkaline Comet Assay (OECD TG 489, 2016)** **Reliability:1** **GLP** **Key study**	MITC Purity : 98.1 % Vehicle: Corn oil	Crj: CD(SD) Rat Male Frequency of treatment: All animals used for the test were orally administered twice at 21 hours interval <u>No. of animals per sex per dose:</u> Negative control (Corn oil): 5 Positive control (EMS): 3 MITC group: 5 (20 and 40 mg/kg dose), 6 (60 mg/kg	<u>*Comet assay analysis:*</u> Positive control (200 mg/kg): The mean value of DNA tail (%) for liver and stomach were respectively equal to 10.07 ± 0.58 and 29.06 ± 4.14 Negative control: The mean value of DNA tail (%) for liver and stomach were respectively equal to 0.72 ± 0.16 and 2.63 ± 1.17 MITC: The mean value of DNA tail (%) for liver and stomach were respectively equal to:	A decrease in spontaneous motor activity and piloerection were observed in the 60 mg/kg group. No abnormalities were found in any of the other groups.	[redacted] (2020) IUCLID: A8.5.5-009

		dose) 20, 40 and 60 mg/kg diet	20 mg/kg bw: 0.82 ± 0.21 and 1.79 ± 0.43 40 mg/kg bw: 0.78 ± 0.11 and 2.25 ± 0.49 60 mg/kg bw: 0.83 ± 0.10 and 1.60 ± 0.20 Regarding liver DNA damage, the range of the group mean % tail DNA in the MITC-treated group was 0.78-0.83 % showing no significant increase when compared with the negative control group in which the group mean % tail DNA was 0.72 %. A statistically significant increase in the group mean % tail DNA was observed in the positive control group treated with EMS in which the group mean % tail DNA was 10.07 %. Regarding hedgehog and liver histopathology, no substantial increase in hedgehog frequency was observed in any of the treatment groups. The range of the mean percentage of hedgehogs in the MITC-treated groups was 0.67 to 1.33 %. The mean percentage of hedgehogs in the negative and the positive		

			control group was 0.80% and 1.11 %, respectively. In the 60 mg/kg group, there were no statistically significant changes in the incidences of histopathological findings, but an increasing tendency in the incidence of centrilobular vacuolation of hepatocytes was observed. Focal necrosis of hepatocytes was observed in one animal. Regarding DNA damage in stomach, the range of the group mean % tail DNA in the MITC-treated group was 1.60–2.25 %, showing no significant increase when compared with the negative control group in which the group mean % tail DNA was 2.63 %. At the highest dose of 60 mg/kg, the % tail DNA showed the minimum value of 1.60 %. This non-significant and slight decrease in DNA migration had been observed at the same dose in the preliminary comet assay). A statistically significant increase in the group mean % tail DNA was observed in the positive control group treated with EMS in which		

			the group mean % tail DNA was 29.06 %. Regarding hedgehog and liver histopathology, no substantial increase in hedgehog frequency was observed in any of the treatment groups. The range of the mean percentage of hedgehogs in the MITC-treated groups was 3.87 to 6.80%. The mean percentage of hedgehogs in the negative and the positive control group was 4.13 % and 16.89 %, respectively. In the 60 mg/kg group, there were no statistically significant changes in the incidences of histopathological findings, but increasing tendencies in the incidences of edema in the submucosa and erosion/ulcer were observed. These findings implied that non-significant and slight decrease in DNA migration at this dose might be induced by cytotoxicity It was concluded that MITC did not induce DNA damage in the liver or stomach in rats under the conditions used in this study.		

Table A-82: Summary table of human data on genotoxicity

No human data is available.

A.3.8.2.1 Short summary and overall relevance of the provided information on germ cell mutagenicity

In vitro genotoxicity of Dazomet

The reverse bacterial gene mutation assays ([redacted] 1980a, 8.5.4-001; [redacted] 1987, 8.5.4-003; [redacted], A 2008, 8.5.4-014;), conducted with Dazomet were negative, both in the absence as well as in the presence of rat exogeneous metabolization.

The forward mammalian gene-mutation assays provided inconsistent evidence of genotoxicity. In the HPRT assays [redacted] 1989, 8.5.4-005; [redacted] 1986, 8.5.4-011), increases in mutation frequency occurred in the replicate assays in the absence of S9, although there was no consistent dose-dependency. The increases at the toxic dose could be substance-related. In the presence of S9, one positive result was observed, but dose-dependency was lacking and the finding was not confirmed in the other assay, and thus considered equivocal. In the TK assay ([redacted] 1980b, 8.5.4-007), 2/3 replicate tests were equivocally positive in the absence of S9. Although there was no dose-response, the findings were observed in two independent assays. In the presence of S9, one test was negative, while one replicate test was positive in conditions of extreme toxicity (5 % relative total growth).

The overall weight of evidence for the *in vitro* mammalian gene-mutation assays would point towards equivocal mutagenicity in the absence of S9, while the response was negative in the presence of S9.

The potential to induce chromosomal aberrations was tested in mouse lymphoma cells ([redacted] 1979, 8.5.4-008) and in human lymphocytes ([redacted]1989, 8.5.4-005; [redacted] 1986, 8.5.4-011). Clastogenicity was demonstrated in the two replicate experiments in mouse lymphoma cells, in the absence of S9, but not in the presence of S9. In an earlier study on mouse lymphoma cells, equivocal increases of chromosome aberration incidence were observed ±S9 (dose-dependency was not demonstrated, but the findings could not be ignored as rare rearrangements were observed). It was unfortunate that in the TK gene-mutation assay ([redacted] 1980b, 8.5.4-007), no colony sizing had been performed, to ascertain if normal growing cells (large size, gene mutation) or slow-growing cells (small size, chromosome aberration, either structural or numerical were involved. As the bacterial mutation tests were negative, it was plausible that the colonies were originating from a clastogenic or aneugenic event.

In human lymphocytes, no chromosomal structural damage was observed, neither in the absence nor in the presence of S9. In this study, contrary to that in the assay with mouse lymphoma cells, a discrimination between gaps and breaks was made, and only the gap incidence was increased. As gaps are considered of low genotoxicological relevance, the test is considered negative in this respect.

In vivo genotoxicity of Dazomet

The *in vivo* assays in somatic cells provided for Annex II inclusion failed the applicant's reliability check. This concerns all GLP studies, non-GLP studies and publications.

Since *in vitro* studies gave no clearly negative results, and to address the EU requirements for mutagenicity, clastogenicity and aneuploidy, a GLP compliant Comet and bone marrow

micronucleus test was performed. The results are discussed below under “new information”.

For the germ cell studies ([redacted]1985, A8.5.5-006) , a higher-tier genotoxicity study of clastogenicity in sperm cell of the Chinese Hamster was negative.

In conclusion, there was no potential observed for Dazomet to induce gene mutations in bacterial cells. The *in vitro* genotoxicity studies on Dazomet in mammalian cells did not exclude a potential for DNA damage in the absence of S9. However, in conditions where Dazomet (or its metabolites) were detoxified by the phase II enzymes (*in vitro* and *in vivo*), the evidence of DNA-damage was merely equivocal or negative. No chromosome damage was observed in germ cells.

New information

Since some *in vitro* studies gave positive or equivocal results for mammalian gene mutation and clastogenicity, *in vivo* testing was generally triggered. However, the recommended *in vivo* follow up studies failed the reliability check and the validity check as they do not comply with the current European testing requirements for both endpoints. As a consequence, to address the occurred data gaps for mutagenicity and clastogenicity, a Comet assay (OECD TG 489) with integrated micronucleus determination (OECD TG 474) in SD rats was performed according to the latest test guidelines.

According to the EFSA Scientific Opinion[13], evidence of bone marrow exposure is needed to conclude that a substance is not genotoxic based on a negative mammalian erythrocyte MN test. The same is true for the Comet assay, where the exposure of the test substance to the investigated tissues should be demonstrated (as stated in OECD TG 489). There is a scientific debate ongoing, and meanwhile published during the 7th International workshop on genotoxicity testing[14], that bone marrow cytotoxicity, as measured by a decrease in immature erythrocytes compared to total erythrocytes (% PCE), occurred only at 30 % of the chemicals tested whereas 70 % did not show any bone marrow toxicity as seen by %PCE. It was concluded that bone marrow toxicity occurs only in a minority of cases.
To be on the safe side, it was therefore decided to include blood analytics of a specific Dazomet metabolite (M5 = N-acetylcystein-conjugate of MITC) to demonstrate that the active substance was sufficiently absorbed after oral administration thus being systemically available since it was concluded by EFSA that *systemic bioavailability of a test substance can be considered as a line of evidence of bone marrow exposure*. Additionally, the concentration of the Dazomet metabolite M5 in liver tissue was measured to demonstrate target tissue exposure which is mandatory for the validity of the Comet assay.

Both tests gave clear negative results: under the conditions used in the micronucleus assay, no increase in the frequency of MN-PCE was observed for female rats administered Dazomet, and in the Comet assay, there were no statistically significant changes in % tail DNA measured in either the liver or stomach of female rats at any dose level.

Since there were, however, no clear indications of bone marrow toxicity (decrease in % PCE),

[13] EFSA Scientific Committee, [redacted] Scientific Opinion on the clarification of some aspects related to genotoxicity assessment. EFSA Journal 2017;15(12):5113, 25 pp. https://doi.org/10.2903/j.efsa.2017.5113

[14] [redacted] (2019) *In vivo* genotoxicity testing strategies: Report from the [redacted] Mutation Research 847:403035

and in line with the EFSA Scientific Opinion, the following lines of evidence for systemic bioavailability were considered:

Test substance (and/or metabolites) detected in the bone marrow in a toxicokinetic study
In distribution and metabolism studies with ^{14}C-Dazomet (please refer to A.3.1. Toxicokinetic), radioactivity was detected in bone marrow of SD rats.

Systemic toxicity observed in the bone marrow micronucleus test
Within the newly initiated MN study with Dazomet ([redacted]., 2020, A8.5.5-008), the rats showed several treatment-related clinical signs indicating systemic toxicity: lethargy, uncoordinated movement, decreased movement and slight head shaking.

Systemic toxicity observed in toxicity studies
Clinical signs indicating systemic toxicity have been found across all available oral and inhalation, single or repeated dose toxicity studies with Dazomet (e.g., apathy, staggering, trembling, shaking, aggressiveness, uncoordinated movements in swimming tests)

Test substance (and/or metabolites) detected systemically in a toxicokinetic study
In distribution and metabolism studies with ^{14}C-Dazomet (please refer to A.3.1. Toxicokinetic), radioactivity was detected in liver and plasma, and the main portion of radioactivity was excreted via urine.

Test substance detected systemically in a specific blood/plasma analysis.
In connection with the newly initiated MN study with Dazomet ([redacted], 2020, A8.5.5-008), the concentration of a metabolite specific for Dazomet (M5 = N-acetylcysteine conjugate) was determined and detected in plasma and liver of SD rats.

Furthermore, a bone marrow micronucleus assay was performed with 14-C-MITC ([redacted] A8.5.5-009) which is the main metabolite of Dazomet and which is known to have similar biokinetic properties as Dazomet after oral administration (see A.3.1. Toxicokinetic). It was clearly shown that the radiolabelled test substance has reached the bone marrow without concurrent induction of bone marrow cytotoxicity (decrease % PCE).

Therefore, from the given evidence it can be judged that Dazomet was sufficiently absorbed after oral administration to SD rats in the *in vivo* micronucleus / Comet study and that Dazomet or its metabolite reached and exposed the bone marrow.

Thus, there is sufficient evidence of bone marrow exposure to conclude on the validity of the negative outcome of this study.

The same is true for the Comet assay. As the specific Dazomet metabolite (M5) was identified in plasma and liver tissue, the exposure to the target organ liver was verified. The exposure of the stomach tissue as the second target tissue is proven in that the stomach as the organ of first contact is always exposed to the test substance after oral administration.

Both, the Comet assay and the micronucleus assay have been considered as valid by an independent toxicological expert ([redacted] 2020a, A8.5.5-008).

Photomutagenicity

The Ultraviolet/visible molar extinction/absorption coefficient of Dazomet and its major metabolites is higher than 1000 L × mol^{-1}× cm^{-1}. A new study was performed to investigate the photomutagenic potential of Dazomet. Since there is to date no international agreed and validated test guideline available, the study was performed in compliance with the current OECD TG 471, Bacterial Reverse Mutation Test with modifications for photochemical genotoxicity testing. The test item was exposed to UV-irradiation in the presence of the tester strains, and evaluated up to the limit of toxicity. Under the given conditions of a valid test, Dazomet was not photo-mutagenic.µ

***In vitro* and *in vivo* genotoxicity of MITC**

In human lymphocytes, no structural chromosome aberrations were detected when treated with MITC up to cytotoxic doses in the presence or absence of metabolic activation. In a dose-range study, the presence of endoreduplication was demonstrated at high doses, which were not tested in the main assay because of this reason.

The remaining studies provided for Annex II inclusion, both *in vitro* and *in vivo*, did not pass the reliability check against the current OECD test guidelines, because they utilized a test system which is meanwhile regarded to be of no regulatory or scientific relevance or were literature publications with substantial study and/or reporting deficiencies.

To address the European requirements for genotoxicity testing, a complete data package of *in vitro* studies covering mutagenicity in bacteria and mammalian cells, clastogenicity and aneuploidy is provided for the renewal application.

As the *in vitro* tests in mammalian cells gave positive results for mutagenicity and chromosomal damage, and no acceptable *in vivo* follow up test was available, a GLP compliant Comet assay and a bone marrow micronucleus test were performed in rats. The results are discussed below under “new information”.

New information

In vitro

The available *in vitro* bacterial reverse mutation test from 1986 deviated significantly from the current OECD TG 471 and triggered the performance of a new test meeting all validity criteria. This also applied to the mammalian chromosome aberration assay from 1987, which meanwhile can be regarded as supporting information only due to significant deviations from the current test guideline. In addition, only the consequences of clastogenic genotoxicity mechanisms can be detected with this kind of assay whereas the detection of aneuploidy was not covered. To address both shortcomings, an *in vitro* Mammalian Cell Micronucleus Test (OECD TG 487) was performed to detect the potential of MITC to induce structural and/or numerical chromosome aberrations.

Considering the European requirements of genotoxicity testing, the mutagenic potential should also be determined in mammalian cells. Within the Annex I inclusion genotoxicity data package there was no adequate guideline conform study available. There was a comprehensive open literature study, which, however showed significant limitations.

Therefore, the data requirement of mammalian mutagenicity had to be newly addressed.

In total, for the renewal application of Dazomet a bacterial reverse mutation test (OECD TG 471), an *in vitro* mammalian cell micronucleus test (OECD TG 487) and an *in vitro* mammalian cell gene mutation test (OECD TG 490) have been performed to investigate the genotoxic potential of MITC *in vitro*.

The bacterial reverse mutation test was negative both with and without S9 enzymatic activating system.

In the *in vitro* micronucleus test, at a non-toxic concentration, incubation with 0.59 µg/mL MITC led to an increase in the percentage of micro-nucleated cells (MN = 2.03 %) and hypodiploid cells (HD = 1.97 %) which were greater than the tolerance interval of the historical negative controls (0.69 for %MN and 0.22 for %HD). In addition, an increase in %HD (0.25 %) that was greater than the tolerance interval of the negative controls was observed at 0.39 µg/mL MITC. Although these increases were not significant when evaluated using the z' statistic, the increases in %MN and %HD were determined to be dose-related ($p < 0.01$). The results for MITC in this study met two of the OECD criteria for a positive response, i.e., the increases were concentration-related when evaluated with an appropriate trend test, and the results were outside of the normal characteristic distribution of the historical negative control data. However, the third criteria for a positive response, i.e., at least one of the test concentrations exhibits a statistically significant increase (using the z' statistic) compared with the concurrent negative control, was not met. Therefore, the data were evaluated further by the Study Director to establish biological relevance. Applying the more stringent 3-fold rule statistic (historically used by pharmaceutical industry), both, the %MN and the %HD induced by MITC at a non-toxic dose of 0.59 µg/mL were 4.3 and 11-fold greater, respectively, than the concurrent negative control. Therefore, in accordance with the 3-fold rule, MITC was evaluated formally as a genotoxin in the *in vitro* micronucleus test.

In the *in vitro* mammalian cell gene mutation assay, at an almost cytotoxic concentration (relative total growth (RTG) = 16 %), 2.5 µg/mL MITC induced an increase in mutant frequency (IMF) over the negative control (i.e., 147) which exceeded the GEF of 126 recommended by the OECD. This increase was evaluated and found to be statistically significant ($p = 0.00064$) for a dose response. In accordance with OECD guidelines, care should be taken when interpreting positive results only found between 20 and 10% RTG. Therefore, MITC was capable of inducing mutations in the mammalian cell gene mutation test in cultured L5178Y TK+/- 3.7.2C cells when tested up to the limit of toxicity in the presence of a metabolic activation system (+S9). In accordance with the OECD guidelines, because the positive response was found between 20 and 10% RTG, the results should be interpreted with caution.

In vivo

Since valid *in vitro* tests for chromosome damage and mutagenicity in mammalian cells gave both positive results, adequate *in vivo* follow-up testing was triggered. In accordance with the European requirements of genotoxicity testing, an *in vivo* Comet assay (OECD TG 489) was initiated to address the mutagenicity issue occurred under *in vitro* conditions.

With respect to the chromosome damage, an *in vivo* erythrocyte micronucleus test in the

mouse was available showing no effect on the incidence of micro-nucleated polychromatic erythrocytes. However, the study could meanwhile only be considered as not reliable due to several substantial deviations from the current OECD guidance. Therefore, a new *in vivo* micronucleus test in rats (OECD TG 474) was initiated. As the exposure of the bone marrow is still under debate (for details please refer to the *in vivo* genotoxicity assessment of Dazomet), radiolabelled test substance [14C]MITC was used in the medium dose group to verify the exposure to the bone marrow in the absence of a significant reduction of the %PCE, indicating bone marrow toxicity.

Both tests gave clear negative results: under the conditions used in the micronucleus assay, no increase in the frequency of MN-PCE was observed for rats administered Dazomet, and in the Comet assay, there were no statistically significant changes in % tail DNA measured in either the liver or stomach of female rats at any dose level. Both assays met the acceptability criteria for a valid test.

For verification of the negative results, tissue exposure was demonstrated for the Comet assay and the micronucleus assay:
For the Comet assay, a decrease in spontaneous motor activity was observed which is considered direct evidence of systemic bioavailability, and consequently, indirect evidence of target tissue exposure. In addition, [14C]MITC was detected in bone marrow in the micronucleus test conducted by the same animal species, strain, and administration route as this Comet assay. The exposure of the stomach tissue as the second target tissue is proven in that the stomach as the organ of first contact is always exposed to the test substance after oral administration.

For the micronucleus assay, as stated above, radiolabelled test substance was administered to the one dose group to verify MITC exposure to the bone marrow. It was clearly demonstrated that orally administered MITC was absorbed into blood system and distributed into bone marrow, and this result provides clear evidence that bone marrow cells of the rats in this micronucleus test were exposed to MITC after oral administration.

A.3.8.2.2 Comparison with the CLP criteria

No information is available on the genotoxicity of Dazomet in humans. Therefore, it does not meet the criteria for classification in category 1A.

No information is available on *in vivo* heritable germ cell mutagenicity in mammals. There are negative results from *in vivo* somatic cell mutation assays (Micronucleus and Comet) and a negative spermatogonial chromosome aberration test. Thus, the criteria for classification in category 1 B are not met.

Classification for germ cell mutagenicity category 2 may be considered on the basis of positive mammalian somatic cell mutagenicity tests *in vivo*, other positive *in vivo* somatic cell genotoxicity tests that are supported by positive results from *in vitro* mutagenicity assays or positive *in vitro* mammalian mutagenicity assays for substances that also show chemical structure activity relationship to known germ cell mutagens. Since both *in vivo* mammalian somatic cell mutation assays (Micronucleus and Comet) gave clear negative results the criteria for classification in category 2 are not met.

A.3.8.2.3 Conclusion on classification and labelling for germ cell mutagenicity

Not classified - Conclusive but not sufficient data for classification

A.3.8.2.4 Overall conclusion on genotoxicity related to risk assessment

Not applicable for the CLH report.

A.3.9 Carcinogenicity

A full set of carcinogenicity studies for the active substance Dazomet and its active metabolite MITC were provided for the Annex II inclusion and thus peer reviewed by European competent authorities and eCA Belgium.

During the last years, most of the guidelines for carcinogenicity testing have been reviewed and adapted to the state of science, a re-evaluation of existing studies was conducted to check for deviations which are no longer compatible with the current evaluation criteria.

Dazomet CAR Section 2.4.1.1. (Belgium, March 2010):

Active substance Dazomet
Carcinogenicity studies were conducted in rats and mice. In female rats, at the highest dose, liver toxicity and an increased incidence of mixed cell and basophilic foci in the liver were seen in the carcinogenicity study. The high dose males showed an increased incidence and severity of diffuse hepatocellular fat deposition and hepatocellular vacuolisation in the liver. Confirming findings were seen in a chronic toxicity study. In mice, the target organ was also the liver, with increased liver weights and fat deposit as well as an increased incidence of basophilic foci being observed at the highest dose. In high dose females, there was a (non-significant) increase in adenomas. This tumorigenic potential is not considered relevant to humans as it is only found in a sensitive mouse strain and at very high dose levels. In conclusion, Dazomet was considered not carcinogenic.

Degradation product/metabolite MITC
Considering carcinogenicity, only summarized information was made available. The studies were generally performed before the introduction of GLP or testing guidelines and are often limited in the scope of the investigations. Consequently, validation of these studies is not possible and this information should be regarded as supportive evidence only. According to these studies MITC was found not carcinogenic in rats and mice.

New information:

No new data was submitted for Dazomet or MITC with respect to carcinogenicity. Nor have any new studies been found during the open literature search that would question the results of the existing GLP studies. Even though the submitted studies no longer fully meet the standard of the current test guidelines, they do not deviate in such an extent that would justify the performance of new vertebrate tests. Thus, the evaluation in the Dazomet Assessment Report (Belgium, 2010) remains valid.

Table A-83: Summary table of carcinogenicity studies in animals

Method, Duration of study, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	NOAEL, LOAEL	Results (Please indicate any results that might suggest carcinogenic effects, as well as other toxic effects, for all dose levels)	Remarks (e.g. major deviations)	Reference
Oral feed **EPA OPP 83-2 (OECD TG 452)** **Key study** **Reliability: 1**	Wistar rat Males/ Females 50/sex/ group	Dazomet Purity: 98.2 % Vehicle: mixed with food 0, 5, 20, 80 ppm 24 months	The **NOAEL** in this study was 20 ppm, equivalent to **0.9 mg/kg bw/d** in male and female rats	**Gross-pathological** examinations as well as organ weight determinations did not show test substance related effects at any dose levels. Test substance related effects were limited to **following histopathological changes** in the liver of the high dose animals: **Males**, slightly increased incidence/severity of diffuse hepatocellular fat deposition and hepatocellular **Females**, slightly increased incidence of mixed cell and basophilic	-	[redacted]. (1989a, 1989b), [redacted] (1989), (Pathology report) IUCLID: A8.11-001

				foci in the liver and of combined incidence of all altered liver cell foci There was **no test substance related increase in the incidence of any neoplasia** in any group		
Oral feed **OECD TG 451** **Key study** **Reliability: 1**	B6C3F1 mouse Males/Females At interim sacrifice: Satellite groups: 10 mice per sex and per group At terminal sacrifice: Main test groups: 50 mice per sex and per group	Dazomet Purity: 98.2 % Vehicle: mixed with food 0, 20, 80, 320 ppm Corresponding to: 4, 16 or 68 mg/kg bw/day (male) and 6, 22 or 93 mg/kg bw/day (female) 78 weeks	**Toxicity NOAEL = 20 ppm = 4 mg/kg bw/day** based on increased liver weight, basophilic liver cell foci, hepatocyte lipidosis, liver adenoma, urinary bladder lipofuscin deposits, spleen hemosiderosis and ovary cysts at 80 ppm **Carcinogenicity NOAEL = 80 ppm = 16 mg/kg bw/day** based on increased liver	Gross-pathological examinations revealed following changes in the liver: increased numbers of animals with focal discoloration, increased number of animals bearing liver masses, increased absolute/ relative liver weights at 320 ppm, increased absolute liver in 80 ppm females only. Histopathology revealed the following **Non neoplastic changes:** **80 ppm:** increased centrilobular lipid deposition in the liver of males, increased incidence of haemosiderin deposition in the spleen in	-	[redacted]. (1989c), [redacted] (1990, Amendment), [redacted](1989, Amended Pathology report), [redacted] (1989, Pathology report including photo documentation dated 15 Sep 1988) IUCLID: A8.11-002

			cell adenoma in females at 320 ppm No carcinogenic potential towards the mouse	males **320 ppm:** increased centrilobular lipid deposition in the liver in males and females, increased incidence of haemosiderin deposition in the spleen in males and females, increased extramedullary haematopoiesis in the spleen in males and females, increased incidence of basophilic foci in females		
Drinking water **No guideline specified** **Supportive study** **Reliability: 4**	ICR:JCR mice Males/Females	MITC Purity: 20 % Vehicle: drinking water 0, 5, 20, 80, 200 ppm; Daily over 106 weeks	No carcinogenic effects	At 80 and 200 ppm, a reduced treatment-related in body weight gain was reported for both males and females	-	[redacted] (1990) IUCLID: A8.11-003
Drinking water **No guideline specified** **Supportive study** **Reliability: 4**	CD-1 rats, Males/Females	MITC Purity: 20 % Vehicle: drinking water 0, 2, 10, 50 ppm; Daily over 104 weeks	No carcinogenic effects	Male rats given 50 ppm MITC had a reduced body weight gain compared to controls throughout the study.	-	[redacted] (1990) IUCLID: A8.11-004

Table A-84: Summary table of human carcinogenicity data

No human data is available.

Table A-85: Summary table of other relevant studies for carcinogenicity

Type of data / report, Reliability, Key / supportive study	Test substance (including purity), Vehicle	Relevant information about the study	Main effects, Observations	Reference
Morphological transformation of BALB / 3T3 cells. **In compliance with Test method B.21 of directive 88 / 302 / EEC** **GLP** **Supportive study** **Reliability: 1**	Dazomet Purity: not reported 10 % solution in water, (solved in DMSO 1 %) Exposure concentration/dose: Epicutanous patch-test, conc. 1 % by weight on dried cotton layer and 100 ppm in aq.	Sex: Male and female Known Diseases : No disease reported. Number of persons : 100 volunteers each. Overall time period of exposure: 5 days contact, 21 days induction and 2 days challenge.	Clinical Signs: No primary irritation, but skin reaction at challenge (conc. 1 %); at 100 ppm no irritation or skin reaction. Results of examinations: Positive patch-test reactions in 19 of 200 subjects at conc. 1 % by weight). Effectivity of medical treatment: Not stated. Outcome: Not stated.	[redacted] (1980) IUCLID: A8.11-005

A.3.9.1 Short summary and overall relevance of the provided information on carcinogenicity

In a carcinogenicity study in rats ([redacted]. 1989b; [redacted] 1989a; [redacted] 1989b, A8.11-001) the only test substance related effects were noted during the histopathological examination of the liver. In high dose (80 ppm) males a slightly increased incidence and severity of diffuse hepatocellular fat deposition and hepatocellular vacuolization were observed. In high dose females there was a slightly increased incidence of mixed cell and basophilic foci in the liver. Also the combined incidence of all altered liver cell foci was slightly increased in high dose females. The NOAEL in this study was 20 ppm (0.9 mg/kg bw/d). Dazomet was not carcinogenic in rats.

In a carcinogenicity study in mice ([redacted]. 1989c, [redacted] 1990, A8.11-002), Dazomet at the high dose level (320 ppm) induced toxicity consisting of body weight reduction in males, and an apparent anaemic effect indicated by increased haemosiderin deposits in the spleen and extramedullary haematopoiesis. The target organ was the liver, in which toxic (increased liver weights and fat deposit) as well as proliferative changes were observed. The proliferative effect on the liver was indicated by an increased incidence of basophilic foci. The incidence of hepatocellular neoplasm's is the final result of an independent peer review group and consultation with the original pathologist. The slight increase in adenomas in 320 ppm females was statistically not significant in Fischer's Exact test. It did show a positive trend with the Cochran Armitage test. Together with the increased incidence of basophilic foci in 320 ppm females, the slight increase of adenomas in 320 ppm females suggest a proliferative effect on the liver. As there were no carcinomas and there was no liver tumor related increased mortality this effect is not considered as an indication for a carcinogenic potential of Dazomet. The question on the potential tumorigenic potential of Dazomet in mice is thus confined to the biological significance of an increase of liver adenoma incidence of 6 % in controls to 14 % at the high dose level in females.

The NOAEL in this study was 20 ppm, equivalent to 4 mg/kg bw/d in males and 6 mg/kg bw/d in females. Dazomet was not carcinogenic in mice.

While no indication for a true carcinogenic effect of Dazomet on female mouse liver was observed it should be noted that the test substance was shown to be clearly hepatotoxic to all species tested in long-term studies (rats, dogs and mice). Especially in mice, the administration of high dose levels of Dazomet resulted in a statistically significant increase in absolute and relative liver weight. Moreover, only at this high dose level an increase in the number of basophilic foci was seen. These phenotypic altered cells are thought to represent a sub-population of cells, which have a slight growth advantage as opposed to their neighbors possible due to increased resistance against the hepato-toxic chemical. The increase in relative and absolute liver weight as well as the increase in the number of basophilic foci indicate that Dazomet (as an apparent hepatotoxic chemical) induces a proliferative response in female mouse liver. It is well known that the induction of a proliferative stimulus on the liver of B6C3F1 mice can result in the induction of benign liver tumors.

The 28 days repeat dose ([redacted], 1987, A8.9.5.2-002) administration of MITC to Wistar rats shown *focal squamous metaplasia in the area of the respiratory epithelium in 3 male and all female animals treated with 100 mg/m³.* This pre-neoplastic change of the respiratory epithelium observed in response to toxic injury induced by the corrosivity of MITC. Therefore

we are of the opinion that this is a noncancerous change in the cells.

The long-term administration of MITC to CD rats at a dose of 50 ppm via the drinking water resulted in a reduced body weight gain (males) as well as a reduction in drinking water consumption ([redacted]1990). The NOAEL was 10 ppm. In a carcinogenicity study with MITC in mice, both male and female animals of the 80 ppm and 200 ppm treatment groups had a reduced body weight gain compared to controls ([redacted]1990). The NOAEL was 20 ppm. MITC was not carcinogenic in rats and mice.

In a morphological transformation assay using BALB/3T3 cells, there was no induction of the number of transformed foci after *in vitro* exposure, demonstrating that dazomet has no transforming activity in BALB/3T3 cells, further supporting the findings from the other carcinogenicity studies that dazomet does not pose a carcinogenicity hazard.

Table A-86: Compilation of some factors that may be taken into consideration in classification and labelling

See text above. No carcinogenic effects were detected for Dazomet. No other data was provided. Regarding MITC no new data was submitted with respect to carcinogenicity. Nor have any new studies been found during the open literature search that would question the results of the existing GLP studies. Even though the submitted studies no longer fully meet the standard of the current test guidelines, they do not deviate in such an extent that would justify the performance of new vertebrate tests. Only Supportive study (no guideline specified) has been submitted by the applicant regarding MITC, these studies showed a reduction of body weight gain as well as a reduction in drinking water consumption compare to controls without carcinogenic effect. A short term repeated dose toxicity showed focal squamous metaplasia in the area of the respiratory epithelium which could be due to a compensatory phenomenon caused by the corrosive effect induced by MITC. We have few *in vivo* studies of bibliographic quality (low reliability). It is difficult to conclude based on the available information.

A.3.9.2 Comparison with the CLP criteria

Substances are classified in Category 1 for carcinogenicity where there is human evidence of a carcinogenic potential of the substance or when there is sufficient evidence from animal studies to demonstrate animal carcinogenicity. Substances are classified in Category 2 where there is some evidence to this effect but is not sufficiently convincing to place the substance in Category 1 based on the strength of evidence.

Since there is no sufficient evidence of Dazomet having carcinogenic potential neither in humans nor in animals (as shown in long-term studies with rats and mice), the criteria for classification are not met, and no classification is warranted.

Regarding MITC no new data was submitted with respect to carcinogenicity. Nor have any new

studies been found during the open literature search that would question the results of the existing GLP studies. Even though the submitted studies no longer fully meet the standard of the current test guidelines, they do not deviate in such an extent that would justify the performance of new vertebrate tests. Only Supportive study (no guideline specified) has been submitted by the applicant regarding MITC, these studies showed a reduction of body weight gain as well as a reduction in drinking water consumption compare to controls without carcinogenic effect. A short term repeated dose toxicity showed focal squamous metaplasia in the area of the respiratory epithelium which could be due to a compensatory phenomenon caused by the corrosive effect induced by MITC.We have few *in vivo* studies of bibliographic quality (low reliability). It is difficult to conclude base on the available information.

A.3.9.3 Conclusion on classification and labelling for carcinogenicity

Since there is no sufficient evidence of Dazomet having carcinogenic potential neither in humans nor in animals (as shown in long-term studies with rats and mice), the criteria for classification are not met, and no classification is warranted.

A.3.9.4 Overall conclusion on carcinogenicity related to risk assessment

Not applicable for the CLH report.

A.3.10 Reproductive toxicity

A full set of reproductive toxicity studies for the active substance Dazomet and its active metabolite MITC were provided for the Annex II inclusion and thus peer reviewed by European competent authorities and eCA Belgium.

During the last years, most of the guidelines for reproductive toxicity testing have been reviewed and adapted to the state of science, a re-evaluation of existing studies was conducted to check for deviations which are no longer compatible with the current evaluation criteria.

Dazomet CAR Section 2.4.1.1. (Belgium, March 2010)

Active substance Dazomet

In a two-generation study in rats the only observations were the liver toxicity and some effects on body weight development in the parental generation. There was no effect seen on reproductive parameters or in the offspring. $NOAEL_{parental}$ = 0.5 mg/kg bw/d; $NOAEL_{offspring}$ = 18 mg/kg bw/d; $NOAEL_{reproduction\ parameters}$ = 18 mg/kg bw/d. In the developmental toxicity studies in the rat foetotoxic effects (increased incidence of runts) were noted at a very slight maternal toxic dose level (characterised by a trend to decreased food consumption, a slight decrease in uterus weight, and corrected bw gain at 10 mg/kg bw/d). Additionally, a more than 10% increase in bilateral and total dilated renal pelvis (foetal- and litter-based) as well as in total hydroureters (litter-based) at all tested doses was observed, although without a dose-response relationship. In the rabbit, foetotoxic effects (decreased foetal weight, increased number of resorptions/post-implantation loss, increased rib/sternebrae variations) were only noted in the presence of marked maternal toxicity (1 fatality, clinical signs), thus indicating that these effects were secondary to maternal toxicity. With the available data it cannot be

excluded that the embryo/foetotoxic effect seen in the rat study are the result of direct embryo/foetal exposure to Dazomet and not the result of maternal toxicity. Consequently, in the absence of further clarifying data it cannot be ruled out that classification is warranted. We want to inform that possible classification as toxic to reproduction Cat. 2 is not excluded by the BE RMS. $NOAEL_{marternal}$ ~ 3 mg/kg bw/d; $NOAEL_{developmental}$ < 3 mg/kg bw/d (↑ number of runts at 10 mg/kg bw/d, ↑ hydroureters and dilated renal pelvis at 3 mg/kg bw/d).

Degradation product/metabolite MITC

Considering fertility, only summarized information was made available. Consequently, validation of these studies is not possible and this information should be regarded as supportive evidence only. There was no effect on reproductive parameters or in the offspring according to the briefly reported two-generation study in rats.

The developmental studies led after oral administration of MITC to the rat to mild foetotoxic effects (increased incidence of runts) but at the next higher (maternal toxic) dose when compared with Dazomet, malformations, both visceral and skeletal, remained unaffected. In the rabbit, MITC showed the same toxicological profile as Dazomet, as the maternal toxicity LOAELs were comparable (10 -15 mg/kg bw/d). In the offspring, MITC did not alter the resorption rate or foetal viability up to and including the top-dose (10 mg/kg bw/d). The treatment with MITC was without effect on the number of malformations in the rabbit. $NOAEL_{maternal}$ = 3 mg/kg bw/d; $NOAEL_{developmental}$ = 10 mg/kg bw/d.

New information

For clarification whether or not an increased incidence of runts within the rat studies with Dazomet and MITC should be considered as an adverse effect, detailed historical control data was provided and newly evaluated ([redacted], 2020b, A8.10.1-002).

A.3.10.1 Sexual function and fertility

Table A-87: Summary table of animal studies on adverse effects on sexual function and fertility

Method, Duration of study, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels, Duration of exposure	NOAELs, LOAELs (e.g. maternal/parental toxicity, effects on sexual function and fertility)			Results (for all dose levels, specify critical effects on sexual function and fertility for parental animals (and offspring if relevant), report e.g. incidences and severity of the effects for all dose levels)	Remarks (e.g. major deviations)	Reference
			Parental	F1	F2			
Two-generation reproductive toxicity **OECD TG 416** **Oral feed** **Key study** **Reliability: 1**	Wistar rats Males/ Females 24/sex/ group	Dazomet Purity 98.2 % Vehicle: mixed with food Duration of exposure before mating: At least 70 days Duration of exposure in generation F0,	NOAEL: 0.5 mg/kg bw/day (5 ppm) LOAEL: 30 ppm (about 3 mg/kg bw/day)	NOAEL: 180 ppm (≥ 18 mg/kg bw/day) LOAEL: 30 ppm (about 3 mg/kg bw/day)	NOAEL: 180 ppm (≥ 18 mg/kg bw/day)	No systemic toxic effects in the offspring at any dose level. No effect on reproductive function	-	[redacted] (1989b) and [redacted] (1989a, (Pathology report) IUCLID: A8.10.2-001

		F1 (males, females) F0 parental generation: At least 70 days premating exposure, continued until sacrifice F1 parental generation: At least 98 days premating exposure, continued until sacrifice 5, 30, 180 ppm						
Two-generation reproductive toxicity **Oral feed** **Supportive study** **Reliability: no 4**	Sprague Dawley Rat Male/Female	MITC Purity: not reported Vehicle: mixed with food 2, 10, 50 ppm (3, 10, 30 mg/kg bw/d) The F0 generation animals were treated for a 70-day maturation	10 ppm (male) 50 ppm (female)	10 ppm (offspring) 10 ppm (fertility)	10 ppm (offspring)	No adverse effects reported for fertility and reproductive performance of the parents. No adverse effects reported for the viability, growth and development of the offspring. From a	-	[redacted] (1990) IUCLID: A8.10.1-002

		period before mating to produce F1a litters, which were reared to weaning. F1 generation animals were selected from F1a offspring's at weaning. F1 generation animals were treated for 77 days prior to pairing to produce F2a litters, which were also reared to weaning.				toxicological point of view: reduction in body weight gain reported for the males of the F1 generation at 50 ppm MITC.		

Table A-88: Summary table of human data on adverse effects on sexual function and fertility

No human data is available.

Table A-89: Summary table of other relevant studies for sexual function and fertility

No other data is available.

A.3.10.1.1 Short summary and overall relevance of the provided information on adverse effects on sexual function and fertility

Considering the toxicity of Dazomet to fertility, a 2-generation study was conducted by [redacted] (1989b, A8.10.2-001). Within this study, a depression in body weight and body weight gain was reported for the F0/F1 females including the gestation/lactation periods as well as for the F1 males, although, these effects did not always reach statistical significance. Furthermore, various clinical chemical parameters including alanine-aminotransferase activities, serum globulin, albumin concentration and total protein contents were examined and found to be affected in males and females (only high dose and control examined). Gross pathological examination revealed that the relative liver weights were increased in F0 males and both sexes of the F1 parental generation. Histopathology revealed fatty liver change predominantly in males (F0 and F1 parental) and to a much lesser degree in females. At the mid dose group only slightly reduced body weights/body weight gains in F1 males were noted. In addition, fatty liver change predominantly in males (F0 and F1 parental) and to a much lesser degree in females were noted while there were no adverse effects at the low dose. There were no systemic toxic effects in the offspring at any dose level. There was also no effect concerning reproductive function in this study. Thus the following NOAELs were achieved for Dazomet: NOAEL parental animals (males/females): 5 ppm (about 0.5 mg/kg bw/day); NOAEL offspring (males/females): $\geq$ 180 ppm (about 18 mg/kg bw/day); NOAEL fertility parameters:$\geq$ 180 ppm (about 18 mg/kg bw/day).

For MITC a two-generation study has been reported within a publication summarizing information on toxicity testing for pesticide registration in Japan ([redacted] 1990). According to this publication the study was performed at Hazleton laboratories in Europe 1987. Within this reported study parental toxicity in males was noted by a reduced body weight gain at the high dose. The dose related reduction of water consumption was considered to reflect palatability problems of the water/test compound mixture rather than being assigned to a toxic effect. There were no other effects noted in the parental animals. Their fertility and reproductive performance was not impaired by MITC administration. This also holds for the viability, growth and development of the offspring. Thus the following NOAELs were achieved for MITC: NOAEL parental animals (males): 10 ppm; NOAEL parental animals (females): 50 ppm; NOAEL offspring (males/females): 10 ppm; NOAEL fertility parameters:10 ppm.

Please take into consideration only summarized information was made available. Consequently, validation of these studies is not possible and this information should be regarded as supportive evidence only.

A.3.10.1.2 Comparison with the CLP criteria

Substances are classified in Category 1 for reproductive toxicity where there is human evidence of adverse effects on sexual function and/or fertility or when there is evidence from animal studies (and other studies where relevant) to provide a strong assumption that this will be the case. Substances are classified in Category 2 where there is some evidence to this effect but is not sufficiently convincing to place the substance in Category 1. As no human information is available regarding effects on the reproductive system by Dazomet and information from a reliable two-generation study in rats showed that Dazomet has no adverse effects on fertility and reproductive performance of male and female animals, these criteria are not met and no classification is warranted.

A.3.10.1.3 Overall conclusion on sexual function and fertility related to risk assessment

Not applicable for the CLH report.

A.3.10.2 Developmental toxicity

Table A-90: Summary table of animal studies on adverse effects on development

Method, Duration of study, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels	NOAELs, LOAELs (e.g. maternal, teratogenicity, embryotoxicity, offspring, parental, reproductive toxicity)	Results, maternal/parental (e.g. corrected body weight gain, for all dose levels)	Results, developmental (e.g. pup survival, structural abnormalities, altered growth, functional deficiencies, incidences and severity of the effects for all dose levels)	Remarks (e.g. major deviations)	Reference
Gavage **OECD TG 414** **Key study** **Reliability: 1**	Wistar rat 25 females per group	Dazomet Purity≥ 97 % Olive oil 3, 10, 30 mg/kg bw/d Day 6 to 15 post coitum Post exposure period : The test substance was	LO(A)EL maternal toxic effects 10 mg/kg bw/d NO(A)EL maternal toxic effects 3 mg/kg bw/d NO(A)EL embryotoxic effects 3 mg/kg bw/d	Maternal data 30 mg/kg bw/day ↓food consumption ↓body weight (d20) ↓body weight (d8-20) ↓body weight gain (d0 d6) ↓body weight gain (from d6-15) ↓corrected body weight (d20)	**Study performed in 1987:** At 30 mg/kg bw/d: Reduction of food consumption, the mean food consumption for the dams of the 30 mg/kg group was 18.6 g/animal/day (81 % of control) versus 23 g/animal/day (100 %) in controls. Reduction of body weights, body weight gain and	3 mg/kg bw/d: the doses were selected upon the results of a preliminary range-finding study ([redacted] unpublished report 92R0318/8570, 29 Jan 1986). Following concentrations were tested 10 mg/kg	[redacted] (1987a) IUCLID: A8.10.1-001 [redacted](2020b) IUCLID: A8.10.1-002

		administered from day 15 to day 19. The animals were sacrificed on day 20 and foetuses were delivered by caesarean section.	NO(A)EL teratogenic effects > 30 mg/kg bw/d	↓corrected body weight gain (d0-20) ↓uterus weight 10 mg/kg bw/day ↓food consumption ↓uterus weight	corrected body weight gain: The body weight gain for the 30 mg/kg dams was 31.3 g (67 % of control) versus 46.4 g (100 %) for controls. The corrected body weight was also decreased at 30 mg/kg, with a mean value of 50.5 g (76 % of control) versus 66.4 g in controls. At 10 mg/kg bw/d: Reduction of food consumption, in fact, a trend with respect to reduced food consumption was recognizable at the beginning of treatment (reduced to 97 % of control). Slight reduction of the corrected body weight gain, the corrected body weight gain was reduced to 92 % of the control. At 3 mg/kg bw/d: No feed reduction has been observed No body weight	bw/d: the doses were selected upon the results of a preliminary range-finding study ([redacted] unpublished report 92R0318/8570, 29 Jan 1986). Following concentrations were tested 30 mg/kg bw/d: The doses were selected upon the results of a preliminary range-finding study ([redacted] unpublished report 92R0318/8570, 29 Jan 1986). Following concentrations were tested.	

					reduction has been observed Regarding clinical symptom, the 3 doses (3, 10 and 30 mg/kg bw/d) administered didn't lead to any disturbances of the general behavior . Only one animal (No.64) of test group 3 showed a partial alopecia. No mortality has been observed at any dose. Regarding necropsy observations, with the exception of dams Nos. 79 and 98 of test group 4 (30 mg/kg bw/d); which showed a hydrometra and did not become pregnant there were no findings at all in any group. Regarding uterus weight, there were no statistically		

					significant differences between the groups. However, mean uterus weights of the dams of test groups 3 and 4 (10 or 30 mg/kg bw/d) were somewhat lower than that of test groups 1 and 2 (0 or 3 mg/kg bw/d), which might be related to the test substance administration. Regarding reproduction efficiency, the conception rate varied between 80 and 88 %. No substance related and/or statistically significant differences could be noted in the conception rate in the mean number of corpora lutea and total implantations, live fetuses, dead implantations, as well as in the values calculated for the pre and post-implantation losses.		

					The differences evident were considered to be incidental and within the normal range of deviations for animals of this strain and age. Weight of fetuses: The mean fetal weights are slightly lowered in test group 4 which might be attributed to the administration of the test substance. The number of runt/group was increased in group 3 and 4, however, without a clear dose response relationship. A substance related effect cannot be completely excluded. Weight of placentae: The mean placental weights in group 2, 3 and 4 were not influenced by the administration of the tested substance to the dams. The differences observed in comparison to the		

					control are without any dose response relationship and without any biological relevance. Sex distribution of fetuses: The sex distribution in test group 2-4 was comparable with that for the control group, all differences are regarded as spontaneous because of absence of a dose response relationship. Furthermore, 1 fetuses (0.40 % of fetuses examined per litter) in one litter (4.76 % of litters examined) of test group 4 showed a variation (abnormal position of the hindlimb). No further anomalies, variations or retardations could be found in any group. Examination of the organs of the fetuses:		

					Anomalies (according to the method of Barrow and Taylor) were detected in one fetuses (1.59 % of fetuses examined per litter) in one litter (4.76 % of litters examined) of test group 3 (septal defect) and in 2 fetuses (2.38 % of fetuses examined per liter) in one litter (4.76 % of litters examined) of test group 4 (unilateral microphthalmia). The kind of variations revealed were enlarged renal pelvis and hydroureter (uni or bilateral): - control group: 20 fetuses (20.56 % of fetuses examined per litter) in 11 litters (52.38 % of litters examined) - test group 2 in 37 fetuses (44.92 % of fetuses examined per litter) in 16 litters (80.00 % of litters examined) - test group 3 in 27		

					fetuses (29.52 % of fetuses examined per litter) in 14 litters (66.67 % of litters examined) - test group 4 in 28 fetuses (33.81 % of fetuses examined per litter) in 14 litters (66.57 % of litters examined) Examinations of the skeletons of the fetuses: The anomalies detected were related to the vertebral column: - Control group: 5 fetuses (2.64 % of fetuses examined per litter) in 5 litters (23.81 % of litters examined) - Test group 3: 1 fetus (0.65 % of fetuses examined per litter) in 1 litter (4.55 % of litters examined) - Test group 4: 1 fetus (0.53 % of fetuses examined per litter) in 1 litter (4.76 % of litters examined).		

					Variations: The variations exhibited were related to the ribs sternum and vertebral column: - Control group: 59 fetuses (32.91 % of fetuses examined per litter) in 20 litters (95.24 % of litters examined) - Test group 2: 80 fetuses (47.71 % of fetuses examined per litter) in 20 litters (100.00 % of litters examined) - Test group 3: 78 fetuses (42.59 % of fetuses examined per litter) in 21 litters (95.45 % of litters examined) - Test group 4: 78 fetuses (43.07 % of fetuses examined per litter) in 20 litters (95.24 % of litters examined) Retardations: -In nearly all litters of all groups, sign of retardation were found: - Control group: 106 fetuses (58.07 % of		

					fetuses examined per litter) in 21 litters (100.00 % of litters examined) - Test group 2: 101 fetuses (57.47 % of fetuses examined per litter) in 19 litters (95.00 % of litters examined) - Test group 3: 94 fetuses (50.6 % of fetuses examined per litter) in 20 litters (90.91 % of litters examined) - Test group 4: 104 fetuses (60.23 % of fetuses examined per litter) in 21 litters (100.00 % of litters examined) There were no statistically significant anomalies and/or retardations between treated groups and the controls. However, the number of organ, skeletal and overall variations in the group 2 was significantly		

					increased and there was a trend to increased skeletal and overall variations in test group 3 and 4. Due to missing dose-response relationship, the higher number of variations in these groups in comparison to the controls is without any biological relevance and therefore assessed as incidental. The different anomalies recorded for fetuses after cesarean section and at organ examination were only found in single fetuses of test group 3 and 4, but are also present in our historical control data. Therefore, these anomalies and the higher incidence of skeletal anomalies noted for the control fetuses are assessed as spontaneous findings. Number and kind of most retardations		

					detected were found to about the same extent in treated and untreated animals and/or in the historical control data. There was no indication of malformations or any other embryo/fetotoxic effect at any dose level tested. **Study performed in 2020:** Regarding the number of runts , Even though the litter incidences of the mid and the high dose groups (52 and 38 %), are above the average litter incidence given by the historical control data (37 %) the values are within the range of the single historical control study values (16 – 52 %). The same is true for the foetal incidence. The foetal incidence of the mid		

					dose group (4.1 %) exceeds the average foetal incidence of historical control data (3.1 %), but is still located within the historical control range (1.4 – 4.2 %). Also the absolute number of identified runts (7/7/11/8 for 0/3/10/30 mg/kg bw/day lies within the range of the historical control data (4 – 12 per litter). There is no clear dose dependency observable.		
Gavage **OECD TG 414** **Key study** **Reliability:1**	Wistar rat 25 females per group	MITC Purity≥ 97 % Olive oil 3, 10, 30 mg/kg bw/d Day 6 to 15 post coitum Post exposure period : The test substance	LO(A)EL maternal toxic effects 10 mg/kg bw/d NO(A)EL maternal toxic effects 3 mg/kg bw/d NO(A)EL embryotoxic effects 3 mg/kg bw/d NO(A)EL teratogenic	Maternal data 30 mg/kg bw/day ↓food consumption ↓body weight (d20) ↓body weight (d8-20) ↓body weight gain (d0 d6) ↓body weight gain (from d6-15) ↓corrected body weight (d20)	**Study performed in 1987:** Regarding maternal feed consumption, the mean value of the all pregnant dams was markedly reduced in group 4 animals during the treatment period (days 6-15 p.c.), whereas mean feed consumption of dams treated with 3 or 10 mg/kg bw was comparable to	Principles of method if other than guideline For the re-evaluation of both, the dosing studies with Dazomet and MITC and the historical control data studies, cut-off values of foetal body weighs per litter were determined for the < 75 % and	[redacted] (1987b) IUCLID: A8.10.1-003 [redacted] (2020b) IUCLID: A8.10.1-002

		was administered from day 15 to day 19. The animals were sacrificed on day 20 and foetuses were delivered by caesarean section.	effects > 30 mg/kg bw/d	↓corrected body weight gain (d0-20) ↓uterus weight 10 mg/kg bw/day ↓food consumption ↓uterus weight	controls and or the differences observed were without a clear dose-response relationship. After termination of treatment, the animals treated with 30 mg/kg bw/d still showed diminished feed consumption. The reduced feed consumption observed in the animals of test group 4 is considered to be treatment-related. Regarding body weight (and gain), at 30 mg/kg bw/d the body weight of the pregnant animals was significantly reduced both during the treatment (days 10-15 p.c.) and during the post treatment (days 16-20 p.c.) periods. Body weight gains of these animals were also diminished, particularly during days 6-13 p.c. (treatment period). In group 3	the definition of OECD TG 443. Every foetus with a body weight lower than these cut-off values was newly identified as a runt. The < 75 % evaluation was added within this project to confirm the data (number of runts) given in the additional DAR. Indeed, there was one deviation within the historical control data which was of minor relevance. For the newly identified number of runts, litter incidence and foetal incidence have been calculated and compared to the historical	

					significantly reduced body weight gains could be observed from days 8-10 p.c. too. The influence on the body weight and the body weight gain in test group 4 and the marginal influence on the body weight gain on test group 3 are attributable to the administration of the test substance. The mean body weights/body weight gains of all non-pregnant animals are shown below. Due to the small number of non-pregnants, an assessment of these values would be of little avail. The results of the "corrected" body weight gain, too, (body weight on day 20 p.c. minus body weight on day 0 p.c. minus uterus weights) show a significant (significance 99 %), substance-related decrease in the	control incidences.	

					animals of the 10 and 30 mg/kg bw groups. In test group 2 (3 mg/kg bw/d) corrected body weight gain also was slightly, but statistically significantly (significance 95 %) diminished. However, this lowered value was mainly caused by just one dam (No.50), which was declared pregnant, but had only early resorptions according to Salewski. It consequently showed reduced or even negative body weight gains, especially at the end of the treatment and during the post-treatment periods. Therefore, dam No.50 is “outlier” and the slight decrease in corrected body weight gain in tests group 2 is regarded as incidental.		

					Regarding clinical symptoms, the 3 doses (3, 10 and 30 mg/kg bw/d) administered by gavage did not lead to any severe disturbances of the general behaviour in any of the animals of the study. However, towards the end of the treatment period (days 12-15 p.c.) several dams of the 30 mg/kg bw group (Nos. 80, 81, 91, 92, 93, 94, 96, 97 and 99) showed sticky and/or moist fur in the area of the snout before, and at the same location reddish but mainly dry fur after gavage. Water consumption, which was not measured , but roughly estimated during this study, seemed to be increased in individual dams of test group 3 and 5. The aforementioned findings might be connected with the test substance		

					administered. Furthermore, in some animals of the control; and treated groups spontaneous changes such as partial alopecia, could be detected during the study. They are assessed as spontaneous findings. There was no spontaneous death at any dose. Regarding necropsy observations, with the exception of dam No.38 of test group 2, which showed a slight hydrometra, there were no findings at all in any group. Regarding uterus weight, there were no significant and/or dose-related differences between the group. Because mating took place before the treatment started,		

					the extremely high number of non-pregnants in test group 3 is incidental event. The conception rate varied between 100 and 72 %. No substance related and/or statistically significant differences in the conception rate in the mean number of corpora lutea and implantations live fetuses, dead implantations as well as in the values calculated for the pre and post-implantation losses could be noted. The differences evident were considered to be incidental and within the normal range of deviations for animals of this strain and age. Weight of fetuses: The mean fetal weights in group 2, 3 and 4 were not influenced by the		

					administration of the substance to the dams. The differences observed in comparison to the control are without any dose-response relationship and without any biological relevance. However, the number of runts/group (runts: fetuses weighing ≤ 75 % of the mean fetal weight per litter) was increased in group 4, which might be attributed to the test substance administration. Weight of place: The mean placental weights are significantly lowered in test group 4, which is attributed to the administration of the test substance. Sex distribution of		

					fetuses: The sex distribution in test groups 2-4 was comparable with the control group; all differences are regarded as spontaneous because of absence of a dose-response relationship. Macroscopic examination of the fetuses: After caesarean section, 1 fetus (0.34 % fetuses examined per litter) in one litter (4.76 % of litters examined) of test group 2 and 1 1 fetus (0.33 % of fetuses examined per litter) in one litter (4.35 % of litters examined) of test group 4 exhibited variations of the fore- or hind-		

					limbs (pseudoankylosis or abnormal position). No further anomalies, variations or retardations could be found in any group. Examination of the organs of the fetuses: The examination of the organs of the fetuses after evisceration revealed only variations (enlarged (dilated) renal pelvis, uni- or bilateral), which were detected in any group including the control. This very common finding in the rat strain used in this study occurred in: - control group in 51 fetuses (25.12 % of fetuses examined per litter) in 20		

					litters (80.00 % of litters examined) - test group 2 in 23 fetuses (16.14 % of fetuses examined per litter) in 13 litters (61.90 % of litters examined) - test group 3 in 15 fetuses (9.63 % of fetuses examined per litter) in 10 litters (55.56 % of litters examined) - in test group 4 in 36 fetuses (23.34 % of fetuses examined per litter) in 15 litters (65.22 % of litters examined) No anomalies or retardations were detected in any group. In the examination of the organs of the fetuses according to the method of Barrow/Taylor, one anomaly (anophtalmia) was detected in one fetus (1.85 % of fetuses examined per litter) in one litter (5.56 %		

					of litters examined) of test group 3. The kind of variations revealed again were enlarged renal pelvis and hydroureter (uni-bilateral): - control group: 16 fetuses (17.27 % of fetuses examined per litter) in 8 litters (32.00 % of litters examined) - test group 2 in 12 fetuses (18.33 % of fetuses examined per litter) in 9 litters (42.86 % of litters examined) - test group 3 in 12 fetuses (16.11 % of fetuses examined per litter) in 9 litters (50.00 % of litters examined) - test group 4 in 16 fetuses (16.6 % of fetuses examined per litter) in 11 litters (50.00 % of litters examined) No retardations were seen in any group.		

					Anomalies: The anomalies detected were generally related to the sternum and the vertebral column: - Control group 25 fetuses (14.60 % of fetuses examined per litter) in 17 litters (68.00 % of litters examined) - Test group 2: 15 fetuses (11.84 % of fetuses examined per litter) in 11 litters (52.38 % of litters examined) - Test group 3: 11 fetuses (11.37 % of fetuses examined per litter) in 8 litters (44.44 % of litters examined) - Test group 4: 3 fetuses (1.50 % of fetuses examined per litter) in 3 litters (13.04 % of litters examined) Variations: The variations exhibited were related to the ribs,		

					sternum and vertebral column: - Control group: 79 fetuses (40.45 % of fetuses examined per litter) in 22 litters (88.00 % of litters examined) - Test group 2: 91 fetuses (55.30 % of fetuses examined per litter) in 21 litters (100.00 % of litters examined) - Test group 3: 56 fetuses (40.83 % of fetuses examined per litter) in 18 litters (100.00 % of litters examined) - Test group 4: 56 fetuses (31.60 % of fetuses examined per litter) in 21 litters (91.30 % of litters examined) Retardations: In nearly all litters of all groups, sign of retardations were found: - Control group: 141 fetuses (69.01 % of fetuses examined		

					per litter) in 25 litters (100.00 % of litters examined) - Test group 2: 97 fetuses (58.99 % of fetuses examined per litter) in 21 litters (100.00 % of litters examined) - Test group 3: 83 fetuses (58.65 % of fetuses examined per litter) in 18 litters (100.00 % of litters examined) - Test group 4: 128 fetuses (69.15 % of fetuses examined per litter) in 21 litters (91.30 % of litters examined) Abstract of the macroscopic organ and skeletal findings and their assessment: There were no statistically significant differences between the treated groups and the controls with regard to anomalies, variations and/or		

					retardations. The only exception, which is slightly, but significantly, increased number of skeletal variations in the group 2 is without any biological relevance. Number and kind of most other findings noted were found to about the extent in treated and untreated animals and/or in our historical control data. All observable differences between the different groups, including the rather low number of skeletal anomalies and the consequently low number of overall anomalies in the highest dose group (30 mg/kg bw/d) in comparison to the control are therefore assessed as		

					incidental. **Study performed in 2020:** Within the developmental study with MITC, the litter and the foetal incidence of runts were slightly increased above their respective average control values (37 % and 3.1 %) only in the high dose group (39 % and 3.4 % respectively). However, as for Dazomet, these values still fit well to the range of the individual historical control data studies. The number of identified runts (8/7/5/9 for 0/3/10/30 mg/kg bw/day,) lies well within the range of the historical control data (4 – 12 per litter). There is no clear dose dependency observable.		

					There was no indication of malformations or any other embryo-/fetotoxic effect at any dose level tested.		
Gavage **OECD TG 414** **Key study** **Reliability: 1**	Himalayan Rabbit Number of animals per group 15 females per group	Dazomet Purity ≥96.7 % CMC 5, 15, 45 mg/kg bw/d	LO(A)EL maternal toxic effects 45 mg/kg bw/d NO(A)EL maternal toxic effects 15 mg/kg bw/d NO(A)EL embryotoxic effects 15 mg/kg bw/d NO(A)EL teratogenic effects > 45 mg/kg bw	Maternal data 45 mg/kg bw/day ↓body weight decrease (d14-29, slight) ↓body weight gain (d7 29) ↓uterus weight ↑clinical signs 15 mg/kg bw/day ↓body weight decrease (d14-29, slight) ↓body weight gain (d7 29)	Regarding maternal food consumption of the substance treated dams of all 3 test groups (5, 15 or 45 mg/kg bw/d) was, uninfluenced by the test substance administration. All differences between these groups and the control group, including the statistically significantly increased food consumption of test group 2 and 3 (15 and 45 mg/kg bw/day) before the beginning of the treatment period and that of the 5 mg/kg group during and after the treatment period, are assessed as	-	[redacted] (1993) IUCLID: A8.10.1-004

					being of spontaneous nature and without any biological relevance. Mean gravid uterine weights and net maternal body weight change : The results if the corrected body weight gain (terminal body weight on day 29 p.i. minus weight of the uterus before it was opened minus body weight on day 7 p.i.) do not show any dose-response relationship and no differences of biological relevance between the groups. There were no substantial differences concerning the uterus weights between the controls and test groups 1 and 2 (5 and 15 mg/kg bw/d). All these values lie within the range of		

					biological variation; however, the mean gravid uterus of the high dose group (45 mg/kg bw/d) was statistically significantly reduced and reached only about 33 % of the control value. This has to be related to the test substance administration and is in line with the high number of resorptions, the consequently increased post-implantation loss and the lower number of live foetuses/doe in this group. Summary of maternal clinical observations : There were no abnormal clinical findings in any doe of test groups 0, 1 and 2 (0, 5 and 15 mg/kg bw/d) during the whole study period (days 0-29 p.i.). In test group 3 (45 mg/kg bw/d) one		

					doe (n°.52) showed poor general state and piloerection on day 8 p.i. and was found dead on day 9 p.i. Two other does of this test group, which did not have any live fetuses, but early resorptions only, showed blood in bedding (n°.58, day 23 and 25-28 p.i.; n°.59, days 22-28 p.i.). These clinical findings are assessed as being substance-induced. One doe (n°.52) of test group 3 (45 mg/kg bw/d) died intercurrently on day 9 p.i. The intercurrent death of this dam might be directly or indirectly related to the test substance administered. Summary of maternal necropsy : Animal n°.52 of the 45 mg/kg group which died intercurrently showed an acute		

					haemorrhagic tracheitis but no indications for any misgavage. The intercurrent death if this dam might be directly or indirectly related the test substance administered. Moreover, at necropsy one animal each of test groups 0 and 3 (0 and 45 mg/kg bw/d) showed lungs with edema; this findings has to be related to the sacrifice of the animals. Blind ending uterine horns were recorded for one intermediate (n°.36) female; as a consequence of this spontaneous finding this animal did not become pregnant. None if these necropsy findings is related to the test substance administration. The conception rate varied between 80 % (test group 0		

					(control)) and 100 % (test groups 1 and 3 (5 and 45 mg/kg bw/d)). Concerning test groups 1 and 2 (5 and 15 mg/kg bw/d), there were no substance related and/or statistically significant differences in conception rate, in the mean number of corpora lutea and implantation sites or in the values calculated for the pre- and the post-implantation losses, the number of resorptions and be incidental and within the normal range of deviations for animals of this strain and age. In test group 3 (45 mg/kg bw/d), however, the resorption rate was drastically increased, due to the fact, that 5 out of 15 pregnant does of this group (n°49, 51, 54, 58 and 59) had		

					no viable fetuses at all but only early resorptions. As a consequence, the post-implantation loss of the 45 mg/kg group was distinctly increased (68.2 %), which is assessed as a clear substance-induced embryonic effect. Moreover, the mean number of live fetuses/doe was statistically significantly reduced in the 45 mg/kg group. As already stated before the post-implantation loss values (17.6 % or 15.9 % respectively) for test groups 1 and 2 (5 or 15 mg/kg bw/d) are fully in the historical control range (3.0 % - 23.1 %), even if these values are higher (without any statistical significance) that the actual control value (8.3 %). Furthermore, a clear dose response relationship is not given, if the post-		

					implantation loss values for the 5 and 15 mg/kg groups are compared. As a consequence, these values are assessed as being fully in the range of biological variation. Mean placental and fetal body weights : The mean placental weights in the test group 1-3 (5, 15 and 45 mg/kg bw/d) were not influenced by the test substance administration. The differences observed in comparison to the control are without biological relevance and lie within the range of biological variation. The mean fetal weights were not influenced by the oral administration of the test substance. All values are administration of the test substance. All values are within the range of		

					biological variation and not show any dose response relationship. The external examination of the fetuses revealed no malformations in any of the groups. Only one type of external variation (pseudoankylosis) was found and it was seen in one fetus of the 45 mg/kg group and 2 fetuses from 2 litters of the 15 mg/kg group. Pseudoankylosis is a rather common fetal external variation, which can be also found in control fetuses of the rabbit strain used. Therefore, this finding is assessed as being of spontaneous nature and without any relation to dosing. No so-called unclassified observations (like placenta necrobiotic) were recorded for		

					any of the fetuses. The examination of the organs of the fetuses revealed several types of soft tissue malformations in fetuses of all groups. A septal defect was recorded for one low dose and one high dose fetus. Another type of malformation (agenesia of gallbladder) was found in two control, two intermediate and one high dose fetus. All soft tissue malformation before are also present at a low incidence in the historical control data and are considered to be spontaneous in nature. Variations were detected in each group including the control. Aside from a separated origin of carotids, a very common finding in the rabbit strain used, another soft		

					tissue variation (hearth with traces of interventricular foramen/septum membranaceum) was also found quite frequently. Hypoplasia of gallbladder was recorded for 4 controls, 6 low dose, 3 intermediate and one high dose fetus. All soft tissue variations occurred without a clear dose response relationship and/or can be found at a comparable incidence in the historical control data. One se-called unclassified observation (focal liver necrosis) was noted for one control fetus only. Malformations of the fetal skeletons were noted in each group including the control. These malformations were related to the vertebral column		

					(cervical vertebral body/bodies dumbbell-shaped (asymmetrical), sacral vertebrae fused and/or the ribs (bifurcated ribs). Skeletal malformations appeared in one or two fetuses (from one or two litters) of each group. All of the described or very similar skeletal malformations are also present at comparable incidences in the historical control data. Therefore, all skeletal malformations are considered as being of spontaneous nature. The skeletal variations elicited were related to the skull (splitting of skull bones, epactal bone between nasal and frontal bones), the ribs (rudimentary cervical, shortened or absent 12th or		

					accessory 13th ribs), the vertebral column (accessory thoracic vertebra) and the sternum (sternebra of irregular shape, fused or accessory sternebra). Most of the skeletal variations appeared without any relation to dosing and/or without statistically significant differences between the control group and the substance-treated groups. The number of affected fetuses/litter with skeletal variations, affected fetuses/litter with skeletal variations, however, is statistically significantly increased in the 45 mg/kg group and this is predominantly due to the higher number of fetuses/litters with fused sternebra and accessory 13th ribs. For both findings the respective fetal and/or litter		

					incidences are outside the historical control range. Therefore, the increased occurrence of both of these findings is related to the oral administration of the test substance. In all groups signs of retardations (incomplete or missing ossification of skull bones, vertebral column, sternebrae and talus) were found; they occurred at a comparable frequency in the control and the substance treated groups. All differences between the groups concerning fetal skeletal retardations are without any biological relevance; this includes the statistically significantly lower number of high dose fetuses/litters with incompletely ossified thoracic vertebral body/bodies,		

					sternebrae and with total skeletal retardations. Foetal data No indication of malformations or other developmental effects at non-maternal toxic dose levels.		
Gavage **OECD TG 414** **Key study** **Reliability: 1**	Chinchilla Rabbit 64 mated females, 16 females per group	MITC Purity ≥ 98 % Corn oil 1, 3, 10 mg/kg bw/d Day 6 to 18 post insemination	LO(A)EL maternal toxic effects 10 mg/kg bw/d NO(A)EL maternal toxic effects 50mg/kg bw/d NO(A)EL embryotoxic effects ≥10 mg/kg bw/d NO(A)EL teratogenic effects ≥ 10 mg/kg bw/d	Maternal data 10 mg/kg bw/day ↑mortality ↓food consumption (d6 19) ↓body weight (d6 19, slight) ↓body weight gain (d6 19) 5 mg/kg bw/day ↓body weight gain (d6 19, slight)	There were no maternal mortalities or clinical findings that could be attributed to the test substance administration. One animal of the high dose group died on day 11 probably due to a gavage error. Food consumption was reduced in the 10 mg/kg group over the entire treatment period (ca. 16.9 %), while body weight development was affected during the first third of the MITC treatment at this dose level. Reproduction	-	[redacted] (1986b) IUCLID: A8.10.1-005

					parameters as assessed by pregnancy rate, number of total resorptions, corpora lutea, implantations, live foetuses or pre-/post-implantation loss showed no adverse effect due to the test substance administration. Foetal parameters, as assessed by sex ratios, foetal body weight, external and visceral examination as well as the head and skeletal development were not adversely affected by the treatment with MITC. No test substance-related malformations were noted. Foetal data No indication of malformations or other developmental effects		

Table A-91: Summary table of human data on adverse effects on development

No human data is available.

Table A-92: Summary table of other relevant studies for developmental toxicity

No other data is available.

A.3.10.2.1 Short summary and overall relevance of the provided information on adverse effects on development

Dazomet and MITC were examined for their respective prenatal toxicity in Wistar rats ([redacted] 1987b; [redacted] 1987a; A8.10.1-001 and A8.10.1-003). Following treatment with Dazomet, food consumption and body weight of the dams during the treatment period (days 6-15 p.c.) and post treatment period at the high dose were reduced. Bodyweight gain was diminished during the treatment period and corrected bodyweight was also decreased. At the mid dose group there was a trend with respect to reduced food consumption at the beginning of treatment and a slight decrease in corrected body weight gain. No adverse effects were noted in dams treated with 3 mg/kg bw/d. Uterus weights were slightly reduced at the high and mid dose while fetal weights were slightly reduced only at the high dose. The number of runts was slightly increased at the mid and high dose. There was no other effect on embryonic and fetal development at any of the investigations made in this study. In addition, no test substance related malformations were observed. Thus the following NOAELs were achieved for Dazomet: NOAEL maternal toxicity: 3 mg/kg bw/d; NOAEL embryo-/fetotoxicity: 10 mg/kg bw/d; NOAEL malformations: $\geq$ 30 mg/kg bw/d. A study performed with rabbits, which were treated with Dazomet from day 7 until day 19 post-insemination (p.i), resulted in a statistically significant body weight loss during the treatment period and impaired weight gain during the post treatment period (days 19-29 p.i.) at the high dose of 45 mg/kg bw/d ([redacted] 1993, A8.10.1-004). Also, at this dose uterus weights were statistically significantly reduced (mean of 125 g versus 382 g in control). One dam died intercurrently and two further rabbits were found to have blood in the bedding during several days post treatment. Embryo-/fetal examination revealed a clear increase in resorption rate (mainly early resorptions) and consequently the post implantation loss was increased (68.2 %) at 45 mg/kg bw/d. This was due to the fact, that 5 females had no viable fetuses at all. The number of live fetuses/dam was also decreased with statistical significance at 45 mg/kg bw/d (mean of 3.4 versus 7.2 in control). An increased occurrence of 2 skeletal variations (accessory 13th rib(s) and fused sternebrae) was observed at the maternal toxic dose of 45 mg/kg bw/d. There were no effects on dams or fetuses in the low and mid dose group (5 and 15 mg/kg bw/d). There were no malformations that could be attributed to the test substance administration at any dose level. Thus the following NOAELs were achieved: NOAEL maternal toxicity: 15 mg/kg bw/d; NOAEL embryo-/fetotoxicity: 15 mg/kg bw/d; NOAEL malformations: $\geq$ 45 mg/kg bw/d.

Please note: During peer review of the Dazomet active ingredient authorisation procedure for EU plant protection products, questions have been raised about the interpretation with respect to the adversity/toxicological relevance of the occurrence of enlarged renal pelvis, hydroureter and unilateral microphthalmia in rats after exposure to Dazomet ([redacted], 1987, A8.10.1-001 and A8.10.1-003). It was concluded by the RMS Belgium, that the apparent increase of some variations in the treated groups were above control, but in the absence of a proper dose-dependency, the relationship with the treatment remained uncertain. In addition, these variations are known to occur spontaneously at similar rates in the Wistar rats. Two foetuses with unilateral microphthalmia in one litter were observed at the top-dose. As only one litter was involved, (although it was noted that the anomaly was extremely rare in this Wistar strain) and in addition, the secondary effect of maternotoxicity could not be

discounted, it was questionable whether the finding could be attributed to a specific effect of Dazomet on the foetuses. Accordingly, these effects have not been considered for NOAEL setting.

Following treatment with MITC, food consumption of the rats especially during the treatment period (days 6-15 p.c.) at the high dose of 30 mg/kg bw/d was reduced ([redacted] 1987a, A8.10.1-001 and A8.10.1-003). Body weights and body weight gain during treatment and post treatment period were also reduced. Some clinical findings were noted in some animals at the end of the treatment with 30 mg/kg bw/d and included reddish snout and increased water consumption. At 10 mg/kg bw/d, body weight gain was lower at the beginning of treatment and corrected body weight gain was also decreased. Water consumption was increased in individual animals at this dose level. No adverse effects were noted in dams treated with 3 mg/kg bw/d. Placental weights were reduced at 30 mg/kg bw/d and the numbers of runts were slightly increased. No other findings with respect to embryo-/fetotoxicity were noted at this dose level. There was no other effect on embryo-/and fetal development at the low and mid dose levels of 3 and 10 mg/kg bw/d, respectively. No malformations that could be attributed to the administration of MITC were noted at any of the doses. Thus the following NOAELs were achieved for MITC: NOAEL maternal toxicity: 3 mg/kg bw/d; NOAEL embryo-/fetotoxicity: 3 mg/kg bw/d and NOAEL malformations: $\geq$ 30 mg/kg bw/d.

Within a further study on MITC performed with Chinchilla rabbits ([redacted] 1986a, b, A8.10.1-005), the test substance caused maternal toxicity at a dose of 10 mg/kg bw/d in the form of impairment of food consumption and body weight. No adverse effects on reproduction parameters (pregnancy rate, number of total resorptions, corpora lutea, implantations, live fetuses or pre-/post implantation loss) and embryo-/fetal development – including the occurrence of malformations – could be noted even at the high dose, which was maternal-toxic. The following NOAELs were derived from this study for MITC: NOAEL maternal toxicity: 3 mg/kg bw/d; NOAEL embryo-/fetotoxicity: $\geq$ 10 mg/kg bw/d and NOAEL malformations: $\geq$ 10 mg/kg bw/d.

New information – DAZOMET:
No new studies have been found during the open literature search that would provide new data for hazard or risk assessment and/or would question the results of the existing GLP studies.

An increased incidence of runts had been stated to occur in the teratogenicity rat study with Dazomet (A8.10.1-001). In the absence of any other relevant embryo- or fetotoxic effects, the developmental NOAEL of the study was based on the occurrence of runts during Annex II inclusion.

The number of runts per group was increased in test groups 10 and 30 mg/kg bw/d, however, without a clear dose-response relationship. A substance-related effect could not be completely excluded by the study author. Within the study, the author classified those foetuses as runts if their individual body weight was less than 75 % of the mean foetal body weight of the litter. RMS Belgium followed this definition. There is, however, no internationally agreed definition for runts, but there are several proposals about what body weight a foetus is underdeveloped or not. In addition to the value <

75 % as applied by the study authors, the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) proposed a value of less than 50 % of the mean foetal body weight of the litter[15]. In one of the recent guidelines for reproductive toxicity testing (OECD TG 443), the OECD proposes to consider foetuses with a body weight less than two standard deviations (< 2 x SD) of the mean body weight of the litter as runts. For clarification whether the increased incidence of runts should be considered as treatment-related or a random event, for this renewal application, the notifier decided to re-evaluate the individual foetal weights of all test groups as well as the corresponding historical control data according to the OECD approach to reflect the most recent and officially acceptable state within the plant protection product regulation.
The detailed results of the re-evaluation, individual foetal weights of the Dazomet study and the historical control data are provided in [redacted](2020b), A8.10.1-002.
For the re-evaluation of both, the dosing studies with Dazomet and the historical control data studies (for more information please refer to the study 8.10.1-002), cut-off values of foetal body weighs per litter were determined for the < 75 % and the definition from OECD TG 443. Every foetus with a body weight lower than these cut-off values was newly identified as a runt.
During the re-evaluation it became clear that the overall number of foetuses newly identified as runts increased across all test groups, the control group and the historical control data since the OECD criterium (< 2 x SD) is more stringent than the study author proposal (<75 %) increasing the statistical resolution of the results, which enables a more reliable evaluation compared to the study author / RMS approach with only a small number of identified runts.

It was shown for Dazomet that even though the litter incidences of the mid and the high dose groups (52 and 38 %), are above the average litter incidence given by the historical control data (37 %), the values are nevertheless within the range of the single historical control study values (16 – 52 %).

The same is true for the foetal incidence. The foetal incidence of the mid dose group (4.1 %) exceeds the average foetal incidence of historical control data (3.1 %), but is still located within the historical control range (1.4 – 4.2 %). Also, the absolute number of identified runts (7/7/11/8 for 0/3/10/30 mg/kg bw/day) lies within the range of the historical control data (4 – 12 per litter). There is no clear dose dependency observable.

In the absence of any other effects of toxicological relevance, the developmental NOAEL should be changed from 3 mg/kg bw/day to 30 mg/kg bw/day as this was the highest dose tested.

New information – MITC:
No new studies have been found during the open literature search that would provide new data for hazard or risk assessment and/or would question the results of the existing GLP studies.

Comparable to the developmental toxicity study in rats with Dazomet, an increased

[15] ECETOC Monograph No. 31, Guidance on Evaluation of Reproductive Toxicity Data, 2002: http://www.ecetoc.org/wp-content/uploads/2014/08/MON-031.pdf

incidence of runts has also been observed after oral exposure to MITC. The results have been re-calculated in the same way as described above for the Dazomet study. Since the developmental toxicity study was performed about five months earlier at the same test institute with the same rat strain it is possible to compare the re-calculated results of the MITC study to the same historical control data as provided for the Dazomet study.
It was shown for MITC that the litter and the foetal incidence of runts were slightly increased above their respective average control values (37 % and 3.1 %) only in the high dose group (39 % and 3.4 % respectively). However, as for Dazomet, these values still fit well to the range of the individual historical control data studies.

The number of identified runts (8/7/5/9 for 0/3/10/30 mg/kg bw/day) also lies well within the range of the historical control data (4 – 12 per litter). The conclusion is also the same as for the Dazomet results: An increased incidence of runts should not be considered as an adverse effect any longer since there is no clear dose dependency observable and the number and litter/foetal incidence of runts lies well within the range of the historical control data.

In the absence of any other effects of toxicological relevance, the developmental NOAEL should be changed from 10 mg/kg bw/day to 30 mg/kg bw/day as this was the highest dose tested.
The detailed results of the re-evaluation, individual foetal weights of the MITC study and the historical control data is provided in [redacted](2020b), A8.10.1-002.

A.3.10.2.2 Comparison with the CLP criteria

Classification in Category 1 is applied where known adverse effects on development in humans were observed or when there is evidence from animal studies (and other studies where relevant) to provide a strong presumption that this will be the case. Substances are classified in Category 2 where there is some evidence to this effect but are not sufficiently convincing to place the substance in Category 1.

There is no information available on the developmental toxicity of Dazomet in humans. Information from reliable animal studies in two species, i.e. rats and rabbits, showed that Dazomet has no effects on foetal development. Therefore, the criteria for classification are not met and no classification for developmental toxicity is proposed.

A.3.10.2.3 Overall conclusion on effects on development related to risk assessment

Not applicable for the CLH report.

A.3.10.3 Effects on or via lactation

Table A-93: Summary table of animal studies on adverse effects on or via lactation

No animal data is available.

Table A-94: Summary table of human data on adverse effects on or via lactation

No human data is available.

Table A-95: Summary table of other relevant studies for adverse effects on or via lactation

No other data is available.

A.3.10.3.1 Short summary and overall relevance of the provided information on effects on or via lactation

No special data or studies are available regarding effects on or via lactation. As no adverse effects on reproductive toxicity and developmental toxicity were observed for Dazomet in the available studies also no indication on effects on or via lactation was observed.

A.3.10.3.2 Comparison with the CLP criteria

In the absence of any effects on reproductive toxicity and developmental toxicity no classification for effects on or via lactation is considered necessary.

A.3.10.3.3 Overall conclusion on effects on or via lactation related to risk assessment

Not applicable for the CLH report.

A.3.10.4 Conclusion on classification and labelling for reproductive toxicity

Not classified – conclusive but not sufficient data for classification.

A.3.10.5 Overall conclusion on reproductive toxicity related to risk assessment

Not applicable for the CLH report.

A.3.11 Aspiration hazard

Table A-96: Summary table of evidence for aspiration hazard

Not applicable, substance is a solid.

A.3.11.1 Short summary and overall relevance of the provided information on aspiration hazard

Not applicable, substance is a solid.

A.3.11.2 Comparison with the CLP criteria

Not applicable, substance is a solid.

A.3.11.3 Conclusion on classification and labelling for aspiration hazard

Not applicable, substance is a solid.

A.3.12 Neurotoxicity

Due to its structural relationship with organophosphate compounds, neurotoxicity studies for the active substance Dazomet were provided for the Annex II inclusion and thus peer reviewed by European competent authorities and eCA Belgium. The data set was and is still complete in accordance with the data requirements. Therefore, no new studies are submitted for the renewal application of Dazomet.

No new studies have been found during the open literature search that would provide new data for hazard or risk assessment and/or would question the results of the existing GLP studies.

In addition to those studies specially designed for neurotoxicity testing and already evaluated in the Dazomet Assessment Report (Belgium, 2010), further newly initiated studies with relevance for neurotoxicity assessment are also listed in Table A.94. A brief overview of relevant findings is provided.

Dazomet CAR Section 2.4.1.1. (Belgium, March 2010):

Active substance Dazomet
The potential neurotoxicity was investigated in an acute and sub-chronic neurotoxicity study in the rat. The findings in the acute study were only a reflection of an impairment of the general state of health. Neither were neurotoxic changes induced in the subchronic study. Dazomet does not have a specific neurotoxic potential in rats.

Degradation product/metabolite MITC
The neurotoxicity of MITC was not investigated.

Table A-97: Summary table of animal studies on neurotoxicity

Method, Duration of exposure, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels	NOAEL, LOAEL	Results	Remarks (e.g. major deviations)	Reference
Acute neurotoxicity study **Gavage** **It is compliant to OPPTS 870.6200 of US EPA and also largely to OECD TG 424 from 1997** **GLP compliant** **Key study** **Reliability: 2**	Wistar rats 10/sex/dose	Dazomet Purity > 96.3 % CMC (vehicle) Males: 50, 130, 450 mg/kg bw/d Females: 15, 50, 130 mg/kg bw/d Duration of treatment / exposure 14 days	**Toxicity NOAEL (males) < 44 mg/kg bw/day** based on increased salivation, lacrimation and decreased rearing and motor activity at 44 mg/kg bw/day **Toxicity NOAEL (females) < 13 mg/kg bw/day** based on decreased motor activity at 13 mg/kg bw/day **Neurotoxicity NOAEL = 392 mg/kg bw/day** (highest dose tested)	<u>392 mg/kg bw/day</u> ↓body weight (m) ↓body weight gain (m) *FOB:* ↑half open eyelids (ptosis) ↑urine staining on the anogenital region ↑salivation/lacrimation ↓activity/rearing activity ↓Motor activity ↓foot-splay at landing (slight) <u>130 mg/kg bw/day</u> ↓body weight (m) ↓body weight gain *FOB:* ↑half open eyelids (ptosis) ↑urine staining on the anogenital region ↑salivation/lacrimation	-	[redacted]. (1994a) IUCLID: A8.13.2-003

				↓activity/rearing activity ↓Motor activity ↓foot-splay at landing (slight) <u>44 mg/kg bw/day</u> ↓body weight (f) *FOB:* ↑half open eyelids (ptosis) ↑urine staining on the anogenital region ↑salivation/lacrimation ↓activity/rearing activity ↓Motor activity ↑forelimb grip strength (questionable tox relevance, f) <u>13 mg/kg bw/day</u> *FOB:* ↓Motor activity (f) <u>No relevant neuropathological findings</u>		
Sub-chronic (90-day) neurotoxicity study **Oral: feed** **OPPTS 870.6200**	Wistar rats 10/sex/dose	Dazomet Purity > 96.3 % Duration of treatment / exposure 50 months	**Toxicity NOAEL < 50 ppm** **< 4 mg/kg bw/day** based on increased hepatocyte fatty change at 50 ppm	<u>450/400 mg/kg bw/day</u> ↓body weight ↑liver weight ↑liver – fatty chances *FOB:* No relevant findings	-	[redacted]. (1994b) IUCLID: A8.13.2-004 or A8.9.5.1-004

GLP compliant **Key study** **Reliability: 1**		Dose levels: *nominal* 0, 50, 200 or 450 (m) 0, 50, 200 or 400 (f) Corresponding to *actual* 0, 4, 15, or 34 (m) mg/kg bw/day 0, 4, 16, or 34 (f) mg/kg bw/day	**Neurotoxicity NOAEL = 400/450 ppm = 34 mg/kg bw/day** (highest dose tested)	↓foot-splay at landing (questionable tox relevance, f) *Figure eight-maze:* No relevant findings <u>200 mg/kg bw/day</u> ↑liver weight ↑liver – fatty chances *FOB:* No relevant findings *Figure eight-maze:* No relevant findings <u>50 mg/kg bw/day</u> ↑liver – fatty chances *FOB:* No relevant findings *Figure eight-maze:* No relevant findings <u>No relevant neuropathological findings</u>		
***In vivo* Mammalian Alkaline Comet Assay (Liver and stomach tissue)**	Sprague-Dawley Male	MITC Purity 98.1 % Corn oil MITC group 20 and 40 mg/kg: 5	**NOAEL=** 20 mg/kg bw	<u>60 mg/kg bw</u> ↓spontaneous motor activity ↑piloerection ↓body weight ↓body weight gain	-	[redacted] (2020) IUCLID: A8.13.2-001 or A8.5.5-009

OECD TG 489 (2016) **Oral: feed** **GLP** **Reliability: 1** **Supportive study**		MITC group 60 mg/kg: 6 Negative control (Corn oil):5 Positive control (EMS): 3 Orally administered twice at 21 hours interval by intragastric gavage at a volume of 10 mL/kg body weight.		<u>40 mg/kg bw</u> No relevant findings <u>20 mg/kg bw</u> No relevant findings		
Mammalian Erythrocyte Micronucleus Test **Gavage** **OECD TG 474 (2016)** **GLP** **Radiolabelled MITC** **Reliability: 1** **Supportive study**	Sprague-Dawley (Crl:CD (SD)) Female 5/sex/dose except for 60 mg/kg bw, 6 rats has been tested	MITC (98.1 % purity) Corn oil (vehicle) Dose level (2 doses, 24 h spaced, oral) 0, 20, 40, 60 mg/kg bw	**NOAEL**= 20 mg/kg bw/d	<u>60 mg/kg bw</u> ↓spontaneous motor activity ↑piloerection ↓body weight ↓body weight gain <u>40 mg/kg bw</u> ↓body weight gain <u>20 mg/kg bw</u> No relevant findings	-	[redacted] (2020) KCA 5.7.1/05 Report No.: 20-0040 IUCLID: A8.5.5-010 Also A8.13.2-002

Uterotrophic bioassay in rodents **OECD TG 440 (2018)** **GLP** **Reliability: 1** **Supportive study**	Wistar rats 30 females (ovariectomized) 6 rats per group (5 groups)	Dazomet Purity 98.2 % Corn oil Dose level (for 3 days) 0, 15, 30 or 60 mg/kg bw/day	**NOAEL**= 15 mg/kg bw/d	<u>60 mg/kg bw/day</u> ↓body weight ↓body weight gain <u>30 mg/kg bw</u> ↓body weight gain (absolute) <u>15 mg/kg bw</u> No relevant findings	-	[redacted] (2020b) IUCLID: A8.13.2-006
Endocrine disrupter mammalian screening – *in vivo* **OECD TG 441 (2018)** **GLP** **Reliability: 1**	Male Wistar rats (castrated) Number of animals per sex per dose: 6 males/ group Total number of rats: 60 males	Dazomet Purity 98.2 % Corn oil Dose level (for 10 days) 25, 50 or 75 mg/kg/ bw/day	**NOAEL**= 25 mg/kg bw/d	<u>75 mg/kg bw/day</u> ↓body weight gain (absolute, d1-2) ↓body weight gain (absolute and relative, d1-10) <u>50 mg/kg bw</u> No relevant findings <u>25 mg/kg bw</u> No relevant findings	-	[redacted] (2020b) IUCLID: A8.13.2-005

Table A-98: Summary table of human data on neurotoxicity

No human data is available.

A.3.12.1 Short summary and overall relevance of the provided information on neurotoxicity

The potential neurotoxicity of Dazomet was investigated in an acute and a 90-day study in rats.
Within the acute neurotoxicity study ([redacted].1994a, A8.13.2-003), Dazomet was administered to groups of 10 male and 10 female Wistar rats by gavage as a single oral administration. The doses selected were 0, 50, 130 and 450 mg/kg body weight for males and 0, 13, 50 and 130 mg/kg bw for females (analytical values). The general state of health as well as the body weights were checked. Functional observational batteries (FOB, including home cage observations for posture, tremor, convulsions, sensorimotor tests such as the pupillary reflex test, open field examination for posture, tremor, convulsions) and motor activity measurements (MA) were carried out on all animals 7 days before dosing, the day of dosing (covering the time with peak effects) and days 7 and 14 days after dosing. The animals were sacrificed for the purpose of neuropathological examination (central and peripheral nervous system). The neuropathological examinations did not reveal any test substance related changes at any dose level.

Within the 90-day neurotoxicity study in rats ([redacted]. 1994b, A8.13.2-004) Dazomet was administered to 10 male and 10 female Wistar rats per dose group at dietary dose levels of 0, 50, 200, 400 (females only) and 450 ppm (males only) over a period of 3 months. The animals were daily observed for clinical symptoms and mortalities. A thorough examination including palpation was performed once per week. Body weight and food intake were measured weekly and on the days when functional observation batteries were carried out. Functional observation batteries and motor activity measurements were carried out on all animals 7 days before the start of the administration, and on study weeks 4, 8 and 13. The animals were sacrificed for the purpose of neuropathological examination (central and peripheral nervous system). No mortality or clinical signs of toxicity occurred in the study at any dose level. Body weight and body weight gain were affected in high dose males and females. At the end of the administration period, animals of these groups weighed 92 % (males) and 90 % of the respective control groups. Body weight gain was reduced by 12 % in males and 24 % in females. Relative liver weights were increased in 400 ppm and 200 ppm females. Fatty change in the liver was observed in mid and high dose males and females, as well as in 3 out of 5 low dose males. The NOAEL in this study for systemic toxicity was 50 ppm or 4 mg/kg bw for female rats and < 50 ppm (4 mg/kg bw for male rats). There were no signs of neurotoxicity at any dose level.

<u>New information:</u>
For the renewal application of Dazomet, five new vertebrate studies have been performed with Dazomet and MITC and were provided under their respective data points. Also, observations from other than neurotoxicity studies provide relevant information that can help to detect a possible neurotoxic potential of an active substance since cage-side observations of behaviour and clinical state are mandatory in any vertebrate study.
In a combined micronucleus/Comet assay in rats (please refer to A8.13.2-001) Dazomet was orally administered at doses of 31.75, 62.5, 125 or 250 mg/kg bw/day on three consecutive days. In all dose groups, unspecific signs of neurotoxicity occurred (lethargy, decreased/uncoordinated movement, slight head-shaking) with increasing severity, which were however of the same quality as observed in the other acute or short-term dosing studies. Body weight gain, as an indicator of general systemic toxicity, was significantly reduced from

dose 125 mg/kg upwards. There was no further concern with respect to neurotoxicity.

In order to assess the endocrine potential of Dazomet, an uterotrophic assay and a Hershberger assay have been conducted in young rats (please refer to A8.13.2-005 and A8.13.2-006). In the uterotrophic assay, female rats were dosed with 0.3, 15, 30 or 60 mg/kg bw once daily for a period of 3 consecutive days. In the Hershberger assay, male rats were dosed with 25, 50 or 75 mg/kg bw once daily for a period of 10 consecutive days. There were no mortality or clinical signs observed at any dose tested.

For the investigation of *in vivo* genotoxicity of MITC, the main metabolite of Dazomet, a new micronucleus and a Comet assay have been initiated in rats. In both studies, the animals were orally dosed on two consecutive days with 20, 40 and 60 mg/kg bw. In both assays, a decrease in spontaneous motor activity and piloerection were observed in the 60 mg/kg bw group. All these clinical signs were disappeared by 24 hours after the second dosing.

A.3.12.2 Comparison with the CLP criteria

The conclusion on the classification and labelling can be found in section A.3.2.4, A.3.2.5 and A.3.7.4.

A.3.12.3 Conclusion on neurotoxicity related to risk assessment

Not applicable for the CLH report.

A.3.13 Immunotoxicity

Immunotoxicity was not evaluated in the Dazomet Assessment Report (Belgium, 2010). In this active substance renewal application, we submit an assessment of immunotoxicity for the first time. We refer to a previously submitted study report ([redacted]. (1987b) A8.13.4-004) as well as a few study reports which we are submitting for the first time ([redacted] 1996, A8.13.4-001; [redacted] 1992, A8.13.4-002; [redacted] 2005, A8.13.4-003).

Table A-99: Summary table of *in vitro* immunotoxicity studies

No *in vitro* data is available.

Table A-100: Summary table of animal studies on immunotoxicity

Method, Duration of exposure, Route of exposure, Guideline, GLP status, Reliability, Key/supportive study	Species, Strain, Sex, No/Group	Test substance (including purity), Vehicle, Dose levels	NOAEL, LOAEL	Results	Remarks (e.g. major deviations)	Reference
OECD TG 409 **90 days (sub-chronic)** **Oral feed** **Key study** **Reliability: 2**	Beagle dogs Males/ Females 4/sex/group	Dazomet Purity: 98.2 % Vehicle: mixed 25, 100 and 400 ppm	<u>NOAEL:</u> Males: 100 ppm (2.5 mg/kg bw/d) Females: 100 ppm (2.3 mg/kg bw/D)	LO(A)EL 200 ppm in males (corresponding to 5.7 mg/kg bw/d) 200 ppm in females (corresponding to 5.2 mg/kg bw/d) NO(A)EL 100 ppm in males (corresponding to 2.5 mg/kg bw/d) 100 ppm in females (corresponding to 2.3 mg/kg bw/d) Other A concentration of 400 ppm was shown to be too high based on decreased food consumption and body weight. At 400/200 ppm, Dazomet caused a haemolytic anemia associated with	Initially the test dose for group 3 was 400 ppm; starting from day 24 of treatment, the dose was reduced to the half.	[redacted] (1987b) IUCLID: A8.13.4-004

				increased haemosiderin deposits in the spleen. Relative liver weights were increased without pathological changes.		
OECD TG 409 **90 days (sub-chronic)** **Oral feed** **Key study** **Reliability: 1**	Beagle dogs Males/ Females 4/sex/group	Dazomet Purity: 98.3 % Vehicle: mixed with food 0, 1.5, 4.5, 13.5/9 (♀) and 13.5 mg/kg (♂) bw/d	Male or female: 1.5 mg/kg bw/d (NOAEL) 4.5 mg/kg bw/d (LOAEL)	Dazomet caused unscheduled kill of one female during the 13.5 mg/kg bw/day treatment period. Vomiting of feed, low food consumption and body weight, and the effect on the kidney were detected in males at 13.5 mg/kg bw/day and females at 13.5/9 mg/kg bw/day. Low Ht, Hb, and RBC and high PLT were detected in males at 13.5 mg/kg bw/day. The effects on the liver of both sexes and spleen of females were detected at 4.5 mg/kg bw/day or	13.5/9: the dose was changed from 13.5 mg/kg bw/day to 9 mg/kg bw/day at week 11 One female showed atrophy of the thymus, the finding was considered to occur under malnutritional conditions as indicated by the low food consumption and body weight.	[redacted] (2020) IUCLID: A8.9.5.1-010

				more. The effect on the stomach was detected in the female subjected to unscheduled kill. No treatment-related changes with toxicological significance were observed in either sex at 1.5 mg/kg bw/d		
Exposure for 5-7 days **Gavage** **No guideline followed** **No, not conducted under GLP/Officially recognised testing facilities (open literature)** **Supportive study** **Reliability: 4**	B6C3F1 + Fischer 344 rats Female No clear indication about the number of tested animals	MITC (15, 30 or 45 mg/kg bw/d) Purity: not reported Vehicle: Drinking water Duration of treatment / exposure: 5 days	-	Consistent immunological effects of MITC were only observed at a high dose (45 mg/kg bw/d). 55 mg/kg bw/d was considered near-MTD, and the oral LD50 of MITC in the female mouse was about 100 mg/kg bw/d Therefore, the involvement of systemic toxicity was suspected (although the authors reported a terminal b.w. which differed <10 % from the study controls).	-	[redacted] (1996) IUCLID: A8.13.4-001

4 time course studies: mice were dosed daily by gavage for 3, 5, 10 and 14 days **Gavage** **No guideline followed** **No, not conducted under GLP/Officially recognised testing facilities (open literature)** **Reliability: 3 Supportive study**	B6C3F1 mouse Female No clear indication about the number of tested animals	Sodium methyldithiocarbamate dihydrate (SMD: 300 mg/kg bw/d) Purity 90-95 % Vehicle: water Purity: not reported Duration of treatment/exposure: 14 days	-	The authors concluded that the effects were observed in the absence of a significant decrease in body weight, suggesting that most of the effects of SMD on the immune system are not secondary to generalised toxicity.	In the previous evaluation, the RMS noted the following: NK-cells effects were noted at 200 mg/kg b.w. and higher, but it remains dubious if the effects were specifically immunotoxic, as doses of >80 mg/kg bw/d are likely to induce systemic toxicity in the mouse (i.c. b.w. effects >10 % in the ♀ mouse, see DAR Metam-Na, oral administration for 28 days). The terminal body weights of animals treated with Metam-Na were <10 % lower than vehicle controls at most sacrifice times, but b.w. gains were negative at all doses of Metam. On day 10, when the highest spleen/thymus	[redacted] (1992) IUCLID: A8.13.4-002

					weight decreases were noted, terminal body weight was 13 % ($p<0.01$) below control level.	
The total exposure time (gavage) is not clearly stated **No guideline followed** **No, not conducted under GLP/Officially recognised testing facilities (open literature)** **Reliability: 3** **Supportive study**	B6C3F1 mice Female No clear indication about the number of tested animals	SMD (0, 50, 100, 200, 300 mg/kg bw/d) MITC (0, 17, 45 mg/kg bw/d) Purity: Not reported Vehicle: water	-	Metam-Na was shown to modify dose-dependently both serum and intraperitoneal cytokines in ♀ B6C3F1 mice (treated by single gavage at 50, 100, 200 or 300 mg/kg bw/d). Cytokine IL-12 was decreased, and IL-10 increased at 50 and 200 mg/kg bw/d and above respectively (in mice challenged i.v. 10' post-dose to 60 µg bacterial lipopolysaccharide (LPS)/animal). The authors demonstrated that the modification at the top-dose was caused by the inhibition of the cellular signalling MAP-kinases p38 and JNK in	The observation that MITC causes similar effects as SMD on IL-10 and IL-12 expression suggests the possibility that MITC resulting from breakdown of SMD is mostly responsible for the effects of the SMD. Further studies should demonstrate if there are effects mediated by SMD that are not caused by MITC. Exacerbation of asthma has been reported following exposure to SMD or MITC, and this would be consistent with	[redacted] (2005) IUCLID: A8.13.4-003

				peritoneal macrophages, and consequently an increased (IL-10) or decreased (IL-12) mRNA expression. Finally, it was demonstrated that Metam-Na (at 200 or 300 mg/kg) decreased the resistance to E.coli induced peritonitis (mortality rate after injection of 0.8 x108 – 2 x 109/mouse) within a time- frame (24-48h) in the mouse. The main breakdown product MITC was only tested for its capacity to decrease IL-12 levels in serum (at doses of 17 and 45 mg/kg). With a significant decrease at a dosage of 17 mg/kg.	increased IL-10 and decreased IL-12 leading to a shift toward a Th2 response.	

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Table A-101: Summary table of human data on immunotoxicity

No human data is available.

A.3.13.1 Short summary and overall relevance of the provided information on immunotoxicity

The available data package for Dazomet and MITC were re-viewed with special emphasis to findings in organs which are involved in or reflect immune function, and which are generally examined within the standard toxicological data package. These were in detail: spleen, thymus, lymph nodes, bone marrow and white blood cells.

Within the available ADME studies with radiolabelled Dazomet or MITC, an important radioactive concentration was found in the thymus cortex and considered a particular feature of the compounds. However, there was no accumulation potential observed. Nevertheless, a concern may occur whether the (transient) increased concentration of Dazomet (or its metabolites) lead to damage of the thymic tissue.

Within the whole data package of Dazomet and MITC, no effects on thymus (weight or tissue) were seen in rats and mice. In the dog study, however, thymic involution was observed in dogs treated with Dazomet (A8.13.4-004).

For Dazomet, the effect occurred in two top-dose females. Thymic involution was not correlated to any clinical pathology parameters, nor were the organs weights affected by treatment. As no haematological alterations were observed in the white cell compartment, it quite plausible that the latter effect was a consequence of the severe systemic toxicity (vomiting, decreased body weight gain) in the female dogs at the high-dose. Furthermore, the thymus effects were not replicated in the 1-year dog study (A8.9.5.1 -013), which confirmed most other endpoints found in the 90-day study.

The thymus is considered to be the most sensitive organ for predicting immunotoxicity but is also sensitive to stress[16]. As no further signs of immunotoxicity were observed in the 90-day dog studies, the occurrence of thymic involution (A8.9.5.1-010) is rather driven by primary stressors like reduced food consumption/increased incidence of vomiting and related reduction of body weight gain.

In short-term and chronic studies with rats and mice, spleen effects like increased weights, haemosiderin deposits and haematopoiesis have been observed. These kinds of effects, however, are not considered to be evidence of immunotoxicity, rather the normal functioning of the spleen.

Within the open literature, three publications have been found describing a potential immune-toxic effect of Metam-Na (active substance with MITC as the main active metabolite) and MITC

[16] [redacted]. (2015) EFSA supporting publication 2015:EN-782; Retrospective analysis of the immune-toxic effects of plant protection products as reported in the Draft Assessment Reports for their peer review at EU level

in mice ([redacted] 1996, A8.13.4-001; [redacted] 1992, A8.13.4-002 and [redacted] 2005, A8.13.4-003). Several immunopathological and immune-functional parameter have been influenced after acute or sub-acute administration via different routes. It was, however, noticeable that the immune-toxic effects of MITC occurred at high doses (MITC immune-toxicity: 17 mg/kg bw/d) with over systemic toxicity (dazomet sub-chronic toxicity: 1.5 mg/kg bw/d). Therefore, the involvement of systemic toxicity should be considered as causative rather than true immunomodulatory effects.
In conclusion, no effect has been identified which would be based on an impaired immunological function.

A.3.13.2 Comparison with the CLP criteria

The conclusion on the classification and labelling can be found in chapter STOT RE.1 (liver), no effect has been identified which would be based on an impaired immunological function.

A.3.13.3 Conclusion on immunotoxicity related to risk assessment

Not applicable for the CLH report.

A.3.14 Endocrine disruption

Not applicable for the CLH report.

Table A-102: Summary table of *in vitro* studies on endocrine disruption

Not applicable for the CLH report.

Table A-103: Summary table of animal data on endocrine disruption

Not applicable for the CLH report.

Table A-104: Summary table of human data on endocrine disruption

Not applicable for the CLH report.

Table A-105: Summary table of other evidence on endocrine disruption

Not applicable for the CLH report.

A.3.15 Further Human data

Considering the medical surveillance on manufacturing (BPR Annex II 8.12.1), although Dazomet can cause skin and eye irritation in exposed manufacturing plant personnel, only 17 cases of human irritation to skin and eyes were reported over a period of at least 10 years ([redacted], personal communication, 2000b, A8.12.1-001). In fact, human Dazomet irritation under work place conditions in industry is low, due to appropriate protective measures.

Especially in non-aqueous systems, the release of MITC from Dazomet might be so low, that it does not show a sensitising potential under the conditions described. In this case it is also referred to animal studies (GPMT) where Dazomet was not a skin sensitiser when applied in olive oil.

Clinical cases and poisoning incidents (BPR Annex II 8.12.2) related to MITC generating compounds such as Dazomet were reported by [redacted] (1980, A8.12.1-002) for MITC. The author described the case of poisoning of a 24-year-old woman who did not notice that some Dazomet hat got into her rubber boot, which she wore for about 24 hours. After 24 hours a first to second degree acid burn developed and during the following days a bullous eruption spread over one foot/leg to about 5 % of the body surface. A liver biopsy showed a hypersensitivity hepatitis of non-specific type and the transaminases (GOT, GPT) were clearly increased. According to the author, the reversible damage of the liver parenchyma was conditioned by the oral contraceptive the patient took the contraceptives can produce liver tumours and/or cholestasis that impair liver function, furthermore cytolysis may also occur during the first months of contraceptive treatment due to a transient increase in aminotransferase levels.), but caused by percutaneously uptake of MITC. A second liver biopsy did not show any adverse effects, and liver enzymes had returned to normal. One year after the exposure, the patch test to a 0.05% aqueous solution of Vapam (soil disinfectant based on metam sodium and acting in the same way as Dazomet, by hydrolytic release of MITC) was performed and was still found to be strongly positive. It can be concluded that if MITC generating compounds like Dazomet are exposed to a larger area of the body and not removed immediately, systemic poisoning (transient, reversible liver damage) can occur and local skin sensitisation effect.

A fatal case of intoxication in India was reported by [redacted] (1981, A8.12.2-002). A 23-year-old female chemical student intentionally drank water containing 50 g MITC (no further details given). The patient noticed severe retrosternal burning and epigastric pain immediately after ingestion and began to vomit. A few minutes later she showed generalized tonic and clonic seizures and became unconscious. The patient arrived at the hospital deeply comatose with pulse 98/min and blood pressure 90/60 mm/hg, slightly dilated pupils and complete loss of all reflexes and motor activity. Although gastric lavage and peritoneal dialysis was performed immediately, the patient died 8 hours after admission to the hospital. Necropsy showed extensive necrosis of the oesophagus, stomach and proximal part of the duodenum. This case clearly demonstrates the acute toxicity of MITC in humans following oral ingestion.

A 67-year-old male farmer presented with an acute onset of itchy bullae and erythema on his feet ([redacted] 2013, IUCLID A8.12.2-003). He had a history of diabetes mellitus. On physical examination, multiple bullae and erythema on the left sole, foot, and lower leg were observed, as well as erythema on the right foot. Additional bullae developed on the right sole 2 days later. To resolve the severe pruritus and extensive bullae formation prednisolone 20 mg/day was administered for 3 days, followed by 10 mg/day for 10 days. Diflorasone diacetate was used as topical steroid. During the 3 months after steroid cessation, bullae with pruritus occasionally developed on the patient's feet. Frequent interviews and several laboratory examinations, including skin biopsy, skin cultures, and blood tests, did not reveal the cause.

Eventually, the patient's occupation and the lesion sites led doctors to suspect his rubber boots. Patch tests were performed on the patient's boots. Thin square pieces (5 × 5 mm) of the outer

surface, inner surface, inner insole, and bottom insole of the boots were applied, avoiding pressure effects with an adhesive bandage, for 48 h. Results were obtained after 2 and 3 days of patch test application on the basis of the scoring system by the International Contact Dermatitis Research Group. Positive results were obtained for the outer surface (D2+/ D3+), inner surface (D2+/D3+), inner insole (D2++/D3++), and bottom insole (D2++/D3++). Since contact dermatitis was suspected, patch tests with the constituents of the boots, which were rubber chemicals and matrices of the boot material provided by the manufacturer, were subsequently performed. However, all results were negative. Patch tests performed with new but identical boots were also negative.

Therefore, it was hypothesized that some material absorbed by the rubber boots was the cause of his condition. The patient recalled spraying Dazomet in his fields 17 days before the onset of his first symptoms. One week after spraying Dazomet, he cultivated the fields wearing his boots. The patient also recalled wearing the boots while spraying other fields 4 days before the onset of symptoms and while working in the fields the following day. Although he washed the boots after each working day, he had worn them for more than 10 h a day before symptom onset and for a few hours a day after cessation of systemic steroids. Gas chromatography analysis of the outer and inner surfaces and the inner and bottom insoles of the boots revealed MITC concentrations of 0.7, 15.6, 16.0, and 11.6 ppm, respectively. These concentrations were equivalent to those of Dazomet, i.e., 2, 35, 36 and 26 ppm, respectively. Although the patient had previously used Dazomet once every 5 years, this was the first episode of skin eruptions. Patch testing of 10 volunteers with the patient's boots showed negative results; therefore, a diagnosis of allergic contact dermatitis due to MITC was made.

Numerous observations on exposure of the general population (BPR Annex II 8.12.3) to Dazomet/MITC are available. [redacted] (1992, A8.12.1-009) reported the case of a paper mill worker with a 3-month history of sore itching upper and lower eyelids, with erythema and scaling. The reaction occurred at least 4 hours after finishing work and lasted for more than 24 hours. It could be found out that the occurrence of these reactions was closely related to introduction in the paper mill of a new biocide, Busan 1058, containing 24% Dazomet as active ingredient. Patch testing with this product was positive.

[redacted] (1973, A8.12.1-011) from the skin clinic of the Auckland hospital in New Zealand reported two cases of bullous dermatitis related to Dazomet. The first case was a worker in a hardboard factory who came accidentally in contact with Dazomet (right forearm) while diluting a concentrated solution of the substance in water prior to flushing it through water pipes to prevent the growth of algae. The worker immediately washed his forearm, however, a few days later he became an acute itching dermatitis. Patch testing with a 0.25% aqueous solution of Dazomet gave a positive reaction. The second case was a glasshouse tomato grower with a case history: an acute dermatitis, which he developed one year earlier during handling of a formalin solution. This man came accidentally in contact with Basamid, a granulated form of Dazomet, while he was spreading the granules by hand prior to hoed them in the soil. Some granules accidentally fell into his gumboots. The man developed a severed dermatitis. Patch tests as well as an open test were positive.

According to these findings, Dazomet appeared to be a strong sensitiser, a primary irritant and possibly a vesicant, and may cause contact dermatitis in occupational exposure.

A test report to BASF India Limited from the [redacted] ([redacted]1998, A8.12.1-005) is available,

which reports the results of a field operator exposure test conducted in the field conditions to assess the possible effects of handling and application of Basamid granular. For the purpose of this test ten healthy male workers were selected based on their medical history and exposure to pesticides. The applicators spent a period of 6 h /day for 3 consecutive days in handling and incorporating Basamid granular (active content of Dazomet 98-100 %) into the soil at the concentration of 40 g/sq.m. No incidence of adverse changes was seen in the health parameters. The haematological and biochemical values did not show much changes and the post exposure values were comparable to those of pre-exposure values. The tested urine parameters were also normal before and after exposure.

In an older study a total of 19 out of 200 volunteers (10 %) reacted positive with respect to skin sensitisation when 1 % Dazomet was applied dry to the test persons (Patch test; [redacted] 1966, A8.12.1-015). An aqueous solution of 0.01 % Dazomet however was negative. In a case report of pruritus and papulous reaction after handling various pesticides ([redacted] 1993, A8.12.1-010), the potential contact to Dazomet was reported to result in no skin reaction. The Patch-test reaction to Dazomet (0.1 % in pet.) was negative.

[redacted]. (1982, A8.12.1-006) reported that the dermatological department of the University of Erfurt/Germany performed human patch tests in patients sensitized to Afugin® a local human antimycotic drug (3,5-Dibenzylperhydro-1,3,5-thiadiazin-2-thion), closely related to Dazomet (3,5-Dimethylperhydro-1,3,5-thiadiazin-2-thion) and related compounds releasing either benzene-isothiacyanate like Afugin® or beta-phenylethyl-isothiacyanate. In addition patients sensitised to Nematin® (Sodium methyl-dithiocarbamate) were tested to closely related structures including methylisothiacyanade (MITC) a known metabolite of Nematin® and Dazomet. The patients were tested under occlusive conditions for 24 hours (Gothatest ®) at specified concentrations who varied from test substance to test substance. All skin reactions 24, 38 and 72 hours after the test were evaluated as positive.

Patients sensitized to Afugin® reacted positive to the benzene-derivates but not phenylethyl-derivates, indicating that the side chain might influence the result of the test. Patients sensitised to the known MITC generator Nematin® (0.01 % aqueous preparation) reacted positive (4 out of 4 patients) and also 1 patient tested for MITC (0.01 % in petrolatum) reacted positive. Dazomet was also tested (1 % in petrolatum) and only 1 out of 4 patients sensitized to Nematin® reacted positive. The authors suggested that the methyl moiety of MITC would be the relevant allergens structure while the isothiocyanate group would be responsible for the haptene conjugation due to its high affinity to proteins.

MITC has been identified as a strong allergen to humans also the exposure under practical use conditions in the described cases came from Nematin® an agricultural nematicide generating MITC when farmers handling treated potatoes with their hand and MITC was formed under acidic conditions of the exposed skin. Dazomet reacted to a much lower degree (1 out of 4 patients). The formation of MITC under dermatological test conditions might have been impaired as Dazomet was applied in petrolatum stabilizing the molecule. It is noteworthy that Dazomet is not a skin sensitizer in the Guinea Pig Maximisation Test (GPMT) when petrolatum has also been used as vehicle. MITC itself is a strong skin sensitizer in the GPMT.

In addition to the case of local reaction and systemic poisoning already mentioned above, [redacted] (1980, A8.12.2-001) from the [redacted] reported on 9 cases of occupational dermatoses related to MITC which he was asked to give expert opinion within a time frame of 2 years. The

patients have been handling MITC generating soil disinfectants like Dazomet, Metham sodium used in agriculture and horticulture, especially garden nurseries. The patients were all reporting several cases of similar skin reaction in colleagues who have not seeked dermatological advice. Although the patients were only exposed to MITC and MITC generating biocides for a short time (few hours to few days) 8 out of 9 showed a strong positive reaction (++ or +++) to Vapam® even when the test was repeated 1 year later. According to the author the workers were handling a 10 % aqueous Vapam® or Nematin® formulation containing 32.7 or 29.5 % MITC. The tests further showed that no cross-reaction between MITC and benzene isothoiocyanate (BIT) was evident.

It can be concluded that MITC can cause strong skin irritation as well as sensitisation. Based on the exposure information given by the patients, MITC must be regarded as a potent skin sensitizer.

In 1970, [redacted] (A8.12.1-012) reported on 16 cases indicative of a contact dermatitis due to the compound Vapam, an MITC generating nematicide based on Metham sodium, in agricultural workers handling Vapam-treated potatoes. The authors observed bullous skin reactions. Seven of these 16 cases were subjected to the patch test. The concentrations of the Vapam formulation ranged from 1.5 to 10 % and airborn aerosols from a 10 % preparation also were tested. All 7 patients reacted to the applied concentrations and the authors concluded that the reactions seen were not only toxic reactions but also of the allergic type. Even airborne vapours in a room did cause such reactions. While under practical field conditions the skin reaction in a female agricultural worker was noted 3 weeks after start of exposure, skin findings as soon as two days after re-exposure were noted one year later. MITC generation was assumed to play an important role in the development of the dermatitis (toxic and allergic).

It is presumed that MITC generated from Nematin (Vapam) was responsible for toxic and allergic contact dermatitis in agricultural workers. Even vapours in a closed room were sufficient to cause skin reactions in sensitised persons (airborne contact dermatitis).

Within a short communication, [redacted] (1978, A8.12.1-014) from the [redacted] also mentioned the occurrence of dermatitis in agricultural workers of areas where Metham sodium is used for potato treatment, which already had been observed and reported as early as 1970 by [redacted] (1970, A8.12.1-012). [redacted] (1978, A8.12.1-014) noticed that such cases of dermatitis still were seen in 1978, almost under hot, moist weather conditions. The primary cause for such dermatitis is therefore explained by the formation of MITC by hydrolysis of the parent compound Metham sodium under acid conditions when the compound is in contact with sweating wet skin. In order to find out whether Metham sodium as such or one of its degradation products was the actual allergen, a series of patch tests in patients were undertaken for Metham sodium (trade name Nematin) as well as for further chemically related substances including 2-thion-3, 5-dimethyl-3, 5-thiadiazine (Dazomet 1 %, vehicle not given) and MITC (0.1 % aqueous). The author ([redacted] 1978, A8.12.1-014) reported that older solutions of Nematin always produce stronger allergic patch test reactions than fresh ones. Furthermore an aq. 0.5% Nematin solution corresponding to 0.15 % Metham sodium causes toxic bullous reactions. Within the series of chemically related substances, Dazomet and MITC were reported to result in positive skin reactions with no further information given. As methyl mustard oil is formed from hydrolysis of Metham sodium on sweating wet skin surface as well as from the hydrolysis of thiodiazines such as MITC and Dazomet, [redacted] (1978, A8.12.1-014) suggested that methyl mustard oil may be the main allergen since its isothiocyanate group

binds easily to protein. According to the author, Metham sodium may also cause a toxic dermatitis like other mustard oil forming agents.

It can be retained that MITC but also Dazomet were tested positive for skin sensitisation in human subjects. In addition it is assumed that these compounds can cause a toxic dermatitis too.

Within a study investigating the role of pesticides with respect to toxic and allergic dermatitis of the skin, [redacted] (1986, 1987, A8.12.1-007) tested 36 substances with 652 subjects from different areas (males and females; agricultural workers, ex agricultural workers, other) to establish the optimal test concentrations and the frequencies of irritant and allergic reactions. Dazomet was tested at concentrations of 0.25 % or 0.1 % in petrolatum. MITC was not tested in this study. The frequency of skin irritation and sensitisation was low. There was no skin reaction in agricultural workers. Allergenic responses were noted in ex-agricultural workers at 0.25 % (1 out of 32) and 0.1% (1 out of 37). In the other 'non-agricultural' collective an irritant response was noted at 0.25 (1 out of 191) and 0.1% (1 out of 198).

These results show that Dazomet has a low irritant and sensitizing potential in this study and there is no indication that agricultural workers are more at risk. However it should be noted, that Dazomet was tested in petrolatum which might have prevented the generation of the potent allergen MITC, and MITC has also not been tested in this study.

[redacted] (1973, A8.12.1-011) reported bullous dermatitis in a hardboard factory worker and in a farmer following use of Dazomet or of Dazomet and Chloropicron, respectively was reported by. Patch testing showed a positive reaction to Dazomet (0.25 % in aq.) in the hardboard factory worker and to Dazomet (0.125, 0.25 and 0.5 % in aq.) and Chloropicron (0.5 % in aq.) in the farmer. It appears that use of Dazomet can cause skin irritations and sensitisation.

Seven cases (all male agricultural workers) of contact dermatitis due to the exposure to Dazomet were reported by [redacted]. (1993, A8.12.1-008). The primary lesions (mainly bullous skin reactions) that were observed were reversible and healing process lasted for a few days to 3 weeks. Only one of the 7 patients was subjected to an epicutaneous test using aqueous solutions of Dazomet ranging from 0.01 % to 02 %. Even at the lowest concentration of 0.01% Dazomet, an irritant response was observed which was characterized by a bullous skin reaction with sensation of burning.

Comparing the results of the present study (positive skin reaction) to those of the study of [redacted] and coworkers (negative skin reaction; see above), the difference between the respectively obtained results was explained by the fact that in the study of [redacted] and in contrast to the study of [redacted]., Dazomet was tested in petrolatum instead of water: Dazomet is not dissociated in organic solvents. Nevertheless the authors would not rule out a sensitising effect of Dazomet due to its degradation to the known allergen MITC.

Summarizing this study it can be retained that Dazomet can cause irritant dermatitis in doses as low as 0.01% in water, and has been shown to be irritant under practical work conditions in 7 agricultural workers. An allergic response to Dazomet has not been studied by the authors, but was assumed due to its breakdown product MITC, a strong allergen.

[redacted]. (1995, A8.12.1-013) reported the outbreak of dermatitis among a group of 42 workers

cleaning up a spill of Metham sodium (33 % aqueous solution) when a train tanker car transporting 19,000 gallons of the soil fumigant derailed and released accidentally its content into the Sacramento river/California on July 14, 1991. Other groups of workers cleaning the spill however did not experience dermatitis. Upon further dilution in the river and in the presence of oxygen, Metham sodium is known to decompose into MITC, hydrogen sulfide and under appropriate environmental conditions, methylamines, carbon disulfide and other compounds. MITC killed most river flora and fauna including fish. A total of 27 out of a group of 42 workers removing large amounts of dead fish experienced dermatitis involving the feet and ankle. Another group of 31 workers did not, although they also became wet. When reviewing the workers it became clear that this group was immediately changing cloth when their lower extremities became wet, however the other group did not, thus working a long time with wetness, occlusive boots, under hot weather conditions. An increase in severity of dermatitis was also noted with respect to time spent working with wet clothing. MITC whose concentration at the spill site was 20-40 ppb was the only chemical monitored. Other strongly irritant chemicals that could have been also responsible for the dermatitis could be especially methylamines produced by the large amount of dead fish when decomposing fast under the summer conditions. A pre-sensitization to the known allergen MITC was ruled out. Thus no patch test for skin sensitisation of MITC has been performed in the workers after the spill. The contributing factors like wetness, occlusive and long exposure, friction and heat explained the possibility that MITC is irritating under these low concentrations.

Although a final conclusion here is not possible MITC and/or methylamines might have led to irritant dermatitis when workers had exposure under wet, occlusive conditions in warm weather. If appropriate measures were taken (immediate changing of cloth, boots) no such effect occurred.

As a consequence of the spill of Metham sodium (33 % aqueous solution) that resulted from the train tanker car derailment mentioned above, MITC was subsequently released into the air as a result of chemical break down under the environmental conditions present at that time ([redacted]. 1994, A8.12.1-003; [redacted]. 1994, A8.12.1-003). In the nearby township of Dunsmuir measured MITC levels ranged from 0.2 to 37 ppb and estimated peak levels ranged from 140 to 1600 ppb. 2129 inhabitants were exposed to MITC vapours and complained of burning eyes, nasal and throat irritation, shortness of breath and non-specific neurological complaints such as dizziness and headache. All these symptoms were consistent with MITC exposure. The onset of symptoms was as early as 12 hours after the spill but generally the day after. New reports of nasal and throat irritation continued for up to 8 days of the spill, eye irritation reports continued for 2 weeks. In this respect it is noteworthy that the highest MITC concentration measured was 4 days after the spill in the Dunsmuir area, which might explain the ‘delayed’ reporting of symptoms. The symptoms generally decreased over time. Seven individuals required hospitalisation. Two of them had pre-existing asthma another one suffered from a chronic obstructive lung disease. Reference exposure levels (REL’s) for 1 hour were proposed by the authors as follows: to prevent discomfort (0.5 ppb); to prevent disability (40 ppb); to prevent live threatening injury (150 ppb).

MITC has been shown to cause irritation of exposed tissues (skin, eye, respiratory- and gastrointestinal tract) as well as dizziness and headache at low concentrations. Levels above 0.5 ppb might produce discomfort and those above 150 ppm inhaled over a period of 1 hour might be severely affecting the health of exposed persons.

Following the same tank car derailment as described above, the authors from pediatric hospitals in [redacted] reported in a short abstract the examination of 13 children 3-6 years after the spill ([redacted]. 1993, A8.12.1-004). Their age ranged from 4 to 13 months, seven of them were females. None of the children hat a prior history of atopy or asthma and five of them had significant environmental tobacco smoke exposure. Following the spill 10 children had acute symptoms of cough and short breath. Cough persisted in 6 children for at least 3 months. One child had significant decrease in FEF25-75 on pulmonary function test. Metacholine challenge tests were administered to all children. None of them were reactive (69 %), one was equivocal (8 %) and 3 were negative (23 %). The prevalence of airway hyper responsiveness in normal children is in the range of 5-7 %.

The authors concluded that MITC exposure as given in this case of a spill results in abnormalities in pulmonary function tests and persistent clinical symptoms.

The aim of an **epidemiological study (BPR Annex II 8.12.4)** performed by [redacted] (1996, A8.12.4-001) was to examine the cancer risk among pesticide users in Iceland. A cohort with 2449 licensed pesticide users, students from horticultural college, members of a pension fund for market gardeners, horticulturists and vegetable farmers were followed up to end of 1993 in the Icelandic cancer registry of cancer incidences. The observed number of cancers was compared with expected values calculated on the basis of cancer incidence for males and females in Iceland. Dazomet was among 21 pesticides sold during 1976-1993 in Iceland according to information from the Committee on Toxic Substances. The standardized incidence ratio (SIR) for all cancers was 0.8. Among females the increased incidence for cancer of the lymphatic and haemopoietic tissue was significant (SIR 5.6 – 95 % confidence interval CI 1.1 – 16.2). The incidence of rectal cancer was three times that expected (SIR 2.9 – 95 % CI 1.1 – 6.4) and even more predominant in licensed pesticide users.

According to the authors the results provide some support for the suggestion that pesticide exposure may lead to cancer of the lymphatic and haemopoietic tissue in females. Some of the pesticides to which licensed pesticide users were exposed may also lead to rectal cancer. As Dazomet was one of 21 pesticides used it is not possible to evaluate its contribution to this study.

Sister chromatid exchange (SCE) and chromosomal aberrations were studied in a population of floriculturists occupationally exposed to organophosphorous, carbamate and organochlorine pesticides ([redacted]. 1985, A8.12.4-003). The people examined were from a community called La Capilla a rural area between Buenos Aires and La Plata/Argentinia. One of the 17 pesticides used the week before blood sampling for cytogenetic/sister chromatid investigations was reported to be Dazomet. Blood was sampled from 36 individuals from a community of 154 persons of Asiatic origin. Sister chromatid exchange and chromosome aberration was compared from floriculturists showing indication of a chronic intoxication to those not showing this effect. In addition the values were compared to a group of non-floriculturists assuming that they had no pesticide exposure. SCE frequencies (6.45 +/- 1.19) were higher in the group of floriculturists showing at least one symptom in chronic intoxication (such as fatigue, numbness, muscle weakness and pain in higher/lower limbs, leg cramps, abdominal pain) when compared to floriculturists showing no such symptoms (5.47 +/- 1.03). In contrast chromosomal aberration was comparable with both groups, however when compared to non-exposed persons, a significant increment of exchange-type aberrations was noted. The study does not allow to draw conclusion of cytogenetic damage or increased SCE activity with respect to a

single pesticide used by the floriculturists. Two further studies are available, which investigated the peripheral blood of humans exposed at the same time to numerous pesticides including among other Dazomet. Within the first study [redacted] (1991, A8.12.4-004) looked for chromosomal aberration/sister chromatid exchange in relationship with an increased incidence of bladder cancer observed among floriculturists in a north western area of Italy (Sanremo, IM). Within the second one [redacted] (1993, 1995, A8.12.4-002) looked for the frequency of micronuclei indicating cytogenetic damage in humans in the Liguria Region of Italy where commercial flower production is located. The findings of these studies taken together with the study of [redacted]. (1985, A8.12.4-003) support the hypothesis that human exposure to pesticides may cause genotoxic damages but the results deserve further investigations in this field. Though, the complex exposure situation does not allow an association of the observed genotoxic effects with respect to any particular pesticide such as Dazomet for example. Nevertheless, adopting protective measures by the floriculturists is strongly recommended.

The toxicity of poisoning by metam sodium, a dithiocarbamate fumigant, the breakdown products of which is, besides others, methyl isothiocyanate (MITC) was evaluated by means of a retrospective, observational case series of metam sodium exposure cases reported to the Angers Poison and Toxicovigilance Centre from 1992 through 2009, which served as the data source of the study reported by [redacted] (2011, A8.12.4-005). A total of 106 cases of metam sodium exposure were recorded and 102 cases were included in this study. All cases of exposure were unintentional. Occupational poisoning occurred in eight cases. The most common route of exposure was inhalation (n = 96). In 79 cases, the patients were people living near fields where metam sodium had recently been applied. Most of the reported symptoms involved irritation of the eyes (n =76), throat and nose (n = 65), attributable to MITC. Cough and dyspnoea occurred in four cases but no persistent, irritant-induced asthma or persistent exacerbation of asthma was observed. Sixteen patients at two different sites of pollution were exposed to emanations from the drainage system in their homes following the illicit discharge of metam sodium into the sewers. Most presented with nausea and headaches, but only four experienced eye or throat irritation. The only lethal case recorded was a truck driver who was found dead of acute lung injury after falling into a tank that had previously contained metam sodium. Two patients who ingested a dilute solution, presented with mild epigastric pain. Four skin exposures caused erythema (n = 2), moderate burns (n = 1), and urticaria (n = 1). According to the poisoning severity score, their symptoms were minor in 99% of cases.

Acute metam sodium exposure usually causes minor symptoms. They vary as a function of the circumstances of exposure, which determine the degradation product that forms. On contact with moist soil, metam sodium decomposes into MITC and causes irritant symptoms. Since a comparable breakdown mechanism can be assumed for Dazomet, the study was presented here in support of the assessment.

Considering the aspects of diagnosis of poisoning (BPR Annex II 8.12.5), specific signs of poisoning and clinical tests, we already mentioned the fatal case of intoxication of a young female student who drank water containing 50 g MITC, which was reported by [redacted] (1981, A8.12.2-002). The patient noticed severe retrosternal burning and epigastric pain immediately after ingestion and began to vomit. A few minutes later she showed generalized tonic and clonic seizures and became unconscious. The patient arrived at the hospital deeply comatose with pulse 98/min and blood pressure 90/60 mm/hg, slightly dilated pupils and complete loss of all reflexes and motor activity. Although gastric lavage and peritoneal dialysis was performed

immediately, the patient died 8 hours after admission to the hospital. Necropsy showed extensive necrosis of the oesophagus, stomach and proximal part of the duodenum. This case clearly showed that MITC is toxic to human following oral ingestion and results in heavy local damages of the gastrointestinal mucosa.

As first aid measures, antidotes and medical treatment (BPR Annex II 8.12.7) in case of a systemically exposure of humans to Dazomet and/or MITC, the BASF medical department proposed within a personal communication following treatment procedures:
In case of a systemically exposure to Dazomet, alcohol consumption must be avoid for 48 hours following exposure.

In case of inhalation of MITC vapors, immediately after inhalation, administration of 5 puffs of Dexamethasone from a metered dose inhaler. Thereafter 2 puffs every 10 minutes until exhaustion of the dose inhaler. As there is no antidote to be administrated to counteract the effects of MITC, therapy may be empiric. Treatment with aerosolised bronchodilatators such as terbuline can be performed in case of patients suffering from bronchiospasm. In this case, 2 to 3 days after exposure, therapy has to be symptomatic. In case of a severe exposure to MITC, a PA chest X-ray and a spirometry should be performed in order to exclude severe pulmonary damages and to control lung function.

The expected effects of poisoning (BPR Annex II 8.12.8) can be summarized as follows:
Dazomet is expected to cause irritation of exposed skin and mucous membranes as well as skin sensitisation especially if degradation to Methylisothiacyanate in aqueous medium occurs. Systemic toxicity can be expected after intensive dermal contact or oral uptake. Again, MITC is formed fast and seems to be the toxic metabolite/ degradation product.

It can be retained that irritation of Dazomet under work place conditions in industry is low, due to appropriate protective measures. Over a period of at least 10 years only 17 cases of irritation to skin and eyes have been reported to the BASF medical department. Especially in non-aqueous systems, the release of MITC from Dazomet might be so low, that it does not show a sensitising potential (BPR Annex II 8.12.6) under the conditions described. In this case it is also referred to animal studies (GPMT) where Dazomet was not a skin sensitizer when applied in olive oil.

Due to the low stability of Dazomet in aqueous systems especially under acidic conditions, most human health effects seen with Dazomet might be due to MITC formation, the main metabolite and degradation product of Dazomet. MITC has a high acute toxicity as experienced from a case of fatal human intoxication where ingestion of 50 g was lethal and caused necrosis of exposed mucosa tissue. Even at low concentrations MITC is strongly irritant to exposed human tissues (skin, eye, respiratory and gastrointestinal tract) causing skin rash, itching and inflammation. Clinical symptoms that can also be expected with systemic (inhalative) exposure of MITC are - besides non-specific findings such as dizziness and headache - euphoria, ataxia, memory loss and muscle pain. MITC is a very potent allergen in humans (based on the limited exposure and high incidence of cases) as already noted in predictive animal tests. A challenge reaction of the skin can even be provoked with airborne MITC vapours. MITC can also cause non-specific airway hyper responsiveness that could persist after cessation of exposure. Respiratory sensitisation is possible. In sensitized persons asthmatic attacks (constriction of the bronchi with severe dyspnoea, wheezing, chest tightness and coughing) are possible.

Several studies examining chromosomal damage and sister-chromatid exchange indicate a higher frequency in pesticide (floricultural) workers, however in none of the studies a direct correlation with Dazomet or MITC was possible. This also holds for increased cancer risk in Icelandic pesticide workers

Table A-106: Summary table of further human data

See Confidential Annex, table 96.

A.3.16 Other data

Phototoxicity (BPR Annex II 8.13.1)

A new *in vitro* phototoxicity study is provided. Dazomet was evaluated for its potential to induce phototoxicity after exposure to light in cultured mouse embryonic fibroblast (BALB/c 3T3) cells (OECD TG 432). The IC50 for Dazomet was determined to be 778 µg/mL without irradiation and 270 µg/mL after irradiation. The Photo Irritation Factor (PIF; the ratio of the IC50 with and without irradiation) was calculated to be 2.89. Since the PIF was greater than 2 but less than 5, Dazomet was considered to be a probable phototoxic test item under the conditions of the test.

Table A-107: Summary table of other data

Type of data / report, Reliability, Key / supportive study	Test substance (including purity), Vehicle	Relevant information about the study	Main effects, Observations	Reference
***In vitro* 3T3 NRU phototoxicity test** **Reliability: 1** **Key study**	Dazomet Purity 96.6 % Vehicle: DMSO or buffered salt solution BALB/c 3T3 mammalian cell line	Since the PIF was greater than 2 but less than 5, the active ingredient of Basamid®, Dazomet, was considered to be a probable phototoxic test item under the conditions of the test. The MPE, which was less than 0.1, suggested that the test item was not phototoxic. The pH of the highest concentration of test item was similar to that of the concurrent controls and was within the physiological pH range of 6.5 to 7.8 (2). All system suitability acceptance criteria were met for the main study, including the positive control, CPZ, which produced a PIF value of 25.4 (phototoxic). The concurrent solvent, growth and positive controls and results for the test item were all accepted as valid.	Probable phototoxic Photo Irritation Factor (PIF) = 2.89 Mean Photo Effect (MPE) = 0.0700	[redacted] (2019d) IUCLID: A8.13.1-001

A.4 Environmental effects assessment

A.4.1 Fate and distribution in the environment

A.4.1.1 Degradation

A.4.1.1.1 Abiotic degradation

Hydrolysis

A hydrolysis test was performed by [redacted] (2003) according to the EPA Pesticide Assessment Guidelines, Subdiv. N; Chemistry: Environmental Fate, § 161-1 at pH 4,5,7,9 and at temperature 25°C (main study) and 35°C (pre-study) on C14-labelled dazomet of specific activity 9.2 MBq/mg in acetonitrile and on MITC. Analysis were carried out by LSC (Liquid Scintillation Counting) for radioactivity and by HPLC for the identification of dazomet and MITC and confirmed by HPLC-MS.

The result presented in table A-106 shows that hydrolysis of dazomet is more efficient at basic pH than for acidic pH at 25 °C. The result of a pre-test shows that this finding is still verified for 35°C. However, the degradation rate at 35°C is higher than the degradation rate at 25°C.

For dazomet the main hydrolysis product identified was MITC. Nevertheless, a serie of metabolites including carbon disulfide, N.N´-Dimethylthiourea and (Methylamino)(thioxo)methanesulfenic acid could be characterized and identified.

Table A-108: Summary table- Hydrolysis

Method, Guideline, GLP status, Reliability, Key / supportive study	pH	Temp. [°C]	Initial TS concentration, C0 [mol/L]	Half-life, DT50 [d]	Coefficient of correlation, r2	Remarks	Reference
EPA Pesticide Assessment Guidelines, Subdiv. N: Environmental Fate § 161-1	4 5 7 9	Main study 25°C (30 days) Pre-study 35°C (2 days)	Dazomet 10 mg/L	0.36 - - 0.12	0.99 0.99 0.99 0.99	1.951 2.748 3.231 5.854 Reaction rate constant, K_h [1/s x 10^5]	[redacted]. (2003) A10.1.1.1-001
	4 5 7 9	Main study 25°C (30 days) Pre-study 35°C (2 days)	MITC 10 mg/L	107.25 - - 11.14	0.88 0.99 0.96 0.99	0.006 0.0005 0.006 0.062 Reaction rate constant, K_h [1/s x 10^5]	

Phototransformation in water

A photolysis test was performed according to FAO (Revised Guideline on Environmental Criteria for the Registration of Pesticides) 1993 and to MAFF (12-Noussan-No. 8147, 2-6-1, 2000) Guidelines on non-labelled and C14 labelled dazomet in water. MITC was used as a reference substance in this study.

Analyses were carried out by means of Liquid Scintillation Counting (LSC) for the determination of the total radioactivity in test water samples. The recovery rate and the characterization of individual radioactive components were carried out by means of High Performance Liquid Chromatography (HPLC) coupled with a radioactivity detector (RD) equipped with a liquid flow cell and the determination of the quantum yield of dazomet by measurement of the degradation rate of a chemical actinometer, p-nitroanisole (PNA) according to [redacted] (1982).

Table A-109: Summary table- Photolysis in water

Method, Guideline, GLP status, Reliability, Key/supportive study	Initial molar TS concentration	Total recovery of test substance [% of appl. AS]	Photolysis rate constant (kcp)	Direct photolysis sunlight rate constant (kpE)	Reaction quantum yield (ΦcE)	Half-life (t1/2E)	Reference
FAO 1993 and MAFF 2000	10 mg/L Dazomet	83.6 % and 85 % (30 days)	0.194 to 0.149	n.d.	n.d.	7.6 and 9.9 hours	[redacted] (2003) A10.1.1.1-002
MAFF 2000	10 mg/L MITC	n.d.	0.00166 to 0.00150	n.d.	n.d.	885 and 980 hours	[redacted] (2001c) A10.1.1.1-003

Estimated photo-oxidation in air

[redacted] (1992b) has evaluated the contribution of different atmospheric components on the photodegradation of MITC in air. The results of the smog chamber investigation of the tropospheric degradation path of MITC, shows that using H2O2 as a precursor of OH, direct photolysis is observed to dominate in the observed decay, OH contributing less than 15% to the degradation. However, the photolytic rate constant increases mainly by increasing O2 levels. Increasing the level of MITC doesn't contribute to significantly increase the photodegradation rate of MITC.

For environmental solar irradiation conditions of July at sea level in the middle Europe, a photolytic rate constant of 1.8 10-6 s-1 is obtained from a convolution of the solar spectrum and the UV absorption (assuming a quantum yield of unity), leading to a half-life of 4.5 days.

Table A-110: Summary table- Photo-oxidation in air

Model	Light protection (yes/no)	Estimated daily (24h) OH concentration [OH/cm³]	Overall OH rate constant [cm³/molecule ec]	Half-life [hr]	Reference
OECD draft "Absolute methods to determine the rate of reaction with OH radicals" (1990)	MITC	3.9 to 4.9 x 10 -13 cm3 sec-1 4.9 x 10-13 cm3 sec-1	n.d. 1.8 x 10-6 sec-1	960 (40 days) 108 (4.5 days)	[redacted] (1992a) A10.3.1-001 [redacted] (1992b) A10.3.1-002

A.4.1.1.2 Biotic degradation, initial studies

Biodegradability (ready/inherent)

Dazomet hydrolyses rapidly to the major product MITC (see point 4.1.1.1). The assessment of the biodegradability is closely connected to both of these substances and is summarized in the following table:

Table A-111: Summary table - biodegradation studies (ready/inherent)

Method, Guideline, GLP status, Reliability, Key/supportive study	Test type[1]	Test parameter	Inoculum			Additional substrate	Test substance concentr.	Degradation		Remarks [positive control]	Reference
			Type	Concentration	Adaptation			Incubation period	Degree [%]		
Dazomet	OECD TG 301D	Ready	BOD	domestic	Effluent from STP	Non-adapted	2 mg/L	28 days	50-60	-	[redacted] (2001a) A10.1.1.2-001
Dazomet	OECD TG 302B	inherent	TOC	industrial	1 g dm/L	adapted	200 mg/L	22 days	90-100	-	[redacted] (1983) A10.1.1.2-003
MITC	OECD TG 301D	Ready	BOD	domestic	Effluent from STP	Non-adapted	2 mg/L	28 days	0-10	-	[redacted] (2001b) A10.1.1.2-002

[1] *Test on inherent or ready biodegradability according to OECD criteria*

Dazomet is therefore considered to be not readily biodegradable.

A.4.1.1.3 Rate and route of degradation including identification of metabolites and degradation products

A.4.1.1.3.1 Biological sewage treatment

Not applicable for the CLH report.

Aerobic biodegradation

Table A-112: Summary table - STP aerobic biodegradation

Not applicable for the CLH report.

Anaerobic biodegradation

Table A-113: Summary table - STP anaerobic biodegradation

Not applicable for the CLH report.

STP simulation test

Table A-114: Summary table - STP simulation test

Not applicable for the CLH report.

A.4.1.1.3.2 Biodegradation in freshwater

Aerobic aquatic degradation

Table A-115: Summary table - Freshwater aerobic biodegradation

Data waiving	
Information requirement	Fresh water aerobic degradation
Justification	Not required because of the use pattern of dazomet in utility poles

Water/sediment degradation test

Table A-116: Summary table - fresh water/sediment degradation

Method, Guideline, GLP status, Reliability, Key/supportive study	Test type[1]	Exposure	Test system		Test substance concentration	Incubation period	Degradation (DT50)	Remarks	Reference
			Water	Sediment					
US EPA Subdiv. N Series 162-4	Biotic	34 d	Pond water	Sandy loam	10 ppm	34 d	**Dazomet** 5 h **MITC** 2 d	-	[redacted] (1994b), Aerobic Aquatic Metabolism of 14C-Dazomet, [redacted], unpublished report 2522

Degradation of 14C-Dazomet was demonstrated throughout the one month (34 days) of aerobic incubation in microbiologically active pond water and sediment. Extensive production of volatile products was noted with greater than 50 % of applied dose recovered in volatiles traps by 34 days. The calculated Dazomet half-life was 5 hours with a 1.33 x 10-1 hour-1 rate constant. The MITC half-life was 2 days with a 3.0 x 10-1 day-1 rate constant. The degradation pathway consisted of two major routes of degradation; hydrolytic cleavage of the thiadiazine ring to yield MITC (Methylisothiocyanate) and metabolism of MITC to produce $^{14}CO_2$. During early samplings an unknown was observed at up to 28.8 % of dose. This unknown was isolated from reverse phase high performance liquid chromatography and analysed using direct probe mass spectrometry techniques. The unknown was subsequently identified as MW154 (phosphorylated MITC). This MITC-phosphate was only a transient, short-lived metabolite which apparently represents the equilibrium with phosphate and degraded back to phosphate and MITC within the first day of the study. From sediment extracts, MMTU (1-methyl-2-thiourea), was observed at a maximum of 3.6 % in non-sterile Day 3 sediment. This MMTU represents release of sediment bound MITC which reacted with the ammonium hydroxide in the extraction solvent to yield MMTU. One further metabolite (day 1 - 3, max. 5.9 %) could not be identified. No CS2 or COS was detected in the Vile's reagent trap.

In conclusion, Dazomet degrades rapidly to MITC with a DT50 of ca. 5 h. MITC, in turn rapidly degrades to CO_2, with a system DT50 of 2 days. After 1 month, more than half of the detected radioactivity was CO_2.

However for classification purpose, Dazomet is not considered to be readily degradable. Indeed according to paragraph 4.1.2.9.4 of the Annex I of the CLP Guidance (2017) , the environmental degradation to consider may be either biotic or abiotic. Hydrolysis can only be considered if the hydrolysis products do not fulfil the criteria for classification as hazardous to the aquatic environment. As MITC fulfils this classification criteria, Dazomet is considered as not rapidly degradable.

A.4.1.1.3.3 Biodegradation in seawater

Seawater degradation study

Table A-117: Summary table - Seawater aerobic biodegradation

Data waiving	
Information requirement	Seawater aerobic biodegradation
Justification	The use of Dazomet is recommended for the internal remedial treatment and protection of wood products such as utility poles. As no application in seawater system is intended, no key studies are required for this endpoint.

Seawater/sediment degradation study

Table A-118: Summary table - seawater/sediment biodegradation

Data waiving	
Information requirement	seawater/sediment biodegradation
Justification	The use of Dazomet is recommended for the internal remedial treatment and protection of wood products such as utility poles. As no application in seawater system is intended, no key studies are required for this endpoint.

A.4.1.1.3.4 Higher tier degradation studies in water or sediment

No data available.

A.4.1.1.3.5 Biodegradation during manure storage

Table A-119: Summary table - Biodegradation during manure storage

Not applicable for the CLH report.

A.4.1.1.3.6 Biotic degradation in soil

A.4.1.1.3.6.1 Laboratory soil degradation studies

Aerobic biodegradation

Table A-120: Summary table - Aerobic biodegradation in soil- laboratory study

Method, Guideline, GLP status, Reliability, Key / supportive study	Test type[1]	Test parameter	Test system				Test substance concentr.	Incubation period	Degradation	Remarks	Reference
			Soil origin	Soil type	pH	OC %					
Aerobic rate of degradation in soil (DT50 /DT90), GLP, Key study	BBA Richtlinie Teil IV, 4-1, SETAC, March 1995,	-	Natural soils (Germany)	Li 25 b (silty sand) Lufa 2.2 (silty sand) Lufa 3A (silty sand)	The soils cover a pH (water suspension) 6.6 – 7.8 and a pH ($CaCl_2$) 5.6 – 7.1	12 glass test vessels per each soil type with 11.9 mg of the dry $^{12}C/^{14}C$ -test item	34 days at 20°C and 64 days at 10°C	**20 °C Dazomet** 0.28 (Li 35b: r2 = 0.97) 0.54 (Lufa 2.2) 0.3 days (Lufa 3A) **MITC** Range of 5.0 - 13.6 days (r2 = 0.80 - 0.97) **10 °C Dazomet** DT50lab = 1.3 day (r2 = 0.89). The degradation of Dazomet resulted in the formation of	[redacted] (2003) A10.2.1-002	Aerobic rate of degradation in soil (DT50 /DT90), GLP, Key study	[redacted] March 1995,

								MITC, which was quickly further degraded to CO2 and non-extractable residues. **MITC** DT50lab = 32.7 days (r2 = 0.89)			

[1] *Test according to OECD criteria*

Examination of Efficiency of 0.5 M H2SO4 Traps used previously in Aerobic Soil Metabolism and Degradation Studies, No guideline, GLP, reliable without restriction, supportive study	Reason for supportive study to [redacted], 2003 BASF Doc. ID 2003/1005447: A study was conducted to demonstrate the efficiency of sulfuric acid traps in trapping volatile methyl isothiocyanate.	Result/Conclusion: In this study the trapping efficiency of 0.5-M aqueous sulfuric acid for volatile methyl isothiocyanate was assessed. Methyl isothiocyanate was passed through a 100-mL 0.5-M aqueous sulfuric acid trap, two 50-mL 0.5-M aqueous sulfuric acid traps and a Tenax® tube. No breakthrough was observed at flow rates of 34 mL/min and 65 mL/min for 45 minutes at room temperature. The aqueous sulfuric acid traps used in the aerobic degradation studies allow for accurate determination of volatile methyl isothiocyanate.

Anaerobic biodegradation

Table A-121: Summary table - Anaerobic biodegradation in soil- laboratory study

Not applicable for the CLH.

A.4.1.1.3.6.2 Higher tier degradation studies in soil

Field dissipation studies (field studies, two soil types)

Table A-122: Summary table - Field dissipation

Not applicable for the CLH.

A.4.1.1.3.7 Short summary and overall relevance of the provided information on degradation and conclusion on rapid degradation for classification and labelling purposes

Dazomet, which is predominantly degraded into MITC in water, shows an extremely rapid degradation in water/sediment systems through biodegradation (DT_{50} = 5 hour at 12 °C), hydrolysis (DT_{50} = 0.59 d at 12 ºC) and photolysis (DT_{50} = 9.9 hour). The criteria of rapid degradation from the ready biodegradability test is not met but according to the CLP criteria evidence from other degradability studies should be taken into account to assess the rapid biodegradability of a substance. In the case of dazomet, although abiotic and biotic degradation studies in water and soil show a rapid dissipation in environment, the active substance is not considered to be readily degradable as its hydrolysis product (MITC) fulfils the criteria for classification as hazardous to the aquatic environment.

The main metabolite, MITC, is not ready biodegradable according to the results of the OECD TG 301D. However, according to available data, it is biodegradable in water/sediment system with a DT50 of 2d where more than 40 % of CO_2 is formed within 7d, reaching a maximum of 48.3 % after 34 d. In addition, MITC is characterised by high volatilisation from soil and water. In air, MITC degrades from UV absorption and oxidation with OH radicals with DT_{50} varying from 4.5d (summer condition) to 40d (winter condition).

A.4.1.2 Distribution

A.4.1.2.1 Adsorption onto/desorption from soils

Table A-123: Summary table - Adsorption/desorption

Not applicable for the CLH.

Table A-124: Summary table – Adsorption/desorption metabolite/ degradant/ transformation- or reaction product

Not applicable for the CLH.

A.4.1.2.2 Higher tier soil adsorption studies

No higher tier soil adsorption studies were performed for Dazomet.

A.4.1.2.3 Volatilisation

Regarding volatilisation, please see Part A, section 1.3 Physical and chemical properties of the active substance.

A.4.1.3 Bioaccumulation

Measured aquatic bioconcentration

Table A-125: Summary table - Measured aquatic bioconcentration

Data waiving	
Information requirement	The experimental determination may not need to be carried out if it can be demonstrated on the basis of physicochemical properties (e.g. log K_{OW} <3) or other evidence that the substance has a low potential for bioconcentration.
Justification	The aquatic bioconcentration factor has been estimated as the log K_{OW} of Dazomet is 0.3 at 25 ºC and the log Kow of MITC 1.2 at 25 °C.

Estimated aquatic bioconcentration

Table A-126: Summary table - Estimated aquatic bioconcentration

Basis for estimation	Log Kow (calculated)	Estimated BCF for fish (freshwater)	Estimated BCF for fish eating bird / predator	Remarks	Reference
BCF for fish based on QSAR, derived from the physchem properties of Dazomet*	0.3 at 25 °C ([redacted], 2002)	2.39	0.359 L/kg_{wwt} (GBPR, 2017)	-	Unpublished calculation, [redacted] (2003), IUCLID 9.1.7
BCF for fish based on QSAR, derived from the physchem properties of MITC*	1.2 at 25 °C ([redacted], 2001)	3.16	2.09 L/kg_{wwt} (GBPR, 2017)	-	Report n° ID IET 00-6015-4, [redacted] (2001), IUCLID 9.1.7

*The new studies are indicated in green.

Dazomet is characterized by a log Kow value of 0.3 ([redacted], 2002) and a calculated BCF value of 2.39 was reported by [redacted] (2003), indicating no significant risk of bioaccumulation of the substance in organisms.

For the degradation product MITC, a log Kow of 1.2 and a calculated BCF value of 3.16 were reported by [redacted] (2001), indicating no significant risk of bioaccumulation of this substance in organisms.

Furthermore, the values calculated according to the equation 93 of GBPR (2017) indicated a

$BCF_{aquatic}$ value of 0.359 L/kg_{wwt} for Dazomet and of 2.09 L/kg_{wwt} for MITC, respectively.

Measured terrestrial bioconcentration

Not applicable for the CLH report.

Table A-127: Summary table - Measured terrestrial bioconcentration

Not applicable for the CLH report.

Estimated terrestrial bioconcentration

Not applicable for the CLH report.

Table A-128: Summary table - Estimated terrestrial bioconcentration

Not applicable for the CLH report.

A.4.1.3.1 Short summary and overall relevance of the provided information on bioaccumulation and conclusion on bioaccumulation potential for classification and labelling purposes

Dazomet is characterized by a log Kow of 0.3 and a calculated BCF value of 0.359 L/kg_{wwt} for fish and of 0.864 L/kg_{wwt} for earthworm, indicating no significant risk of bioaccumulation of the substance in organisms.

For the degradation product MITC, a log Kow of 1.2 and a calculated BCF value of 2.09 L/kg_{wwt} for fish and of 1.03 L/kg_{wwt} for earthworm were reported, indicating no significant risk of bioaccumulation of this substance in organisms.

A.4.1.4 Monitoring data

No monitoring data is available.

A.4.2 Effects on environmental organisms

A.4.2.1 Atmosphere

Not applicable for the CLH report.

A.4.2.2 Toxicity to sewage treatment plant (STP) microorganisms

Inhibition of microbial activity (aquatic)

Table A-129: Summary table - Inhibition of microbial activity

Method, Guideline, GLP status, Reliability, Key/supportive study	Species/ Inoculum	Endpoint	Test material (purity)	Exposure		Results (mg/L)			Reference
				Design	Duration	NOEC	EC10	EC50	
Respiration inhibition test OECD TG 209 (1993) GLP Reliability: 2 Supporting data	Activated sludge microorganisms	Respiration rate	Dazomet (97.1 %)	Static	30 min	ca. 17	ca. 160	> 1.00	Report n°2001/1014685, [redacted] (2001) A9.1.5-001
Standard methods for examination of water, waste water and sludge, DIN 38412, Part 8 (1986) and DIN 38404, Part 2	Peudomonas putida	Growth	Dazomet (99.9 %)	Static	17 hours	1.8	5.7	-	Report n°2560, [redacted] (1988) A9.1.5-002

(1976) GLP Reliability: 2 Supporting data									
Respiration inhibition test OECD TG 209 (1993) GLP Reliability: 2 Key study	Activated sludge microorganisms	Respiration rate	MITC (n.r.)	Static	30 min	ca. 1.5	ca. 25	> 1.000	Report n°99/0547/08/1, [redacted] (1999) A9.1.5-003

Dazomet

Inhibition to aquatic microbial activity was investigated by [redacted] (2001) in a activated sludge respiration inhibition test, according to a OECD TG 209 (1993) and by [redacted] (1988) in a cell growth inhibition test (*Pseudomonas putida*), according to DIN 38412 (Part 8 - extracts, 1986) and DIN 38404 (Part 2, 1976). In the activated sludge respiration test, the results are expressed based on the initial concentration.

In the first test ([redacted], 2001), activated sewage sludge was exposed to an aqueous dispersion of the test material at concentration up to 1000 mg/L for a period of 30 minutes. The rate of respiration was determined after 30 minutes and compared to data for the reference substance 3,5-dichlorophenol. Inhibition was determined and gave the following endpoints : EC_{20} ca. 17 mg/L, EC_{50} ca. 160 mg/L and EC_{80} > 1000 mg/L. Dazomet concentration were not monitored during the test, however, dazomet is known to degrade in water. A concentration response curve is given in the reports. At all nominal concentrations, inhibition of the oxygen consumption by activated sludge was observed between 15 % and 69 %. Validity criteria were met.

In the growth-inhibition test performed by [redacted] (1988), the inhibition of the cell growths was measured by means of photometer at 436 nm. No control of the test substance concentration was performed. The result are expressed base on the nominal concentration. The NOEC was 1.0 mg/L and the EC_{50} was 5.7 mg/L. Dazomet degrades in water to MITC which shows higher toxicity than the parent substance.

MITC

Inhibition to microbial activity to microorganism in water of MITC was investigated by [redacted] (1999), according to OECD TG 209 (1993) guideline. The ECx values were graphically determined.

The test gave a value of 25 mg/L MITC for the 50 % inhibition. The inhibition of the oxygen consumption was observed for all concentration from 17 % (1mg/L MITC) up to 78 % (504 and 1000mg/L MITC). The validity criteria were met.

Conclusion

The $EC_{10/20}$ of dazomet and MITC in activated sludge respiration test is <100 mg/L. Depending on conditions and emission concentrations, disturbances in the biodegradation process of activated sludge wastewater treatment plants are possible. For the PNEC derivation, the NOEC of 1mg/L was used for dazomet and the EC_{10} of 1.5 mg/L was used for MITC.

A.4.2.3 Aquatic compartment

Dazomet is characterised by a short half live in presence of water (DT_{50} = 0.59 d at 12 ºC). The active substance is converted on a mole to mole basis to MITC with a 0.45 ratio. Therefore, the application of dazomet should be regarded as a mixture of dazomet and MITC.

Moreover Dazomet is used in only one product ([redacted]) in a concentration of 99.9 %. The only difference between the pure active substance and the product is an environmentally non-relevant substance at a concentration of 0.1 %. Therefore, the result from the test performed on the pure active or on the product has been used indifferently to set PNECs.

Invalidity of old aquatic toxicity studies

It should be noted that with few exceptions, the old aquatic toxicity studies (evaluated in the Dazomet Assessment Report of 2010) are evaluated as no longer valid due to deficiencies in method validation and/or in recovery and/or due to the use of old guidelines.

For Dazomet, a crucial factor to take into account is the rapid hydrolysis (DT_{90} < 24 hours), whereas for MITC, evaporation from surface water occurs due to its high volatility.

In the framework of the previous evaluation of the active substance, ecotoxicity studies with aquatic species have been submitted and evaluated for both Dazomet and MITC. However, these studies are no longer valid since, amongst other shortcomings, the test item concentrations were based on nominal values, not maintained, not determined analytically and/or not checked at the end of the exposure period. As Dazomet degrades quickly in water, it cannot be concluded that the results obtained in these studies reflect the actual toxicity of Dazomet.

In the new submitted studies, the test design was adapted to ensure exposure of the aquatic species to the actual test item, which is verified with analytical determination in accordance with current guidelines. Accordingly, the effects of Dazomet application on aquatic species have been studied in Dazomet and its degradation product MITC.

A.4.2.3.1 Freshwater compartment

Acute/short-term toxicity (freshwater)

Table A-130: Summary table - acute/short-term aquatic toxicity

Method, Guideline, GLP status, Reliability, Key/supportive study	Species	Endpoint/ Type of test	Test material	Exposure		Results	Remarks	Reference
				Design	Duration	LC/EC_{50} (mg/L)		
Fish								
Acute toxicity, EPA Pesticide Assessment Guidelines, Para 72-1 (1982), Not GLP Reliability : 3 Supportive data	Bluegill sunfish (*Lepomis macrochirus*)	Mortality, sublethal effects	Dazomet (99.3 %)	Static	96 h	> 1.000 – < 2.150 (nominal)	-	Unpublished report N° 84/198, [redacted] (1986a), A9.1.1-001
Acute toxicity, EPA Pesticide Assessment Guidelines, Para 72-1 (1982), Not GLP Reliability : 3 Supportive data	Bluegill sunfish (*Lepomis macrochirus*)	Mortality, sublethal effects	Dazomet (99.3 %)	Static	96 h	>0.464 - <1.000 (nominal)	Repetition of previous study	Unpublished report N° 84/198, [redacted] (1986b), A9.1.1-001
Acute toxicity, EPA 660/3-75-001(1975), Not GLP	Rainbow trout (*Salmo gairdneri*)	Mortality, sublethal effects	Dazomet (n.r.)	Static	96 h	0.16 (nominal)	-	Unpublished report No. 82-E-1509R,

Reliability : 3 Supportive data								[redacted] (1982a), A9.1.1-004
Acute toxicity, OECD TG 203 (1992), GLP Reliability : 2 Key study*	Rainbow trout (*Oncorhynchus mykiss*)	Mortality, sublethal effects	Dazomet (99.6 %)	Flow-through	96 h	0.06 (mean measured)	-	Unpublished report No. 20180135, [redacted] (2019a) A9.1.1-002
Acute toxicity, OECD TG 203 (1992), EPA 72-1 (1982), GLP Reliability : 3 Supportive data	Rainbow trout (*Oncorhynchus mykiss*)	Mortality, sublethal effects	MITC (99.6 %)	Semi-static	96 h	0.0531 (mean measured)	-	Unpublished report 12F0722/015099, [redacted] (2002) A9.1.1-005
Acute toxicity, OECD TG 203 (1992), GLP Reliability : 2 Key study*	Rainbow trout (*Oncorhynchus mykiss*)	Mortality, sublethal effects	MITC (99.6%)	Flow-through	96 h	0.09 (mean measured)	-	Unpublished report No. 20180075, [redacted] (2019b) A9.1.1-003
Invertebrates								
Acute toxicity, AST Directive 84/449/EEC, C.2M´s (1981), Committee on Methods for Toxicity Tests with Aquatic Organisms (1975), Not GLP, Reliability : 3 Supportive data	*Daphnia magna*	Mortality	Dazomet (n.r.)	Static	48 h	0.30 (nominal)	-	Unpublished report 82-E-1509D, [redacted] (1982b), A9.1.2-001
DIN 38412 Part 11, Not GLP, Reliability : 3	*Daphnia magna*	Mortality	Dazomet (n.r.)	Static	48 h	0.427 (nominal)	-	Unpublished report 4/80-1/0227/5/80-

Supportive data								801-A 1/15, [redacted] (1980),9.1.2-006
Acute toxicity, OECD TG 202 (2004), GLP Reliability : 2 Key study*	*Daphnia magna*	Mortality, sublethal effects	Dazomet (99.6 %)	Flow-through	48 h	6.8 (mean measured)	-	Unpublished report 20180134, [redacted] (2019c) A9.1.2-004
Acute toxicity, OECD TG 202 (1984), EEC 79/831 C2 (1990), GLP, Reliability : 3 Supportive data	*Daphnia magna*	Mortality, sublethal effects	MITC (99.6 %)	Semi-static	48 h	0.076 (mean measured)	-	Unpublished report No. 58330, [redacted] (2002), A9.1.2-003
Acute toxicity, OECD TG 202 (2004), GLP Reliability : 1 Key study*	*Daphnia magna*	Mortality, sublethal effects	MITC (99.6 %)	Flow-through	48 h	0.124 (mean measured)	-	Unpublished report No. 20180074, [redacted] (2019d) A9.1.2-005
Algae (growth inhibition)[1]								
Acute toxicity DIN Draft 38412 Part 9 (1981) Not GLP Reliability: 4 Supportive data	*Selenastrum capricornutum*	Growth inhibition	Dazomet (n.r.)	Static	96 h	1.015 (nominal)	-	Unpublished report No. 2/0018/2/84-98/84, [redacted] (1984), A9.1.3-001
Acute toxicity OECD TG 201 (1984) GLP Reliability: 4 Supportive data	*Ankistrodesmus bibraianus*	Growth inhibition	Dazomet (n.r.)	Static	72 h	1.08 (nominal)	-	Unpublished report, n° P88-E057, [redacted] (1989), 9.1.3-006

Acute toxicity OECD TG 201 (2011) GLP Reliability: 1 Key study*	*Pseudokirchneriella subcapitata*	Growth inhibition, yield	Dazomet (96.6 %)	Semi-static	72 h	ErC50 > 2.3 EyC50 = 1.5 (mean measured)	-	Unpublished report No. 20180133, [redacted] (2019a), A9.1.3-003
Acute toxicity OECD TG 201 (1984) GLP Reliability: 3 Supportive data	*Pseudokirchneriella subcapitata*	Growth inhibition	MITC (99.0 %)	Static	72 h	ErC50 = 0.58 EyC50 = 0.28 (mean measured)	-	Unpublished report No. 48881, [redacted] (1998), A9.1.3-005
Acute toxicity OECD TG 201 (2011) GLP Reliability: 2 Key study*	*Pseudokirchneriella subcapitata*	Growth inhibition, yield	MITC (99.6 %)	Static	72 h	ErC50 = 0.189 EyC50 = 0.091 (mean measured)	-	Unpublished report No. 20180073, [redacted] (2018a), A9.1.3-002
Acute toxicity OECD TG 201 (2011) GLP Reliability: 2 Key study*	*Anabaena flos-aquae*	Growth inhibition, yield	MITC (99.6 %)	Static	72 h	ErC50 = 0.375 EyC50 = 0.181 (mean measured)	-	Unpublished report No. 20180139, [redacted] (2019b), A9.1.3-004
Other aquatic plants								
Acute toxicity OECD TG 221 (2006) GLP Reliability: 2 Key study*	*Lemna gibba*	Growth rate, yield, sign of toxicity	MITC (99.6 %)	Flow-through	7 days	Growth rate : 0.29 Yield : 0.20 (mean measured)	-	Unpublished report No. 20180077, [redacted] (2019e) A9.1.10-001

n.r.: not reported. *** The new studies are indicated in green.**

Description of the available acute toxicity studies

Acute (short-term) toxicity to fish – Dazomet

Four acute 96h tests performed with bluegill sunfish (*Lepomis macrochirus*) and with rainbow trout (*Oncorhynchus mykiss*) are available.

The tree first acute 96h static tests were performed according to "Pesticide Assessment guidelines, Subdivision E, Hazard Evaluation Wildlife and Aquatic Organisms", (U.S.), EPA, Washington DC, Para. 72-1, p.66, Oct. 1982 and to the Committee on Methods for Toxicity Tests with Aquatic Organisms, EPA-660/3-75-001, 1975, respectively : two tests with bluegill sunfish (*Lepomis macrochirus*) and an third test with rainbow trout (*Salmo gairdneri*).

In the first test with bluegill sunfish ([redacted], 1986), a 96h LC_{50} above 1.00 mg/L but below 2.15 mg/L was reported, based on initial Dazomet concentration. Because of the absence of a linear test concentration/effect relationship, the authors decided to repeat this study. In the second test with bluegill sunfish, a 96h LC_{50} of 0.464 mg/L was reported, based on initial dazomet concentration. This second study also showed absence of a linear test concentration/effect relationship.

In the test with rainbow trout of [redacted] (1982a), the 96h LC_{50} was 0.16 mg/L.

It is to note that in water, Dazomet is degraded in MITC in few hours. Nominal concentration would therefore not reflect the real concentration of Dazomet during the tests. However as no monitoring of the concentrations has been performed in any of these tests, evidence that the concentration have been maintained is not provided. Moreover in the studies of [redacted] (1986) with bluegill sunfish, deviation from test protocols OECD TG 203 (adaptation time of the animals, monitoring of the test substance) are reported. Furthermore these old studies were not GLP and do not comply with the requirements of OECD TG 203 (2019). As a new study, GLP and complying with OECD TG 203, has been submitted in the frame of the renewal of the active substance, these studies are no longer considered reliable and relevant for the classification and the risk assessment of the active substance.

A fourth acute 96-hour study was performed by [redacted] (2019a) to determine the toxicity of Dazomet to rainbow trout (*Oncorhynchus mykiss*) under flow-through design. The study was performed in accordance with OECD TG 203 (1992).

The LC_{50} of Dazomet was 0.06 mg/L, based on arithmetic means of all measurements made for each test concentration (i.e. after 24, 46, 72 and 96 h). Indeed the recoveries ranged between 17 and 94 % of nominal concentrations for Dazomet, with recoveries increasing with test concentrations. However according to GBPR (2017) when the measured concentrations fall < 80 % of nominal and when they are measured more than 2 times during the course of the test (i.e. at start and the end of test period), the mean measured concentrations should be calculated as a geometric mean as the recoveries were constant for each test concentration. However the differences between the two ways of calculating being of the order of the decimal, it was not considered having a significant impact on the calculation of the endpoints. It is noted that the concentrations of MITC were also measured after 0, 24, 48, 72 and 96 hours, although the endpoints were only determined for the parent compound.

Nevertheless the study was well conducted using an appropriate species and it is considered that the endpoint from this last study can be used to address the acute toxicity to fish. Therefore, the 96-hour LC_{50} of 0.06 mg/L is considered suitable for use in classification and risk assessment.

Acute (short-term) toxicity to fish - MITC

Two acute 96h static tests performed with rainbow trout (*Oncorhynchus mykiss*) are available.

The first 96h semi-static test was performed on the rainbow trout (*Salmo gairdneri*) by [redacted] (2002), according to OECD TG 203 (1992) and EPA 72-1 (1982) test guidelines.
The concentration of MITC was analysed for each concentration group at start and end of the first and the last interval (test initiation, 24 h, 72 h, and 96 h). The concentrations were not kept above 80 % for all test concentrations during the test period : the recoveries ranged between 62 and 93 % of nominal concentrations. The 96 hours LC_{50} value for MITC to rainbow trout was 0.0531 mg/L, based on the arithmetic means of all measurements done for each test concentration. However according to GBPR (2017) when the measured concentrations fall < 80 % of nominal and when they are measured more than 2 times during the course of the test (i.e. at start and the end of test period), the mean measured concentrations should be calculated as a geometric mean as the recoveries were constant for each test concentration. Indeed the difference between the two ways of calculating increase with test concentrations : both arithmetic and geometric mean concentrations represent 91.8 % of the nominal concentration of 22 µg/L, but at the nominal concentration of 220 µg/L, the geomean concentration (186.10 µg/L) represents 84.6 % of nominal while the arithmetic mean concentration (202.5 µg/L) equals 92.0% of nominal. The calculated LC_{50} should thus lower than 0.09 µg/L.

The study was well conducted, using an appropriate species, but it was performed under semi-static design. Given the short degradation of MITC in water (2 days at 12 °C) and its high volatility (vapour pressure of 2500 Pa 20 °C), this design is not considered appropriate for properly measuring the actual toxicity of this substance. The study was therefore only considered as supporting data.

A second acute 96-hour static study was performed by [redacted] (2019b) to determine the toxicity of MITC to rainbow trout (*Oncorhynchus mykiss*) under flow-through design. The study was performed in accordance with OECD TG 203 (1992).

The LC_{50} was 0.09 mg/L, based on arithmetic means of all measurements made for each test concentration (i.e. after 24, 46, 72 and 96 h). Indeed the recoveries of MITC ranged between 62 and 93 % of nominal concentrations. However according to GBPR (2017) when the measured concentrations fall < 80 % of nominal and when they are measured more than 2 times during the course of the test, the mean measured concentrations should be calculated as a geometric mean as the recoveries were constant for each test concentration.

Nevertheless the study was well conducted using an appropriate species and the endpoint from this last study can be thus used to address the acute toxicity to fish. Therefore, the 96-hour LC_{50} of 0.09 mg/L is considered suitable for use in classification and risk assessment.

Acute (short-term) toxicity to aquatic invertebrates – Dazomet

Three acute 48h static tests performed with the crustacean *Daphnia magna Straus* are available.

[redacted] (1982b) investigated the acute toxicity of Dazomet to *Daphnia magna* in a 48h static test carried out according to AST Directive 84/449/EEC, C.2M´s "Proposed Standard Practice for Conducting Static Acute Toxicity Tests on Wastewaters with daphnia" (1981) and Committee on Methods for Toxicity Tests with Aquatic Organisms (1975).

The 48h LC_{50} was determined to be 0.30 mg/L. The 24h LC50 was 0.32 mg/L. The results are expressed based on the nominal concentration as no measure of the test concentration was performed during the test.
The author reported three preliminary tests performed prior to the definitive one, due to high mortality of the control daphnia (60 %), which was attributed to bacterial toxins produced in the water holding reservoir. Despite of cleaning and sterilizing of the reservoirs, the mortality within the control group of the definite test was still 10 %, which is at the borderline of the validity criteria according to OECD TG 202 (control mortality < 10 %). Moreover it should be noted that the test was apparently not performed with closed test vessels.

A second acute test on *Daphnia magna Straus* [redacted], 1980) was performed according to the draft proposal of the German standard method DIN 38412 Part 11. The 48 EC50 value reported in this test was 0.427 mg/L. The 24h EC50 was 0.569 mg/L. These values are also expressed based on nominal concentration.

These old studies, performed under static design, were not GLP and do not comply with the requirements of OECD TG 202 (2004). As a new study, GLP and compliant with OECD TG 202, has been submitted in the frame of the renewal of the active substance, these studies are no longer considered reliable and relevant for the classification and the risk assessment of the active substance.

A third acute 48-hour study was performed by [redacted] (2019c) to determine the toxicity of Dazomet to *Daphnia magna* under flow-through design. The study was performed in accordance with OECD TG 202 (2004).

The LC_{50} was 6.8 mg/L, based on arithmetic means of all measurements made for each test concentration (i.e. after 0, 24 and 48 h). Indeed the recoveries of Dazomet ranged between 66 and 96 % of nominal concentrations. However according to the OECD TG 202, if the concentrations were not satisfactorily maintained within ± 20 % of the nominal values throughout the test, then the results should be based on nominal or measured initial values. Moreover according to GBPR (2017), in such situation and as the concentrations were measured more than 2 times during the course of the test, the mean measured concentrations should be calculated as a geometric mean of all measured value per test concentration. However the differences between the two ways of calculating being of the order of the decimal, it was not considered having a significant impact on the calculation of the endpoints.

Nevertheless the study was well conducted and the endpoint from this study can be used to address the acute toxicity to daphnid. Therefore, the 48-hour LC_{50} of 6.8 mg/L is considered suitable for use in classification and risk assessment.

Acute (short-term) toxicity to aquatic invertebrates – MITC

The effect of MITC on the immobilisation of *Daphnia magna Straus* was investigated in two acute toxicity test.

In the first study ([redacted], 2002), the test was conducted according to a protocol based on OECD TG 202 (1984) and EEC Directive 79/831 (1990).
The study was performed under semi-static design, in sealed vessels due to the volatility of the test substance. Analytical verification of the test substance concentrations was conducted in each concentration at 0 and 24 h, immediately after renewal of the test substance, and at the end of the test. The measured concentrations of the test substance ranged between 23 and 97 % of nominal values and were thus not maintained within 80 % of the nominal concentration during the test. The 48h EC50 was therefore determined as geometric mean based on mean measured concentration.
The respective EC50 values were determined to be 0.076 mg/L (48h) and 0.165 mg/L (24h). Due to the use of an old version of OECD TG 202, the use of a semi-static design which is not appropriate for a compound like MITC and a poor recovery of test item concentration, this study is only regarded as supporting data.

A new study was performed by [redacted] (2019d) to determine the toxicity of MITC under flow-through design. The study was performed in accordance with OECD TG 202 (2004).

The LC_{50} was 0.124 mg/L, based on arithmetic means of all measurements made for each test concentration (i.e. after 0, 24 and 48 h) although MITC concentration ranged between 80 and 102 % of nominal concentrations.

The study was well conducted, without restrictions. It is thus considered that the endpoint from this last study can be used to address the acute toxicity to daphnid. Therefore, the 48-hour LC_{50} of 0.124 mg/L is considered suitable for use in classification and risk assessment.

Acute (short-term) toxicity to algae – Dazomet

Three studies testing the toxicity of dazomet to green algae are available.

The first growth inhibition test on algae ([redacted], 1984) was performed according to DIN draft 38412, part 9 guideline.
In this static test, *Scenedesmus subspicatus* was exposed for 96 hours to Dazomet at the following nominal concentrations: 0, 0.015, 0.031, 0.063, 0.125, 0.25,0.5, 1 and 2 mg/L. Algae growth was measured after 24, 48, 72 and 96 hours by spectrophotometry. The ErC_{50} was 1.015mg/L after 96h and the calculated NOErC was 0.063mg/L, both based on nominal concentration. Indeed no measurement of the test substance concentration was carried out during the test.
During the test, the pH value increased from 7 at the beginning up to 10.45 (0.156 mg/L 96h) after 72 h, without explanation. At this value, Dazomet and MITC have a half-life time of 2.9 h and 11.14 d, respectively. Therefore, EC50 and NOEC value could potentially underestimate the toxicity of Dazomet. Moreover the pH effect on growth rate has not been determined although for a pH of 10, the growth of the algae may have been disturbed. Therefore, the results from this study are not considered reliable and are not used for risk assessment and classification.

A second study with *Ankistrodesmus bibraianus* was performed under static design ([redacted], 1989) according to a protocol based on OECD TG 201 (1984).
In this test green algae were exposed to Dazomet at the nominal concentrations of 0.1, 0.15, 0.25, 0.45, 0.7, 1.2, 2.0, 3.0 and 5.0 mg/L for 72h. The EC_{50} was calculated to be 0.61 mg/L, based on nominal concentration as no measurement of Dazomet concentration was carried out during the test.
It was not specified in the report if the test was performed in closed vessels due to significant volatility of MITC. Moreover the concentration of vehicle (methanol) was not constant between test concentrations, ranging between 100 and 250 µl/L, which is above the recommended concentration 100 µl/L.
Furthermore as the test is very old, it was conducted according to an old version of OECD TG 201 and the following validity criteria were not calculated:

- Mean coefficient of variation for section-by-section specific growth rates in each replicate of control cultures ≤ 35 %

- Coefficient of variation of average specific growth rates during the whole test in control cultures ≤ 7 %.

Therefore, the results from this study are not considered reliable and are not used for risk assessment and classification.

A third test ([redacted] 2019a) with *Pseudokirchneriella subcapitata* has been performed according to an updated version of OECD TG 201 (2011).
In this test green algae were exposed to Dazomet at 0.10, 0.25, 0.63, 1.6 and 3.9 mg/L (nominal concentration) for 72h under semi-static design, with medium renewal each 12h to take into account the fast degradation of the test item. The calculated endpoints for growth rate and yield were ErC50 > 2.3 mg/L and EyC50 = 1.5 mg/L (mean measured).

The endpoints were based on mean measured concentrations of Dazomet, calculated as the time-weighted geometric mean of the concentrations of Dazomet measured at all the sampling dates (i.e. at 0, 6, 12, 24, 30, 36, 48, 54, 60 and 72 hours for fresh samples and at 6 or 12 hours aged samples). However it was noted that the equation used to calculate TWA concentrations is not calculated according to GBPR (2017) but according to OECD TG 211, which is not correct as DT_{50} of Dazomet is < 2 days.

Indeed Dazomet concentrations strongly decrease with time (100–117% of nominal values at T0 but only 11–34 % of nominal values after 12h), although this decrease was dose-dependent, with recoveries increasing with test concentration (e.g. only 16% recovery at 0.1 mg/L after 12h but recovery was 25 % for 3.9 g/L). It is noted that the concentrations of MITC were also measured after 0, 24, 48, 72 and 96 hours, although the endpoints were only determined for the parent compound.

Nevertheless the study was well conducted. The endpoints from this last study can thus be used to address the acute toxicity to algae. Therefore, the 72-hour EyC_{50} of 1.5 mg/L is considered suitable for use in risk assessment while the 72-hour ErC_{50} of 2.3 mg/L is considered for the classification.

Acute (short-term) toxicity to algae and other aquatic plants - MITC

Three studies testing the toxicity of MITC to green algae are available. As MITC exhibits herbicidal activities, another study was conducted on an additional algal species, i.e. cyanobacteria *Anabena flos-aquae*. Moreover a 7-day test with the aquatic plant *Lemna gibba* has also been submitted.

In a first study ([redacted], 1998) the effect of MITC on *Pseudokirchneriella subspicata* was tested according to OECD TG 201 guideline (1984).
The green algae was exposed to MITC at nominal concentrations of 0.03, 0.06, 0.1, 0.19, 0.35, 0.65 and 1.2 mg/L for 72 hours, under static design. Analytical verification of test substance concentrations was carried out in each concentration at the beginning and at the end of the test after 72 hours. The 72 hour EC_{50} for MITC to *Pseudokirchneriella subspicata* was calculated as 0.58 mg/L, based on the initial measured concentrations.

However according to GBPR (2017), in such situation measured concentrations should be calculated using TWA concentrations. Indeed MITC concentrations were not maintained above 80% of the nominal concentrations : 58 – 74 % of the nominal concentrations were recovered at the beginning of the test and after 72 hours, the measured test concentrations were further reduced to 0 – 13 % of the initial nominal values. Moreover the concentration of vehicle (methanol) was not constant depending on test concentrations, ranging between 100 and 250 µl/L, which is above the recommended concentration 100 µl/L. Furthermore as the test is very old, it was conducted according to an old version of OECD TG 201 and the following validity criteria were not calculated :

- Mean coefficient of variation for section-by-section specific growth rates in the each replicate of control cultures ≤ 35 %

- Coefficient of variation of average specific growth rates during the whole test in control cultures ≤ 7 %.

Therefore, the results from this study are not considered reliable.

A second test with *Pseudokirchneriella subcapitata* ([redacted] 2018a) has been performed according to an updated version of OECD TG 201 (2011).
In this test, green algae were exposed to MITC at the nominal concentrations of 14, 28, 56, 113, 225 and 450 µg/L for 72h under static design. The calculated endpoints for growth rate and yield were ErC_{50} = 189 µg/L and EyC_{50} = 91 µg/L (mean measured).
The endpoints were based on mean measured concentrations of Dazomet, calculated as the time-weighted geometric mean of the concentrations of Dazomet measured at all the sampling times (i.e. at 0, 24, 48 and 72 hours). However it was noted that the equation used to calculate TWA concentrations is not calculated according to GBPR (2017) but according to OECD TG 211, which is not correct as DT_{50} of Dazomet is < 2 days. Indeed MITC concentrations decreases with time : from 70 – 73 % of nominal values at T0 to only 52 – 67 % of nominal values after 72h. It is also noted that the shape and size of algae was only recorded at 113 µg/L because the algal cell density at the two highest nominal concentrations of 225 and 450 µg/L was too low for a reliable examination.
Nevertheless the study was considered well conducted. The endpoints from this study can thus be used to address the acute toxicity to algae. Therefore, the 72-hour EyC_{50} of 0.091 mg/L is considered suitable for use in the risk assessment while the 72-hour ErC_{50} of 0.189

mg/L is considered for the classification.

A third test with *Anabaena flos-aquae* ([redacted] 2019b) has been performed according to the updated version of OECD TG 201 (2011).
In this test, cyanobacteria were exposed to MITC at the concentrations of 10, 29, 84, 244, 707 and 2051 µg/L (nominal) for 72h under static design. The calculated endpoints for growth rate and yield were ErC_{50} = 375 µg/L and EyC_{50} = 181 µg/L (nominal).
The endpoints were based on nominal concentrations of MITC as the recovery in the test media ranged between 86 and 106 % of the nominal values at the start of the test, then decreased between 77 % and 89 % of the nominal values. As one of the replicates showed a recovery below the limit of 80 %, the biological results should have been related to the geometric mean measured concentrations of MITC instead. However the differences between the two ways of calculating being of the order of the decimal, it was not considered having a significant impact on the calculation of the endpoints. It is also noted that the shape and size of algae was only recorded at 244 µg/L because the algal cell density at the two highest nominal concentrations of 707 and 2051 µg/L was too low for a reliable examination.

Nevertheless the study was considered well conducted. The endpoints from this last study can thus be used to address the acute toxicity to algae. Therefore, the 72-hour ErC_{50} of 0.375 mg/L is considered suitable for use in the classification.

Furthermore an acute test with *Lemna gibba* ([redacted], 2019e) has been performed according to the following guidelines : OECD TG 221 (2006) and Method C.26 of Commission Regulation (EU) No. 2016/266.

In this test, the aquatic plant was exposed to MITC at the nominal concentrations of 0.064, 0.32 and 1.6 mg/L under flow-through design for 7 days. The calculated EC_{50} are for growth rate 0.29 mg/L (dry weight) and 0.43 mg/L (frond number) and for yield 0.20 mg/L (dry weight) and 0.24 mg/L (frond number). The calculated EC_{10} are for growth rate 0.13 mg/L (dry weight) and 0.18 mg/L (frond number) and for yield 0.091 mg/L (dry weight) and 0.079 mg/L (frond number). The overall NOEC, based on significant effect on yield (number of fronds), was determined to be 0.016 mg/L (nominal), corresponding to 0.014 mg/L (mean measured).

The endpoints were based on mean measured concentrations of MITC, calculated as an arithmetic means of all measurements done for each test concentration (on Day 0, 2, 5 and 7). Indeed the recoveries ranged between 77 and 103 % of nominal concentrations.
However according to GBPR (2017) when the measured concentrations fall < 80 % of nominal and when they are measured more than 2 times during the course of the test, the mean measured concentrations should be calculated as a geometric mean as the recoveries were constant for each test concentration. According to OECD TG 211 guideline, when the measured concentrations is not within ± 20 % nominal or measured initial concentration, endpoints should be based on the geometric mean concentration during exposure or models describing the decline of the concentration of the test chemical. However the differences between the two ways of calculating being of the order of the decimal, it was not considered having a significant impact on the calculation of the endpoints.
Moreover the validity criteria is met according to the report. However no calculations or results were provided to verify the validity of the test.

Nevertheless the study was considered well conducted. The endpoints from this last study can thus be used to address the acute toxicity to aquatic plant. Therefore, the 7-day EC_{50} of 0.20 mg/L (yield, based on dry weight) and the 7-day EC_{10} of 0.079 mg/L (yield, based on front number) are considered suitable for use in the classification.

Chronic/long-term toxicity (freshwater)

Dazomet, which is predominantly degraded into MITC in water, shows an extremely rapid degradation in water/sediment systems through biodegradation (DT_{50} = 5 hour at 12 °C), hydrolysis (DT_{50} = 0.59 d at 12 ºC) and photolysis (DT_{50} = 9.9 hour). Consequently, long-term exposure is not expected for Dazomet. Therefore its metabolite MITC was used to determine the long-term toxicity of the active substance, especially as MITC shows a slower degradation and a higher acute toxicity than its parent to aquatic organisms (for invertebrates and algae).

Table A-131: Summary table - chronic/long-term aquatic toxicity

Method, Guideline, GLP status, Reliability, Key/supportive study	Species	Endpoint/ Type of test	Test material (purity)	Exposure		Results (mg/L)	Reference
				Design	Duration	LOEC/NOEC/EC_{10} (mg/L)	
Fish							
Prolonged Toxicity Test **OECD TG 204 (1982)** **GLP** **Reliability : 3** **Supportive data**	Rainbow trout (*Onchorhynchus mykiss*)	Development, growth, survival	MITC (98.4 %)	Flow-through	4 weeks	Overall NOEC 0.005 (nominal)	Unpublished report 2F0761/895215, [redacted] (1990) IUCLID A9.1.6.1-001
Early life stage (ELS) **OECD TG 210 (2013)** **OPPTS 850.1400** **GLP** **Reliability : 1** **Key study**	Fathead Minnow (*Pimephales promelas*)	Development, growth, survival	MITC (97.2 %)	Flow-through	33 d	Overall NOEC 0.00774 (mean measured) Overall EC_{10} 0.00929 (mean measured)	Unpublished report n° 246A-117, [redacted] (2015) A9.1.6.1-002

Invertebrates							
Chronic toxicity OECD TG 211 (1984), EPA-660/3-75-009 (1975), GLP **Reliability : 3** **Supportive data**	*Daphnia magna*	Survival, Reproduction	MITC (n.r.)	Semi-static	21 d	Overall NOEC 0.0125 (nominal)	Unpublished report No. 99/0547/51/2, [redacted] (2001), A9.1.6.2-001
Chronic toxicity OECD TG 211 (2012) GLP **Reliability : 2-3 Key study**	*Daphnia magna*	Survival, Reproduction, Growth	MITC (99.6 %)	Flow-through	21 d	Overall NOEC 0.0211 (mean measured) Overall EC_{10} 0.035 (mean measured)	Unpublished report No. 20180076, [redacted](2019f) A9.1.6.2-002
Algae							
Acute toxicity OECD TG 201 (2011) GLP Reliability: 1 Key study	*Pseudokirchneriella subcapitata*	Growth inhibition, yield	Dazomet (96.6 %)	Semi-static	72 h	ErC_{10} = 1.2 EyC_{10} = 0.67 (mean measured)	Unpublished report No. 20180133, [redacted] (2019a), A9.1.3-003
Acute toxicity OECD TG 201 (2011) GLP Reliability: 2 Key study	*Pseudokirchneriella subcapitata*	Growth inhibition, yield	MITC (99.6 %)	Static	72 h	ErC_{10} = 0.076 EyC_{10} = 0.051 (mean measured)	Unpublished report No. 20180073, [redacted] (2018a), A9.1.3-002
Acute toxicity OECD TG 201 (2011) GLP	*Anabaena flos-aquae*	Growth inhibition, yield	MITC (99.6 %)	Static	72 h	ErC_{10} = 0.173 EyC_{10} = 0.051 (mean measured)	Unpublished report No. 20180139, [redacted] (2019b),

Reliability: 2 **Key study**							A9.1.3-004
Other aquatic plants							
Chronic toxicity OECD TG 238 (2014), GLP **Reliability : 2** **Key study**	*Myriophyllum spicatum*	Growth, yield, sublethal effects	MITC (99.6 %)	Flow-through	14 d	Overall NOEC 0.0755 (mean measured) Overall EC_{10} 0.046 (mean measured)	Unpublished report No. 20180078, [redacted] (2020) A9.1.10-002

n.r.: not reported

Description of the available chronic toxicity studies

Chronic toxicity to fish – MITC

A 28 days flow-through study was performed by [redacted] (1990) on rainbow trout (*Oncorhynchus mykiss*) with MITC according to OECD TG 204 test guideline.
The test concentrations were 0.001, 0.005, 0.01, 0.02, 0.05, 0.1, 0.2 mg/L (nominal). MITC concentrations were measured weekly in all aquaria except for the lowest concentration of 0.001 mg/l. Since the detection limit of the analytical method was 0.005 mg/l, for the lowest test concentration, the diluted stock solution was analysed instead. Measured values were outside the acceptable ranges for part of the exposure period : at 0.05 mg/L, MITC was not detected on Day 7 and recovery was only 57 % and 60 % of nominal on Day 14 and 28, respectively. Moreover MITC was not detected at 0.005 mg/L due to a too high LOD (0.05 mg/L) and at 0.01 mg/L due to an interfering signal, probably caused by a contamination from the storage container. Although the diluted stock solution was analysed instead, its recovery was only 69 % and 66 % of nominal on Day 21 and Day 28, respectively. Nevertheless the endpoints were expressed in term of nominal concentrations.
The biological endpoints measured during the study were: mortality, clinical signs of toxicity, body weight and length. Fish length and weight were determined at the end of the exposure phase.

No morality occurred in negative and solvent control and up to 0.01 mg/L. Dose-response mortality occurred at higher concentrations : 25 % at 0.02 mg/L, 60 % at 0.05 mg/L and 100 % at 0.1 and 0.2 mg/L.
Toxic signs were observed from 0.01 mg/L, increasing with test concentrations and duration of exposure. They included reduced or no feed consumption, discoloration (dark), apathy, lying on the bottom, swimming near the bottom, spasms and convulsions and narcotic-like state.
The was also a significant difference (Dunnett's test, p= 0.01) between control and treated groups for body weight and length from 0.01 mg/L (nominal concentrations).
Therefore the overall 28-days NOEC was determined to be 0.005 mg/L (nominal), based on body weight and length changes. The LOEC was determined to be 0.01 mg/L.

The validity criteria were not met since MITC concentrations were not maintained within ± 20 % of nominal. Therefore the biological endpoints (NOEC and LOEC) derived from this test are highly questionable, especially as they are expressed in term of nominal concentrations. It was further noted that MITC concentrations were not measured at test concentrations of 0.1 and 0.2 mg/L.
Moreover since 2014, OECD TG 204 is no longer valid, this study is no longer considered reliable and relevant for the classification and the risk assessment of the active substance.

An early-life stage toxicity test was performed to determine the chronic toxicity of MITC to the rainbow trout (*Oncorhynchus mykiss*). The study was performed in accordance with the following guidelines : OECD TG 210 and US EPA OPPTS 850.1400.

The nominal concentrations of the test item were 2.19, 4.38, 8.75, 17.5 and 35.0 µg/L. MITC concentrations were measured on days 0, 13, 20, 28 and 33. The recoveries of MITC concentrations ranged between 81.9 and 104 % of nominal. Therefore measured concentrations were calculated as arithmetic mean of measured concentrations.
The biological endpoints measured during the study were: egg development, hatching rate,

time to hatch, development rate, mortality of embryo, larvae and juvenile fish, visible abnormalities in appearance and behaviour, fish length and weight. Fish length and weight were determined at the end of the exposure phase.
There were no significant differences (Fisher's Exact test, p = 0.05) in time to hatch between the control groups and up to 16.3 µg/L. However a noticeable delay in hatching and a significant decrease in hatching success was noted at 33.4 µg/L.
At 16.3 and 33.4 µg/L, the frequency of the sublethal effects increased significantly and there was a significant decrease in survival (Fisher's Exact test, p = 0.05).
Growth data from the 16.3 and 33.4 µg a.i./L treatment groups were excluded from the statistical analysis due to statistically significant reductions in survival (Dunnett's test, one-tailed test, p = 0.05). There was no significant reduction in total length in treatment groups compared to the pooled controls or in wet or dry weight compared to the solvent control (Dunnett's test, one-tailed test, p = 0.05).

The lowest EC_{10}, based on survival, was calculated to be 9.29 µg/L (mean measured) while the overall NOEC was set at 7.74 µg/L (mean measured) due to effects on sublethal toxicity, mortality and growth (body weight and length). The LOEC was set at 16.3 µg/L (mean measured).

The study was well conducted using an appropriate species. The endpoints from this study can be used to address the chronic toxicity to fish. Therefore, the NOEC of 7.74 µg/L (mean measured) is considered suitable for use in the risk assessment and classification.

Chronic toxicity to aquatic invertebrates – MITC

A study was performed by [redacted] (2001) to determine of the effect on the reproduction of *Daphnia magna* of MITC, in a 21 days semi-static test according to OECD TG 211 (1984) and EPA-660/3-75-009 (1975).

The concentrations of the test item were 0.78, 1.56, 3.13, 6.25, 12.5, 25, 50, 100 µg/L (nominal). The test solutions were changed three times a week, on Monday, Wednesday and Friday. Since the substance is volatile, the test was performed in close vessels field up to the buckler. MITC concentrations were measured only for nominal concentration of 6.25, 25 and 100 µg/L, in vessels run in parallel without animals, on days 0, 7, 14 and 21. The recoveries of MITC concentrations ranged between 80 and 96 % of nominal. Therefore endpoints are expressed in term of nominal concentrations. The biological endpoints measured during the study were: survival of parent and young and reproduction (in term of number of egg and young produced per parent).

There was no mortality in the control but mortality of parent ranged between 0 % and 20 % (not dose-dependent) up to 12.5 µg/L, then it rose to 30 % at 25 µg/L and was 100 % at the two highest test concentrations.
At the end of the test, the mean number of living young per surviving parent was 74.9 ± 23.4 % in control. It ranged between 65.2 and 82.2 % up to 6.25 µg/L (no dose-response effect), then decreased to 52.7 % at 12.5 µg/L and to 45.4 % at 25 µg/L. At the two high test concentrations, no young were produced.
At the end of the test, the mean number of dead young per surviving parent was 10.1 ± 7.3 % in control. It ranged between 8.8 and 13.6 % up to 25 µg/L (no dose-response effect). At the two high test concentrations, no young were produced.

The mean number of aborted eggs per surviving parent was 1.0 ± 1.4 % in control. It ranged between 0.6 and 1.6 up to 25 µg/L (no dose-response effect). At the two high test concentrations, no egg was produced.
Therefore, a 21-day NOEC = 0.0125 mg/L was calculated, based on Duncan's multiple range test. The LOEC was 0.025 mg/L.
It is noted that in control, the coefficient of variation around the mean number of living offspring produced per parent should be ≤ 25 % but it was 31.2 % in the test. Therefore the significance of the effects on reproduction rate are lowered.
Moreover the statistical significance of the effects was not reported and no statistical analysis was provided. In the results, it was also not indicated at which concentrations there was a significant difference with the control. Furthermore the purity of the test substance was not reported.

Therefore, although the validity criteria were met and as the reproduction rate of Daphnia showed no deviation from the existing limits, this study is only considered as a supportive data.

A second test measuring the toxic effect of MITC on the reproduction of *Daphnia magna* was performed according to OECD TG 202 (1984) and EPA-660/3-75-009 (1975). This test was performed over 21 days under a flow-through design.

The nominal concentrations of the test item were 6.25, 12.5, 25, 50 and 100 µg/L. MITC concentrations were measured on days -1, 1, 4, 8, 11, 14 and 18. The recoveries of MITC concentrations ranged between 72 and 101 % of nominal values when calculated from each individual sample but it ranged between 81 and 85 % of nominal values when calculated from mean measured concentrations of the test item. Therefore measured concentrations were calculated as arithmetic mean of all measurements made for each test concentration.
The biological endpoints measured during the study were: survival, growth (body length), reproduction (calculated as the total number of living offspring produced per female surviving until the end of the test) and toxicity signs. Body length were determined at the end of the exposure phase.

In the control, the solvent control and all test concentrations up to 25 µg/L nominal, there was no mortality. At 50 µg/L nominal, one daphnid died and at the highest test concentration, mortality was 80 % ($p < 0.05$, Williams t-test, one-sided smaller).
The first young offspring released from their parents were recorded in the control, the solvent control and at all test concentrations up to 50 µg/L nominal on Day 8. At 100 µg/L nominal, first offspring was observed at Day 11.
No inhibitory effect of the test item on the mean reproduction rate was determined up to 25 µg/L nominal. At 50 µg/L nominal, the offspring was significantly reduced to 84 % of the solvent control (Williams t-test, one-sided smaller, $\alpha = 0.05$). At 100 µg/L nominal, the mean reproduction rate was only 17 % of the solvent control.
No inhibitory effect of the test item on the body length was determined up to 25 µg/L nominal. At 50 µg/L nominal, the body length was significantly reduced to 97 % of the solvent control (Williams t-test, one-sided smaller, $\alpha = 0.05$). At 100 µg/L nominal the mean body length was 84 % of the solvent control value.
The overall 21-day NOEC, determined directly from the raw data, was set at 21.1 µg/L (mean measured) based on significant effect on mortality, reproduction and body length. The LOEC was 40.4 µg/L (mean measured). The lowest EC_{10} value was calculated 35 µg/L (mean

measured), based on mortality.

Although this study fulfils the validity criteria, it was noted that only 10 animals were used per test concentration whereas according to OECD TG 211, 40 animals divided into 4 groups of 10 animals (for each test concentration and each control) should be used when flow-through design is used. A smaller number of organisms may be used but a minimum of 20 animals per concentration divided into 2 or more replicates, with an equal number of animals (e.g. 4 replicates each with 5 daphnids) could be used instead. However, no explanation was provided regarding the reduction of the number of daphnid used.

It was also noted that the mean measured test item concentrations were calculated as arithmetic means over all measurements per test concentration. However according to OECD TG 211 and GBPR (2017), when concentrations falls < 80% nominal during the course of the test (which is the case when taking into account the recoveries measured in each individual sample) and when concentrations have been determined on more than 2 occasions during a test, the time weighted average concentration may be calculated according to Annex 2 of OECD Guidance Document 23 (OECD, 2000).

It was further noted that the feeding amount should be 0.1-0.2 mg C/Daphnia/day according to OECD TG 211. In this study, it was 0.3 mg C/L at the start of the test and was increased up to 0.7 mg C/L (Day 8-21), without explanation.

Therefore although the study was quite well conducted, its reliability was decreased to 2 or 3 (to be discussed). If reliability is set at 2, the endpoint from this study can be used to address the chronic toxicity to freshwater invertebrates and the NOEC of 21.1 µg/L (mean measured) could be considered suitable for use in the risk assessment and classification.

Chronic toxicity to algae or other aquatic plants – MITC

A study was performed to determine the chronic effect of MITC on the macrophyte *Myriophyllum spicatum*, in a 14 days flow-through test according to OECD TG 238 (2014).

The nominal concentrations of the test item were 10, 32, 100, 320 and 1000 µg/L. MITC concentrations were measured on days 3, 7, 10 and 14. The recoveries of MITC concentrations ranged between 58 and 94 % of nominal values. Therefore measured concentrations were calculated as arithmetic mean of all measurements made for each test concentration.
The biological endpoints measured during the study were: growth rate and yield for shoot length, fresh and dry weight as well as signs of toxicity.
The NOEC and LOEC were determined by testing statistically significant differences between the solvent control and the test concentrations with the following tests:

- Main Shoot Length : Dunnett's t-test (one-sided smaller, α = 0.05) for both growth and yield

- Total shoot length and fresh weight : Williams t-test (one-sided smaller, α = 0.05) for both growth and yield

- Fresh and dry weight : Welch t-test (one-sided smaller, α = 0.05) for yield and Dunnett's t-test (one-sided smaller, α = 0.05) for growth rate.

At 23.9 and 75.7 µg/L (mean measured), the main and total shoot length were slightly but not significantly decreased. At 236 and 765 µg/L (mean measured) however, a significant inhibitory effect on both main and total shoot length (yield and growth rate) was observed.
The fresh and dry weight of the plants (yield and growth rate) was significantly reduced at the highest test concentration of 765 µg/L (mean measured).
No abnormalities in appearance of the test plants were recorded in the control, the solvent control and the test concentrations up to 75.7 µg/L (mean measured). At 236 µg/L (mean measured) the plants appeared to be weaker compared to the solvent control and at 765 µg/L (mean measured), the plants were in moribund condition.

The overall NOEC was set at 75.5 µg/L (mean measured) based on significant effect on shoot length and on sublethal toxicity. The LOEC was 236 µg/L (mean measured). The lowest EC_{10} value was calculated 46 µg/L (mean measured), based on yield (main shoot length).

The endpoints were based on mean measured concentrations of MITC, calculated as an arithmetic means of all measurements done for each test concentration. As the recoveries of MITC concentrations ranged between 58 and 94 % of nominal values and concentrations are measured more than 2 times during the course of the test, the mean measured concentrations should be calculated as time weighted average concentration, calculated according to Annex 2 of OECD Guidance Document 23 (OECD, 2000) according to GBPR (2017). According to OECD 238 guideline, when the measured concentrations are not within ± 20 % nominal or measured initial concentration, endpoints should be based on the geometric mean concentration during exposure or models describing the decline of the concentration of the test chemical.
It was also noted that the fulfilment of the validity criteria is not always clear :

- according to the report, the doubling time (Td) of the mean main shoot length was calculated to be 11.8 and 6.4 days for the control and solvent control respectively, but no calculations or results were provided to confirm the fulfilment of this validity criteria.

- the mean coefficients of variation for yield based on measurements of dry weight was 39 % for both control and solvent control, which is slightly higher than the 35 % necessary to fulfil validity criteria. Nevertheless, as all performance criteria for all other endpoints were fulfilled, the Applicant has considered that this should not have an impact on the reliability of the study.

- the test was performed under flow through conditions to ensure constant exposure concentrations to MITC during the test period. As a consequence of the flow through test design, modifications of the environmental conditions were necessary (no addition of sucrose, non-sterile test conditions). Thus, the validity criteria of a static, sterile test may not be fully applied for a flow-through test. However as these modifications were applied to both control and treated vessels, it was not considered to have an impact on the results.

Nevertheless the study was considered well conducted and the endpoints can be used to address the chronic toxicity to aquatic plants. The overall NOEC of 75.5 µg/L (mean measured) is thus considered suitable for use in the risk assessment while the lowest EC_{10} value of 84 µg/L (mean measured), based on the growth rate of the main shoot length, is considered suitable for the classification.

A.4.2.3.2 Sediment compartment (freshwater)

Acute/short-term toxicity (freshwater sediment)

Table A-132: Summary table - acute/short-term toxicity to sediment dwelling organisms

Method, Guideline, GLP status, Reliability, Key/supportive study	Species	Endpoint/ Type of test	Test material (purity)	Exposure		Results (mg/L)	Reference
				Design	Duration	LC/EC50	
Acute toxicity OECD TG 235 (2011) GLP Reliability: 1 Key study	*Chironomus riparius*	Mortality, Sublethal effects	MITC (99.6 %)	Semi-static	48 h	0.055 (mean measured)	Unpublished report No. 20180117, [redacted] (2018b), A9.1.2-002

An acute toxicity study was performed to determine the effect of MITC on the sediment-dwelling organism *Chironomus riparius*, in a 48h semi-static test according to OECD TG 235 (2011). The concentrations of the test item were 6.25, 12.5, 25, 50 and 100 µg/L (nominal). MITC concentrations were measured before and after 24 and 48h, after each renewal of the medium. The recoveries of MITC concentrations ranged between 73 and 123 % of nominal values. Therefore measured concentrations were calculated as arithmetic mean of all measurements made for each test concentration.

After 24h, there was no mortality up to 50 µg/L. At 100 µg/L, there was already 70 % mortality. After 48h, there was no mortality up to 25 µg/L. At 50 µg/L, recorded mortality was 25 % and at 100 µg/L, all larvae were dead. The EC_{50} (48h) was calculated to be 55 µg/L (mean measured).

Immobility and abnormalities of larvae were visually determined after 24 and 48 hours of exposure but no result was reported.
Moreover the test item concentrations ranged between 78 and 123 % of nominal values. According to GBPR (2017), when concentrations falls < 80 % nominal during the course of the test and when concentrations have been determined on more than two occasions during a test, the time weighted average concentration may be calculated according to Annex 2 of OECD Guidance Document 23 (OECD, 2000).
Nevertheless the study was considered well conducted and the endpoints can be used to address the acute toxicity to sediment-dwelling organisms. The EC_{50} (48h) = 55 µg/L (mean measured) is thus considered suitable for use in the classification and labelling of the active substance. Indeed MITC was directly applied to the water column and the test was performed without sediment.

Chronic/long-term toxicity (freshwater sediment)

Table A-133: Summary table - chronic/long-term toxicity to sediment dwelling organisms

Data waiving	
Information requirement	Chronic/long-term toxicity (freshwater sediment)
Justification	Dazomet is intended for the internal remedial treatment and the protection of wood products such as utility poles. Therefore no direct contamination of sediment with Dazomet is to be expected and sediment dwelling organisms are not expected to be at risk. Moreover with its low Koc (260 L/kg), Dazomet is not expected to sorb to sediments. Furthermore it is quickly degraded into MITC in microbiologically active pond water and sediment (DT_{50} = 5 hr, at 12 ºC). MITC in turn rapidly degrades to CO_2 (DT_{50} ~ 2 days). Furthermore, due to its high volatility (vapour pressure = 2500 Pa at 20 °C) and its very low Koc (36 L/kg), MITC is not expected to be at risk for sediment-dwelling organisms.

A.4.2.3.3 Marine compartment

Acute/short-term toxicity (seawater)

Table A-134: Summary table - acute/short-term aquatic toxicity

Data waiving	
Information requirement	Information is required when there is a likelihood that the seawater compartment will become exposed to the active substance.
Justification	It is not likely that the seawater compartment will become exposed from the use of Dazomet or MITC. Indeed Dazomet is intended for the internal remedial treatment and the protection of wood products such as utility poles. Therefore, no direct contamination of the marine compartment with Dazomet is to be expected and the marine compartment is not expected to be at risk.

Chronic/long-term toxicity (seawater)

Table A-135: Summary table - chronic aquatic toxicity

Data waiving	
Information requirement	Information is required when there is a likelihood that the seawater compartment will become exposed to the active substance.

Justification	It is not likely that the seawater compartment will become exposed from the use of Dazomet or MITC. Indeed Dazomet is intended for the internal remedial treatment and the protection of wood products such as utility poles. Therefore, no direct contamination of the marine compartment with Dazomet is to be expected and the marine compartment is not expected to be at risk.

A.4.2.3.4 Seawater sediment compartment

Acute/short-term toxicity (seawater sediment)

Table A-136: Summary table - acute/short-term toxicity to sea sediment dwelling organisms

Data waiving	
Information requirement	Information is required when there is a likelihood that the sea sediment compartment will become exposed to the active substance.
Justification	It is not likely that the sea sediment compartment will become exposed from the use of Dazomet or MITC. Indeed Dazomet is intended for the internal remedial treatment and the protection of wood products such as utility poles. Therefore no direct contamination of the marine compartment with Dazomet is to be expected and the marine compartment is not expected to be at risk.

Chronic/long-term toxicity (sea sediment)

Table A-137: Summary table - long-term/ chronic toxicity to sea sediment dwelling organisms

Data waiving	
Information requirement	Information is required when there is a likelihood that the sea sediment compartment will become exposed to the active substance.
Justification	It is not likely that the sea sediment compartment will become exposed from the use of Dazomet or MITC. Indeed Dazomet is intended for the internal remedial treatment and the protection of wood products such as utility poles. Therefore no direct contamination of the marine compartment with Dazomet is to be expected and the marine compartment is not expected to be at risk.

A.4.2.3.5 Higher tier studies on aquatic organisms

No higher tier studies on aquatic organisms are available or required.

A.4.2.4 Terrestrial compartment

Not applicable for the CLH report.

Toxicity to terrestrial organisms, acute/short-term tests

Table A-138: Summary table - acute/short-term terrestrial toxicity

Not applicable for the CLH report.

Toxicity to terrestrial organisms, chronic/long-term tests

Table A-139: Summary table - chronic/long-term terrestrial toxicity

Not applicable for the CLH report.

A.4.2.5 Groundwater

Not applicable for the CLH report.

A.4.2.6 Birds and mammals

Table A-140: Summary table - toxicity to birds and mammals

Not applicable for the CLH report.

A.4.2.7 Primary and secondary poisoning

Not applicable for the CLH report.

Primary poisoning

Table A-141: Summary table - Primary poisoning

Not applicable for the CLH report.

Secondary poisoning

Table A-142: Summary table - Secondary poisoning*

Not applicable for the CLH report.

A.4.3 Endocrine disruption

Not applicable for the CLH report.

Table A-143: Summary table of ecotoxicological data on endocrine disruption

Not applicable for the CLH report.

A.4.4 Derivation of PNECs

Not applicable for the CLH report.

Table A-144: Derivation of PNECs

Not applicable for the CLH report.

A.4.5 Overall summary of acute and chronic aquatic toxicity data and Comparison with the CLP criteria

Although it is not considered to be readily degradable due to the environmental classification of MITC (please see above), Dazomet, which is predominantly degraded into MITC in water, shows an extremely rapid degradation in water/sediment systems through biodegradation (DT_{50} = 5 hour at 12 °C), hydrolysis (DT_{50} = 0.59 d at 12 ºC) and photolysis (DT_{50} = 9.9 hour). Consequently, short-term and especially long-term exposure is not expected for Dazomet.

Therefore its metabolite MITC is more relevant for classification purpose, especially as MITC shows a slower degradation and a higher acute toxicity than its parent to aquatic organisms (for invertebrates and algae), as well as very high chronic toxicity to aquatic species.

A.4.5.1 Acute aquatic hazard

Table A-145: Summary of key information on acute/ short-term aquatic toxicity relevant for aquatic acute classification

Method	Species	Test material	Results (mg/L)	Remarks	Reference
Fish					
Acute toxicity, OECD TG 203 (1992), GLP Reliability : 2 Key study	Rainbow trout (*Oncorhynchus mykiss*)	Dazomet (99.6 %)	0.06 (mean measured)		Unpublished report No. 20180135, [redacted] (2019a) IUCLID 9.1.1
Acute toxicity, OECD TG 203 (1992), GLP Reliability : 2 Key study	Rainbow trout (*Oncorhynchus mykiss*)	MITC (99.6 %)	0.09 (mean measured)	Main metabolite of Dazomet in water	Unpublished report No. 20180075, [redacted] (2019b) IUCLID 9.1.1
Invertebrates					
Acute toxicity, OECD TG 202 (2004), GLP Reliability : 2 Key study	*Daphnia magna*	Dazomet (99.6 %)	6.8 (mean measured)		Unpublished report 20180134, [redacted] (2019c) IUCLID 9.1.2
Acute toxicity, OECD TG 202 (2004), GLP Reliability : 1 Key study	*Daphnia magna*	MITC (99.6 %)	0.124 (mean measured)	Main metabolite of Dazomet in water	Unpublished report No. 20180074, [redacted] (2019d) IUCLID 9.1.2

Algae					
Acute toxicity **OECD TG 201 (2011)** **GLP** **Reliability: 1** **Key study**	*Pseudokirchneriella subcapitata*	Dazomet (99.6 %)	ErC_{50} > 2.3 EyC_{50} = 1.5 (mean measured)		Unpublished report No. 20180133, [redacted] (2019a), IUCLID 9.1.3
Acute toxicity **OECD TG 201 (2011)** **GLP** **Reliability: 2** **Key study**	*Pseudokirchneriella subcapitata*	MITC (99.6 %)	ErC_{50} = 0.189 EyC_{50} = 0.091 (mean measured)	Main metabolite of Dazomet in water	Unpublished report No. 20180073, [redacted] (2018a), IUCLID 9.1.3
Acute toxicity **OECD TG 201 (2011)** **GLP** **Reliability: 2** **Key study**	*Anabaena flos-aquae*	MITC (99.6 %)	ErC_{50} = 0.375 EyC_{50} = 0.181 (mean measured)	Main metabolite of Dazomet in water	Unpublished report No. 20180139, [redacted] (2019b), IUCLID 9.1.3
Other aquatic plants					
Acute toxicity **OECD TG 221 (2006)** **GLP** **Reliability: 2** **Key study**	*Lemna gibba*	MITC (99.6 %)	Growth rate : 0.29 Yield : 0.20 (mean measured)	Main metabolite of Dazomet in water	Unpublished report No. 20180077, [redacted] (2019e) IUCLID 9.1.10
Other					
Acute toxicity **OECD TG 235 (2011)** **GLP** **Reliability 1** **Key study**	*Chironomus riparius*	MITC (99.6 %)	0.055 (mean measured)	Main metabolite of Dazomet in water Test performed without sediment and therefore relevant for classification	Unpublished report No. 20180117, [redacted] (2018b), IUCLID 9.1.9

The Applicant has submitted a completely new acute data set for both the active substance Dazomet and its metabolite MITC. Indeed previous studies are old, performed according to outdated guidelines and have therefore a poor reliability.

According to the available data, the most sensitive acute endpoint is derived from the *Chironomus riparius* 48h study with MITC (LC_{50} = 0.055 mg/L), performed without sediment, which makes this test relevant for classification of the aquatic species. Moreover it is noted that MITC also showed high acute toxicity to rainbow trout (LC_{50} = 0.09 mg/L) and *Pseudokirchneriella subcapitata* (ErC_{50} = 0.189 but EyC_{50} = 0.091), although the endpoints from these tests are almost twice higher.

Regarding Dazomet, the most sensitive acute endpoint is derived from the *Oncorhynchus mykiss* 96h study (LC_{50} = 0.06 mg/L).

The trigger of ≤ 1 mg/L given in the Table 4.1.0 in Annex I of the Guidance on the Application of the CLP Criteria (Version 5.0, 2017) being exceeded, both Dazomet and MITC can thus be considered to have fulfilled the criterion for category Aquatic Acute 1 (H400: Very toxic to aquatic life). The relevant associated M-factor is 10 according to Table 4.1.3 for CLP guidance. Therefore, the classification for acute aquatic hazard does not change.

A.4.5.2 Long-term aquatic hazard (including information on bioaccumulation and degradation)

Table A-146: Summary of key information on chronic/ long-term aquatic toxicity relevant for aquatic chronic classification

Method	Species	Test material	Results (mg/L)	Remarks	Reference
Fish					
Early life stage (ELS) **OECD TG 210 (2013)** **OPPTS 850.1400** **GLP** **Reliability : 1** **Key study**	Fathead Minnow (*Pimephales promelas*)	MITC (97.2 %)	Overall NOEC 0.00774 (mean measured) Overall EC_{10} 0.00929 (mean measured)	Main metabolite of Dazomet in water	Unpublished report n° 246A-117, [redacted] (2015) IUCLID 9.1.6.1
Invertebrates					
Chronic toxicity **OECD TG 211 (2012)** **GLP** **Reliability : 2-3** **Key study**	*Daphnia magna*	MITC (99.6 %)	Overall NOEC 0.0211 (mean measured) Overall EC_{10} 0.035 (mean measured)	Main metabolite of Dazomet in water	Unpublished report No. 20180076, [redacted](2019f) IUCLID 9.1.6.2
Other aquatic plants					
Chronic toxicity **OECD TG 238 (2014),** **GLP** **Reliability : 2** **Key study**	*Myriophyllum spicatum*	MITC (99.6 %)	Overall NOEC 0.0755 (mean measured) Overall EC_{10} 0.046 (mean measured)	Main metabolite of Dazomet in water Test performed without sediment and therefore relevant for classification	Unpublished report No. 20180078, [redacted](2020) IUCLID 9.1.6.3
Acute toxicity **OECD TG 201 (2011)** **GLP** **Reliability: 1** **Key study**	*Pseudokirchneriella subcapitata*	Dazomet (96.6 %)	Overall EC_{10} 0.67 (mean measured)	Parent compound	Unpublished report No. 20180133, [redacted] (2019a), A9.1.3-003

Acute toxicity **OECD TG 201 (2011)** **GLP** **Reliability: 2** **Key study**	*Pseudokirchneriella subcapitata*	MITC (99.6 %)	Overall EC_{10} 0.051 (mean measured)	Main metabolite of Dazomet in water	Unpublished report No. 20180073, [redacted] (2018a), A9.1.3-002
Acute toxicity **OECD TG 201 (2011)** **GLP** **Reliability: 2** **Key study**	*Anabaena flos-aquae*	MITC (99.6 %)	Overall EC_{10} 0.051 (mean measured)	Main metabolite of Dazomet in water	Unpublished report No. 20180139, [redacted] (2019b), A9.1.3-004

Although Dazomet is only considered inherently biodegradable (only 58 % degradation after 28 days in an OECD TG 301D – see [redacted], 2001a), it is quickly degraded in water through biodegradation (DT_{50} = 5 hour at 12°C), hydrolysis (DT_{50} = 0.59 d at 12ºC) and photolysis (DT_{50} = 9.9 hour). Indeed, in a water-sediment test ([redacted], 1994) Dazomet was no longer detectable in water after 2 days : it was mainly degraded into MITC, which in turn quickly degrades to CO_2: the DT_{50} of MITC was calculated to be 2 days. After one month, half of the detected radioactivity was CO_2. MITC can also be degraded through hydrolysis and (DT_{50} = 295.90 d at 12 °C) and photolysis (DT_{50} = 980 hr), but much more slowly than through biotic degradation.

Consequently, although Dazomet is not considered to be rapidly degradable according to CLP criteria due to environmental classification of MITC (please refer to the CLP Guidance, 2017[17]), long-term exposure is not expected from the parent compound. Therefore MITC is more relevant than Dazomet for long-term hazard due to the much faster degradation of the parent compound in water compared to those of its metabolite.

MITC has a low potential for bioaccumulation in aquatic organisms as its predicted log Kow value is 1.2, which is below the trigger of log Kow ≥ 4. Moreover predicted BCF for fish, calculated according to GBPR (2017), gives a value of 2.09 L/kg_{wwt} for MITC, which is < 500. Therefore, the bioaccumulation criterion is not fulfilled.

The Applicant has submitted a completely new chronic data set for MITC, which is more relevant than Dazomet for chronic exposure and hazard due to the rapid degradation of the parent compound in water. Indeed previous studies are old, performed according to outdated guidelines and have therefore a poor reliability.
According to the available data, the most sensitive acute endpoint is derived from a chronic study on *Pimephales promelas* with MITC, with a NOEC = 0.00774 mg/L and a EC_{10} = 0.00929 mg/L.

Dazomet being not considered rapidly degradable and the trigger of ≤ 0.01 mg/L given in the Table 4.1.0 in Annex I of the CLP Guidance (2017) being exceeded, the substance can thus be considered to have fulfilled the criterion for category Aquatic Chronic 10 (H410: Very toxic to aquatic life with long lasting effects). The relevant associated M-factor is 10 according to Table 4.1.3 for CLP guidance. Therefore, the classification for long-term aquatic hazard does not change but the associated M factor changes.

A.4.5.3 Conclusion on classification and labelling for environmental hazards and comparison with the CLP criteria

Aquatic acute classification according to CLP criteria

The lowest LC_{50} value is 0.06 mg/L for Dazomet and 0.055 mg/L for MITC, which is below the trigger value of 1 mg/L. Dazomet therefore fulfils the criteria for classification as Aquatic Acute 1 (H400). As the lowest LC_{50} value is between 0.01 and 0.1, this leads to an M-factor 10. Therefore, the classification for acute aquatic hazard does not change.

[17] Annex I: 4.1.2.9.4 "The criteria used reflect the fact that environmental degradation may be biotic or abiotic. **Hydrolysis can be considered if the hydrolysis products do not fulfil the criteria for classification as hazardous to the aquatic environment**."

Aquatic chronic classification according to CLP criteria

MITC is more relevant than Dazomet for long-term hazard due to the much faster degradation of the parent compound in water.

Dazomet and MITC are not considered rapidly degradable. Chronic data are available for all trophic levels and the lowest EC_{10} = 0.00929 mg/L (corresponding NOEC is 0.00774 mg/L), which is below the trigger value of 0.1 mg/L. Dazomet therefore fulfils the criteria for classification as Aquatic Chronic 1 (H410). As the lowest NOEC value is between 0.001 and 0.01, this leads to an M-factor 10. Therefore, the classification for long-term aquatic hazard does not change but the associated M factor changes.

A.5 Assessment of additional hazards

A.5.1 Hazardous to the ozone layer

Table A-147: Summary table of data concerning hazardous properties of the substance for the ozone layer

Data waiving	
Information requirement	There is no requirement under the BPR to provide information on hazards to the ozone layer.
Justification	The particular mode of application of Dazomet used as internal remedial treatment of poles combined with the low vapour pressure (5.8 x 10^{-4} Pa at 20°C) and the very short half-life in water (DT_{50} = 5 hr) and soil (DT_{50} = 0.72 d) lead to very limited environmental exposure and air contamination. Regarding MITC, the main degradation product of Dazomet, its high vapour pressure (2500 Pa at 20°C) shows that it has significant volatilisation capacity. Direct photolysis is the major pathway of degradation of MITC, OH contributing to less than 15% of degradation. The photolysis rate constant of MITC ranged between 3.9 and 4.9 x 10^{-13} cm^3 per molecule s^{-1}, which equals a 24-hour day half-life of 108 to 960 hours (i.e. 4.5 to 40 days). However there is no absorption bands in the atmospheric window, and no Cl or F functional group in the molecule. No hazard to the ozone layer is thus expected.

A.5.1.1 Short summary and overall relevance of the provided information on ozone layer hazard

The low vapour pressure and the very short half-life of Dazomet lead to very limited environmental exposure and air contamination.

Regarding MITC, the main degradation product of Dazomet, its high vapour pressure (2500 Pa at 20 °C) shows significant volatilisation capacity. The moderate atmospheric lifetime (DT_{50} = 960 hours) shows a potential for long-range transports. However there is no absorption bands in the atmospheric window, and no Cl or F functional group in the molecule. No hazard to the

ozone layer is thus expected.

A.5.1.2 Comparison with the CLP criteria

Neither Dazomet, nor MITC are listed in Annex I to Regulation (EC) No 1005/2009 of the European Parliament and of the Council of 16 September 2009. Moreover on the basis of the structure and on the physico-chemical properties of MITC (absence of absorption bands in the atmospheric window, moderate atmospheric lifetime, absence of Cl or F functional group in the molecule), MITC is not expected to present a potential danger to the structure and /or functioning of the stratospheric ozone layer.

Conclusion on classification and labelling for hazardous to the ozone layer

Neither Dazomet, nor MITC present a potential danger to the structure and /or functioning of the stratospheric ozone layer.

A.6 Additional Labelling

No additional labelling under the CLH Regulation is proposed.

A.7 Assessment of exclusion criteria, substitution criteria and POP

Not applicable for the CLH report.

A.7.1 Exclusion criteria

Not applicable for the CLH report.

A.7.1.1 Assessment of CMR properties

Not applicable for the CLH report.

A.7.1.2 Assessment of endocrine disrupting properties

Not applicable for the CLH report.

A.7.1.3 PBT Assessment (following Annex XIII to Regulation (EC) No 1907/2006)

Not applicable for the CLH report.

A.7.2 Substitution criteria

Not applicable for the CLH report.

A.7.3 Assessment of long-range environmental transportation and impact on environmental compartments

Not applicable for the CLH report.

D. Appendices

Appendix I: List of endpoints

Not applicable for the CLH report.

Appendix II: Human exposure calculations

Not applicable for the CLH report.

Appendix III: Environmental emission (and exposure) calculations

Not applicable for the CLH report.

Appendix IV: List of terms and abbreviations

Standard term / Abbreviation	Explanation
a.i.	Active ingredient
A.S.	Active substance
AChE	Acetylcholinesterase
Acute Tox.4 (O)	Harmful if swallowed
AOP	Adverse Outcome Pathway
AP	Administration Period
APTT	Active Cephaline Time
ATE	Acute Toxicity Estimate
AUC	Area Under the Curve
BCF	Bioconcentration factor
BE CA	Belgian Competent Authority
BPR	Biocidal Product Regulation
BPR	Biocidal Products Regulation. Regulation (EU) No 528/2012 of the European Parliament and of the Council concerning the making available on the market and use of biocidal products
bw	Body weight
C	Concentration (units can vary and should be precised)
CA	Competent Authority - Evaluating CA (eCA) is the Competent Authority that evaluates the application for an active substance approval or an application for a Union authorisation. - Receiving CA is the Competent Authority that receives an application for a National Authorisation.
CAR	Competent Assessment Report
CIPAC	Collaborative International Pesticides Analytical Council

CIPAC MT	Test methods from the Collaborative International Pesticides Analytical Council
CLP (regulation)	Regulation (EC) No 1272/2008 on Classification, Labelling and Packaging of substances and mixtures
Cmax	Maximum plasma concentration
CMC	Carboxymethylcellulose
DAB	3,3′-Diaminobenzidine
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
DOC	Dissolved Oxygen Content
DT50	Half-time duration
DTx	Degradation time to reach x % of the initial concentration
E.g.	Exampli gratia
EAS	Estrogen-Androgen and Steroidogenesis
EAST	Estrogen-Androgen, Steroidogenesis and Thyroid
Ecx	Effect concentration at which x% effect (mortality, inhibition of growth, reproduction, etc) is observed compared to the control group
ED	Endocrine Disruptor
EEC	European Economic Community
EFSA	European Food Safety Authority
EFSA	European Food Safety Agency
ErC50	Concentration at which 50% of growth is inhibited
EyC50	Concentration at which 50% of yield is inhibited
f	Female
FOB	Functional Observation Battery
G.I.	Gastro Intestinal
g/m3	Ratio gram (of the targeted substance) versus volume (in cubic meters)
g/mol	Ratio gram per mole (unit of the molecular weight parameter)
GBPR (2017)	Guidance on the Biocidal Products Regulation : Volume IV Environment - Assessment and Evaluation (Parts B + C), Version 2.0, October 2017
GC	Gas chromatography
GC-MS	Gas chromatography with Mass spectrometer
GEF	Global Evaluation Factor
geomean	Geometric mean
G.I. tract	Gastro-intestinal tract
GLP	Good Laboratory Practice
GOT (AST)	Aspartate Aminotransferase
GPMT	Guinea Pig Maximization Test
GPT (ALT)	Alanine aminotransferase
GR	Ready to use granule
Hb	Hemoglobin
HepG2	Hepatitis G2
HGPRT	Hypoxanthine-Guanine Phosphoribosyltransferase

Histopath.	Histopathology
HLL	Hind limb length
HPLC	High Performance Liquid Chromatography
HS-GC-MS/MS	Headspace gas chromatography with tandem mass spectrometry
Ht	Hematocrit
Ig	Immunoglobulin
IHT	Inhalation Hazard Test
IL	Interleukin
IUCLID	International Uniform ChemicaL Information Database
IUPAC	International Union of Pure and Applied Chemistry
JNK	c-Jun N-terminal kinases
Koc	Organic carbon/water partition coefficient
LCx	Effect concentration at which x% mortality is observed compared to the control group
LMW	Low molecular weight
LOAEL	Low-observed-adverse-effect level
LOD	Limit of Detection
LOEC	Lowest Observed Effect Concentration
Log Kow	Log Octanol/water partition coefficient
Log POW	logarithm (base 10) of the Octanol/water partition coefficient
LOQ	Limit of Quantification
LPS	Lipopolysaccharide
LRTAP	Long-Range Transboundary Air Pollutant
m	Male
m/z	ratio mass/charge for ion detection in a mass spectrometer
MAP-Kinases	Mitogen-Activated Protein kinases
MATC	Maximal acceptable toxicant concentration
MATM	Methyl Amino Tioxo methanesulfenic acid
MCHC	Mean Corpuscular Haemoglobin Concentration
MCV	Mean Corpuscular Volume
Mean meas.	Mean measured concentration
mg/kg	Ratio milligram (of targeted substance) per kilogram (of sample)
mg/kg b.w.	Mg/kg of body weight
mg/kg dwt	Mg/kg of dry weight
mg/kg wwt	Mg/kg of wet weight
MITC	Methyl isothiocyanate (Dazomet metabolite)
MITC	Methyl isothyiocyanate
MN	Micronucleus
MoA	Mode of action
mRNA	Messenger Ribonucleic Acid
MTD	Maximum Tolerated Dose
MW	Molecular Weight
N.a.	Not applicable
NCE	Normochromatic Erythrocytes
NF stage	Nieuwkoop and Faber stage (developmental stage)

Ng/mL	Ratio nanogram (of targeted substance) and milliliters (of solvent)
NOAEL	No-observed-adverse-effect level
NOEC	No Observed Effect Concentration
Nomin.	Nominal concentration
OECD	Organization for Economic Co-operation and Development
OECD TG xxx	OECD Technical Guidance number xxx
P	Pressure
P.c.	Post-coitum
Pa	Pascal (unit of pressure)
PBT	Persistent, Bio accumulable and Toxic
PCE	Polychromatic Erythrocytes
PE	Polyethylene
PEC	Predicted Environmental Concentration
pH	Minus the logarithm(base 10) of the concentration in hydroniums ions (concentration to be used in moles/liter)
pKa	Minus the logarithm(base 10) of dissociation constant of a (weak) acid
PLT	Platelet Count
PND	Phosphorus nitrogen detector
PNEC	Predicted No-Effect Concentration
POP	Persistent Organic Pollutant
ppm	Part per million
PPP	Plant Protection Product
PT	Product type
(Q)SAR	Quantitative Structure-Activity Relationship
RBC	Red Blood Cells
REACH	Regulation (EC) No 1907/2006 on Registration, Evaluation, Authorization and Restriction of Chemicals
RSD	Relative standard deviation
RTG	Relative total growth
S9	Mixture of unfractionated microsomes and cytosol containing a wide variety of drug-metabolizing enzymes
SCE	Sister Chromatid Exchange
SETAC	Society of Environmental Toxicology and Chemistry
S-FPD	Sulfur-selective flame photometric detection
Skin Irrit.2	Causes skin irritation
Skin sens.1	May cause allergy skin allergy
STOT RE	Toxicity specific to specific target organ target organs (repeat exposure)
STOT RE.1 (liver)	Causes damage to the liver through prolonged or repeated exposure
STOT SE	Toxicity specific to specific target organ target organs (single exposure)
STOT SE.3	Causes damage to the organ(s) follows single exposure
STP	Sewage Treatment Plan
TG	Test Guideline
Th2	T helper 2

TK	Thymidine Kinase
TS	Test Substance
TWA	Time-weighted approach
UN	United Nations
UV	Ultraviolet light spectrum
UV/VIS	Ultraviolet/visible light spectrum
vPvB	Very persistent and very bio accumulable
w/w	Weight to weight
WBC	White Blood Cells
x DA	x Day of aging
λ	Lambda (wavelength of a wave)
µg	Microgram

Appendix V: Overall reference list (including data owner and confidentiality claim)

1. Physical-Chemical properties part:

Author(s)	Year	Section No / Reference No	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner	Data Identified as 'relevant' by the eCA[18] (Yes/No)	Applicability	
							CAR/RAR	CLH
[redacted]	2000a	A3.1.1. Physical state Also A3.1.3. Colour A3.1.4 Odour A3.2. Melting/freezing A3.4. Boiling point A3.11. Thermal stability, identity of breakdown products	Determination of the melting point, the appearance, the thermal stability and the stability in air of Dazomet PAI, Study Code PCP05774, Oct 19, 2000 BASF AG, Agricultural Center Limburgerhof, Germany BASF DocID 2000/1017122, GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2000a	A3.1.3. Colour Also A3.1.1. Physical state A3.1.4 Odour A3.2. Melting/freezing A3.4. Boiling point A3.11. Thermal	Determination of the melting point, the appearance, the thermal stability and the stability in air of Dazomet PAI, Study Code PCP05774, Oct 19, 2000 BASF AG, Agricultural Center Limburgerhof, Germany	N	KST	**y**	**y**	**Y**

[18] Only relevant for the renewal of an active substance. Remove column for active substance approval and CLH process.
For the identification of the relevant data, please see CA-Sept20-Doc.7.1.b - Relevant Renewal Data under Article 95_FINAL

		stability, identity of breakdown products	BASF DocID 2000/1017122, GLP / Unpublished					
[redacted]	2000a	A3.1.4 Odour Also A3.1.1. Physical state A3.1.3. Colour A3.2. Melting/freezing A3.4. Boiling point A3.11. Thermal stability, identity of breakdown products	Determination of the melting point, the appearance, the thermal stability and the stability in air of Dazomet PAI, Study Code PCP05774, Oct 19, 2000 BASF AG, Agricultural Center Limburgerhof, Germany BASF DocID 2000/1017122, GLP / Unpublished	N	KST	**y**	**y**	**Y**
[redacted]	2000a	A3.2. Melting/freezing Also A3.1.1. Physical state A3.1.3. Colour A3.1.4 Odour A3.4. Boiling point A3.11. Thermal stability, identity of breakdown products	Determination of the melting point, the appearance, the thermal stability and the stability in air of Dazomet PAI, Study Code PCP05774, Oct 19, 2000 BASF AG, Agricultural Center Limburgerhof, Germany BASF DocID 2000/1017122, GLP / Unpublished	**N**	KST	**Y**	**y**	**y**
[redacted]	2002	A3.2. Melting/freezing point Also A3.4. Boiling point A3.5. Relative	Merkblätter Gefährliche Arbeitsstoffe, M 045, Supplement 151, July 2002 BASF DocID 2002/1017610 No GLP / Published	**N**	-	**y**	**y**	**Y**

		Density						
[redacted]	2000a	A3.4. Boiling point Also A3.1.1. Physical state A3.1.3. Colour A3.1.4 Odour A3.2. Melting/freezing A3.11. Thermal stability, identity of breakdown products	Determination of the melting point, the appearance, the thermal stability and the stability in air of Dazomet PAI, Study Code PCP05774, Oct 19, 2000 BASF AG, Agricultural Center Limburgerhof, Germany BASF DocID 2000/1017122, GLP / Unpublished	**N**	KST	**y**	**y**	**y**
[redacted]	2002	A3.4. Boiling point Also A3.5. Relative Density A3.2. Melting/freezing point	Merkblätter Gefährliche Arbeitsstoffe, M 045, Supplement 151, July 2002 BASF DocID 2002/1017610 No GLP / Published	N	-	**y**	**y**	**Y**
[redacted]	2002	A3.5. Relative Density	Determination of the Relative Density of Dazomet, Study No.02L00152, 16 May 2002, BASF AG, Ludwigshafen/Rhein, Germany, BASF DocID 2002/1017611 GLP / Unpublished	N	KST	**y**	**y**	**Y**
[redacted]	2002	A3.5. Relative Density	Merkblätter Gefährliche Arbeitsstoffe, M 045, Supplement 151,	N	-	**y**	**y**	**Y**

		Also A3.2. Melting/freezing point A3.4. Boiling point	July 2002 BASF DocID 2002/1017610 No GLP / Published					
[redacted]	2000b	A3.6. Absorption spectra data (UV/VIS, IR, NMR) and a mass spectrum, molar extinction coefficient at relevant wavelengths, where relevant	UV-, NMR-, IR-, MS-Spectra of Dazomet, Study Code PCP05773, Sep 26, 2000 BASF AG, Agricultural Center Limburgerhof, Germany BASF DocID 2000/1016963, GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	1988	A3.7. Vapour pressure	Determination of the Vapour Pressure of Dazomet, Dec. 13, 1988 BASF AG, Agricultural Center Limburgerhof, Germany BASF DocID 88/11670, No GLP / Unpublished	N	KST	**y**	**y**	**Y**
[redacted]	2001	A3.7. Vapour pressure	Methyl isothiocyanate: Determination of vapour pressure, Final Report (September 10, 2001) Laboratory Project ID IET 00-6015-2, The Institute of Environmental Toxicology Uchimoriya-machi 4321, Mitsukaido-shi, Ibaraki 303-0043, Japan	N	KST	**y**	**y**	**y**

			BASF DocID 2001/1024650, GLP / Unpublished					
[redacted]	2004a	A3.7.1. Henry's law constant	Henry´s Law Constant for Dazomet, calculation, 03 Feb. 2004 BASF AG, Product Safety, Ludwigshafen/Rhein, Germany, BASF DocID 2004/1005184 No GLP / Unpublished	N	KST	**y**	**y**	**Y**
[redacted]	2004b	A3.7.1. Henry's law constant	Henry´s Law Constant for MITC, calculation, 03 Feb. 2004 BASF AG, Product Safety, Ludwigshafen/Rhein, Germany, BASF DocID 2004/1005185 No GLP / Unpublished	N	KST	**y**	**y**	**Y**
[redacted]	2000a	A3.8. Surface tension	Surface Tension of BAS 002 01 N, Study Code PCF02242, Dec 12, 2000, BASF AG, Agricultural Center Limburgerhof, Germany, BASF DocID 2000/1018765, GLP / Unpublished	N	KST	**y**	**y**	**y**

[redacted]	2002a	A3.9. Water solubility	Water Solubility of Dazomet, Study No. 01L00627, 19. Feb. 2002 BASF AG, Ludwigshafen/Rhein, Germany, BASF DocID 2002/1017608 GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2001a	A3.9. Water solubility	Determination of Water Solubility of Methyl isothiocyanate, Laboratory Project ID IET 00-6015-3, Institute of Environmental Toxicology, Japan, BASF DocID 2001/1010590 GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2002b	A3.10. Partition coefficient (n-octanol/water) and its pH dependency	Partition Coefficient n-Octanol/Water (log Pow) of Dazomet, Study No. 01L00628, 18. Feb. 2002 BASF AG, Ludwigshafen/Rhein, Germany, BASF DocID 2002/1017609 GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2001b	A3.10. Partition coefficient (n-octanol/water) and its pH dependency	Determination of Partition Coefficient (n-octanol/water) of Methyl isothiocyanate,	N	KST	**y**	**y**	**y**

			Laboratory Project ID IET 00-6015-4, Institute of Environmental Toxicology, Japan, BASF DocID 2001/1010589 GLP / Unpublished					
[redacted]	2000a	A3.11. Thermal stability, identity of breakdown products Also A3.1.1. Physical state A3.1.3. Colour A3.1.4 Odour A3.2. Melting/freezing A3.4. Boiling point	Determination of the melting point, the appearance, the thermal stability and the stability in air of Dazomet PAI, Study Code PCP05774, Oct 19, 2000 BASF AG, Agricultural Center Limburgerhof, Germany BASF DocID 2000/1017122, GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	1988	A3.11. Thermal stability, identity of breakdown products	Dynamische Differenzkalorimetrie (DSC), SIK-No. 95/1222, BASF AG, Ludwigshafen / Rhein, Germany BASF DocID 1988/1001236 No GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2002	A3.12. Reactivity towards container material	Shelf Life in Original Container (Paper-Bag) at 20 °C and 30 °C of the Formulation BAS 002 01 N, 24 Month Storage - Analytical	N	KST	**y**	**y**	**y**

			Results, Study Code PCF02163, Jun 25, 2002 BASF AG, Agricultural Center Limburgerhof, Germany BASF DocID 2002/1007108 GLP / Unpublished					
[redacted]	2002	A3.12. Reactivity towards container material	Shelf Life in Original Container of the Formulation BAS 002 01 N, 24 Month Storage - Physical Properties, Study Code PCF02167, Jun 25, 2002 BASF AG, Agricultural Center Limburgerhof, Germany BASF DocID 2002/1007106 GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2000c	A3.13. Dissociation constant	Determination of the Dissociation Constant of Dazomet, Study Code PCP05589, Jan 10, 2000 BASF AG, Agricultural Center Limburgerhof, Germany, BASF DocID 2000/1000073 GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2019a	A3.14. Granulometry	Determination of physico-chemical properties	Y	KST	**y**	**y**	**y**

			Particle Size Distribution before and after storage (CIPAC MT 46.3, CIPAC MT 170) Consilab Gesellschaft für Anlagensicherheit mbH, Frankfurt/Main, Germany Report No.: CSL-19-0586.01 Document No.: -- GLP, not published					
[redacted]	2000	A4.1. B4.1. Explosives Also A4.6. B4.6. Flammable liquids A4.7. B4.7. Flammable solids A4.8. B4.8. Self-reactive substances and mixtures A4.11. B4.11. Self-heating substances and mixtures A4.14. B4.14. Oxidising solids A4.17.2. B4.17.2. Relative	Evaluation of Safety Characteristics (A9 - A17), SIK-No. 00/0778, Apr. 13, 2000, BASF AG, Safety Engineering, Ludwigshafen, Germany, BASF DocID 2000/1013166, GLP / Unpublished	N	KST	**y**	**y**	**y**

		self-ignition temperature for solids						
[redacted]	1999	A4.1. B4.1. Explosives Also A4.14. B4.14. Oxidising solids	Expert judgement - Absence of explosive and oxidizing properties of dazomet, Internal notice, 16.12.1999 BASF AG, Research Safety Engineering, Ludwigshafen/Rhein, Germany BASF DocID 1999/1007916 No GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2003	A4.1. B4.1. Explosives Also A4.14. B4.14. Oxidising solids	Expert Judgement: Absence of Explosive and Oxidizing Properties of Methylisothiocyanate, Internal notice, 16.12.2003 BASF AG, Research Safety Engineering, Ludwigshafen/Rhein, Germany BASF DocID 2003/1022774 No GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2000	A4.6. B4.6. Flammable liquids Also A4.1. B4.1. Explosives	Evaluation of Safety Characteristics (A9 - A17), SIK-No. 00/0778, Apr. 13, 2000, BASF AG, Safety Engineering, Ludwigshafen, Germany,	N	KST	**y**	**y**	**y**

		A4.7. B4.7. Flammable solids A4.8. B4.8. Self-reactive substances and mixtures A4.11. B4.11. Self-heating substances and mixtures A4.14. B4.14. Oxidising solids A4.17.2. B4.17.2. Relative self-ignition temperature for solids	BASF DocID 2000/1013166, GLP / Unpublished					
[redacted]	2002	A4.6. B4.6. Flammable liquids	Merkblätter Gefährliche Arbeitsstoffe, M 045, Supplement 151, July 2002 BASF DocID 2002/1017610 No GLP / Published	N	-	**y**	**y**	**y**
[redacted]	2000	A4.7. B4.7. Flammable solids Also A4.1. B4.1. Explosives	Evaluation of Safety Characteristics (A9 - A17), SIK-No. 00/0778, Apr. 13, 2000, BASF AG, Safety Engineering,	N	KST	**y**	**y**	**y**

		A4.6. B4.6. Flammable liquids A4.8. B4.8. Self-reactive substances and mixtures A4.11. B4.11. Self-heating substances and mixtures A4.14. B4.14. Oxidising solids A4.17.2. B4.17.2. Relative self-ignition temperature for solids	Ludwigshafen, Germany, BASF DocID 2000/1013166, GLP / Unpublished					
[redacted]	2000	A4.8. B4.8. Self-reactive substances and mixtures Also A4.1. B4.1. Explosives A4.6. B4.6. Flammable liquids	Evaluation of Safety Characteristics (A9 - A17), SIK-No. 00/0778, Apr. 13, 2000, BASF AG, Safety Engineering, Ludwigshafen, Germany, BASF DocID 2000/1013166, GLP / Unpublished	N	KST	**y**	**y**	**y**

		A4.7. B4.7. Flammable solids A4.11. B4.11. Self-heating substances and mixtures A4.14. B4.14. Oxidising solids A4.17.2. B4.17.2. Relative self-ignition temperature for solids						
[redacted]	2021a	A4.10. Pyrophoric solids Also B4.10. Pyrophoric solids	Basamid® Determination of physico-chemical properties Pyrophoric properties of solids (EC A.13. and UN Test N.2). Consilab Gesellschaft für Anlagensicherheit mbH, Frankfurt/Main, Germany Report No.: CSL-19-0586.05 Document No.: -- GLP, Unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2000	A4.11. B4.11. Self-heating substances and mixtures Also A4.14.	Evaluation of Safety Characteristics (A9 - A17), SIK-No. 00/0778, Apr. 13, 2000, BASF AG, Safety Engineering,	N	KST	**y**	**y**	**y**

		B4.14. Oxidising solids A4.17.2. B4.17.2. Relative self-ignition temperature for solids A4.1. B4.1. Explosives A4.6. B4.6. Flammable liquids A4.7. B4.7. Flammable solids A4.8. B4.8. Self-reactive substances and mixtures	Ludwigshafen, Germany, BASF DocID 2000/1013166, GLP / Unpublished					
[redacted]	2021b	A4.12. Substances and mixtures which in contact with water emit flammable gases Also B4.12. Substances and mixtures which in contact with water emit flammable gases	Dazomet Determination of physico-chemical properties Emission of flammable gases at contact with water (EC A.12. and UN Test N.5) Consilab Gesellschaft für Anlagensicherheit mbH, Frankfurt/Main, Germany Report No.: CSL-19-0586.06 Document No.: -- GLP, Unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2000	A4.14. B4.14. Oxidising	Evaluation of Safety Characteristics (A9 -	N	KST	**y**	**y**	**y**

		solids Also A4.17.2. B4.17.2. Relative self-ignition temperature for solids A4.1. B4.1. Explosives A4.6. B4.6. Flammable liquids A4.7. B4.7. Flammable solids A4.8. B4.8. Self-reactive substances and mixtures A4.11. B4.11. Self-heating substances and mixtures	A17), SIK-No. 00/0778, Apr. 13, 2000, BASF AG, Safety Engineering, Ludwigshafen, Germany, BASF DocID 2000/1013166, GLP / Unpublished					
[redacted]	1999	A4.14. B4.14. Oxidising solids Also A4.1. B4.1. Explosives	Expert judgement - Absence of explosive and oxidizing properties of dazomet, Internal notice, 16.12.1999 BASF AG, Research Safety Engineering, Ludwigshafen/Rhein,	N	KST	**y**	**y**	**y**

			Germany BASF DocID 1999/1007916 No GLP / Unpublished					
[redacted]	2003	A4.14. B4.14. Oxidising solids Also A4.1. B4.1. Explosives	Expert Judgement: Absence of Explosive and Oxidizing Properties of Methylisothiocyanate, Internal notice, 16.12.2003 BASF AG, Research Safety Engineering, Ludwigshafen/Rhein, Germany BASF DocID 2003/1022774 No GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2000	A4.17.2. B4.17.2. Relative self-ignition Also A4.1. B4.1. Explosives A4.6. B4.6. Flammable liquids A4.7. B4.7. Flammable solids A4.8. B4.8. Self-reactive substances and	Evaluation of Safety Characteristics (A9 - A17), SIK-No. 00/0778, Apr. 13, 2000, BASF AG, Safety Engineering, Ludwigshafen, Germany, BASF DocID 2000/1013166, GLP / Unpublished	N	KST	**y**	**y**	**y**

		mixtures A4.11. B4.11. Self-heating substances and mixtures A4.14. B4.14. Oxidising solids						
[redacted]	2020	A4.17.3. Also B4.17.3. Dust explosion hazard B3.1.1. Physical state B3.1.2. Colour B3.2 Acidity/Alkalinity B3.4.1.2. Long term storage at ambient temperature B3.5.6. Particle size distribution, content of dust/fines, attrition, friability	Basamid: Long-term storage stability summary – Convance, Derbyshire, UK Report No.: GL31DY Document No.: -- GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2000a	A5.1. Active substance determination	Dazomet, HPLC method for technical and GR formulations, CIPAC No. 146, CIPAC/4109. CIPAC, Harpenden AL5 2 HG, UK BASF DocID 2000/1021646	N	-	**y**	**y**	**y**

			No GLP / Published					
[redacted]	2015-2016	A5.1. Also B5.1. Active substance determination	Report Amendment No. 1 Determination of Dazomet and its Impurities in Five Batches of Dazomet technical granules Report No.: 14K07078-01-5B Document No.: -- GLP, unpublished CONFIDENTIAL information	Y	KST	**y**	**y**	**y**
[redacted]	2016	A5.1. Also B5.1 Active substance determination	Report Amendment No. 2 Determination of Dazomet and its Impurities in Five Batches of Dazomet Technical Chemisches Institut Pforzheim GmbH (CIP), Germany Report No.: 16K09234-01-5B Document No.: -- GLP, unpublished CONFIDENTIAL information	Y	KST	**y**	**y**	**y**
[redacted]	1999	A5.2.1. Monitoring in soil (MITC)	Analytik von Pflanzenschutzmitteln in Boden - Kurzfassungen von Methoden. Mitteilungen der Biologischen Bundesanstalt für Land- und Forstwirtschaft, Volume 364, Page 108, Method-No. 0029-B01,	N	-	**y**	**y**	**y**

			Parey Buchverlag, Berlin 1999 BASF DocID 1999/1007918 Published					
[redacted]	1985	A5.2.1. Monitoring in soil (MITC) Also A5.3. Monitoring in plants (MITC)	Gas chromatographical determination of methyl mustard oil (MITC) in soil and tomatoes, Method number 234, BASF AG, Agricultural Center Limburgerhof, Germany, BASF DocID 1985/1000325, 1985 No GLP, unpublished	N	KST	**y**	**y**	**y**
[redacted]	2014	A5.2.1. Also B5.2.1. Monitoring in soil (MITC)	MITC (Methyl Isothiocyanate): Validation of a residue analytical method for soil. examination of short-term stability on frozen storage of MITC in Soil PTRL Europe, Germany Report No.: P 2157 G Document No.: -- GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2020a	A5.2.1. Monitoring in soil (MITC)	Aerobic soil transformation of methyl Isothiocyanate (MITC) in three top-soils and formation and decline of dimethylurea (DMU) based on OECD TG 307 (closed system) EAG Laboratories GmbH, Germany Report No.: S20-02386 Document No.: not	Y	KST	**y**	**y**	**y**

			assigned GLP, unpublished					
[redacted]	2003	A5.2.2. Also B5.2.2. Monitoring in air	Validation of Analytical Method 532 – Determination of Dazomet (BAS 002 N) in Air by C-MS BASF AG, Limburgerhof, Germany Report No.: 133606 Document No.: 436-002 BASF ID No.: 2003/1000992 GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2004	A5.2.2. Also B5.2.2. Monitoring in air	Report Amendment No. 1 to Final Report - Validation of Analytical Method 532 - Determination of Dazomet (BAS 002 N) in Air by C-MS BASF AG, Limburgerhof, Germany Report No.: 133606 Document No.: 436-004 BASF ID No.: 2004/1009151 GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2001	A5.2.2. Monitoring in air (MITC)	Validation of Analytical method 502. Determination of Methylisothiocyanate-residues (MITC, decomposition product of Dazomet, BAS 002N) in air by GC-MS. Study code 58318 BASF, Limburgerhof, Germany,	N	KST	**y**	**y**	**y**

			BASF DocID 2001/1010667 GLP / Unpublished					
[redacted]	2012	A5.2.2. Also B5.2.2. Monitoring in air (MITC)	MITC (Methyl Isothiocyanate): Validation of an Analytical Method for the Determination of MITC in Air PTRL Europe GmbH, Ulm, Germany Report No.: P 2158 G Document No: -- GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	1997	A5.2.3. Monitoring in water	Methodenbuch Rückstandsanalytik - Kurzfassungen zur Bestimmung von Pflanzenschutzmitteln in Wasser. Bearbeitet von Ralf Fischer, Johannes Siebers und Marion Blacha-Puller. Methodenkurzfassungen für 347 Wirkstoffe bzw. Metabolite. Mitteilungen der Biologischen Bundesanstalt für Land- und Forstwirtschaft, Volume 326, Page 143, Method-No. 0029-01, Parey Buchverlag, Berlin, BASF DocID 1997/1003378, Published	N	-	**y**	**y**	**y**
[redacted]	1997	A5.2.3. Monitoring in water (MITC)	Methodenbuch Rückstandsanalytik - Kurzfassungen zur	N	-	**y**	**y**	**y**

			Bestimmung von Pflanzenschutzmitteln in Wasser. Bearbeitet von Ralf Fischer, Johannes Siebers und Marion Blacha-Puller. Methodenkurzfassungen für 347 Wirkstoffe bzw. Metabolite. Mitteilungen der Biologischen Bundesanstalt für Land- und Forstwirtschaft, Volume 326, Page 333, Method-No. 0150-01, Parey Buchverlag, Berlin, BASF DocID 1997/1003379, Published					
[redacted]	2020b	A5.2.3. Also B5.2.3. Monitoring in water (MITC)	MITC (methyl isothiocyanate): Independent laboratory validation for water EAG Laboratories GmbH, Germany Report No.: S20-06897 Document No.: -- GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2019	A5.2.4. Also B5.2.4. Monitoring in body fluids and tissues (N-Acetyl-S-(N-methylthiocarbamoyl)-L-cysteine)	Development and Validation of a Method for the Determination of N-Acetyl-S-(N-methylthiocarbamoyl)-L-cysteine in Blood and Liver Matrix EAG Laboratories GmbH, Ulm, Germany Report No.: P 5075 G Document No.: --	Y	KST	**y**	**y**	**y**

			GLP, unpublished					
[redacted]	1998a	A5.3. Also B5.3. Monitoring in plants	Raw Agricultural Commodity (RAC) residue trials of Basamid-Granular soil fumigant on strawberries, NPC Inc., Sterling, VA, USA, BASF DocID 1998/5038 GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	1998b	A5.3. Also B5.3. Monitoring in plants	Raw Agricultural Commodity (RAC) residue trials of Basamid-Granular soil fumigant on tomatoes, NPC Inc., Sterling, VA, USA, BASF DocID 1998/5037 GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	1985	A5.3. Monitoring in plants (MITC) Also A5.2.1. Monitoring in soil (MITC)	Gas chromatographical determination of methyl mustard oil (MITC) in soil and tomatoes, Method number 234, BASF AG, Agricultural Center Limburgerhof, Germany, BASF DocID 1985/1000325, 1985 No GLP, unpublished	N	KST	**y**	**y**	**y**
[redacted]	2000b	B3.1.1. Physical state B3.1.2. Colour B3.1.3. Odour Also B3.2 Acidity/Alkalinity	Physical and chemical properties of BAS 002 01 N, BASF AG, BASF DocID 2000/1013123, GLP, unpublished	N	KST	**y**	**y**	**y**

		B3.3 Relative density (liquids) and bulk, tap density (solids) B3.4.1.1. Accelerated storage test B3.5.6. Particle size distribution, content of dust/fines, attrition, friability B3.5.8. Flowability/Pourability/Dustability						
[redacted]	2002	B3.1.1. Physical state B3.1.2. Colour Also B3.4.1.2. Long term storage at ambient temperature B3.5.6. Particle size distribution, content of dust/fines, attrition, friability	Shelf Life in Original Container of the Formulation BAS 002 01 N, 24 Month Storage - Physical Properties, Study Code PCF02167, Jun 25, 2002 BASF AG, Agricultural Center Limburgerhof, Germany BASF DocID 2002/1007106 GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2018	B3.1.1. Physical state B3.1.2. Colour Also B3.2 Acidity/Alkalinity B3.3 Relative density (liquids)	Basamid: Determination of accelerated storage stability Envigo Research Ltd, Derbyshire, UK Report No.: LR24DP Document No: -- GLP, unpublished	Y	KST	**y**	**y**	**y**

		B3.4.1.1. Accelerated storage test B3.5.6. Particle size distribution, content of dust/fines, attrition, friability						
[redacted]	2020	B3.1.1. Physical state B3.1.2. Colour Also B3.2 Acidity/Alkalinity B3.4.1.2. Long term storage at ambient temperature B3.5.6. Particle size distribution, content of dust/fines, attrition, friability	Basamid: Long-term storage stability summary – Convance, Derbyshire, UK Report No.: GL31DY Document No.: -- GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2000b	B3.2 Acidity/Alkalinity Also B3.1.1. Physical state B3.1.2. Colour B3.1.3. Odour B3.3 Relative density (liquids) and bulk, tap density (solids) B3.4.1.1. Accelerated storage test B3.5.6. Particle size distribution, content	Physical and chemical properties of BAS 002 01 N, BASF AG, BASF DocID 2000/1013123, GLP, unpublished	N	KST	**y**	**y**	**y**

		of dust/fines, attrition, friability B3.5.8. Flowability/Pourability/Dustability						
[redacted]	2002	B3.2 Acidity/Alkalinity Also B3.1.1. Physical state B3.1.2. Colour B3.4.1.2. Long term storage at ambient temperature B3.5.6. Particle size distribution, content of dust/fines, attrition, friability	Shelf Life in Original Container of the Formulation BAS 002 01 N, 24 Month Storage - Physical Properties, Study Code PCF02167, Jun 25, 2002 BASF AG, Agricultural Center Limburgerhof, Germany BASF DocID 2002/1007106 GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2018	B3.2 Acidity/Alkalinity Also B3.1.1. Physical state B3.1.2. Colour B3.3 Relative density (liquids) B3.4.1.1. Accelerated storage test B3.5.6. Particle size distribution, content of dust/fines, attrition, friability	Basamid: Determination of accelerated storage stability Envigo Research Ltd, Derbyshire, UK Report No.: LR24DP Document No: -- GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2020	B3.2	Basamid: Long-term	Y	KST	**y**	**y**	**y**

		Acidity/Alkalinity Also B3.1.1. Physical state B3.1.2. Colour B3.4.1.2. Long term storage at ambient temperature B3.5.6. Particle size distribution, content of dust/fines, attrition, friability	storage stability summary – Convance, Derbyshire, UK Report No.: GL31DY Document No.: -- GLP, unpublished					
[redacted]	2000b	B3.3 Relative density (liquids) and bulk, tap density (solids) Also B3.1.1. Physical state B3.1.2. Colour B3.1.3. Odour B3.2 Acidity/Alkalinity B3.4.1.1. Accelerated storage test B3.5.6. Particle size distribution, content of dust/fines, attrition, friability B3.5.8. Flowability/Pourability/Dustability	Physical and chemical properties of BAS 002 01 N, BASF AG, BASF DocID 2000/1013123, GLP, unpublished	N	KST	**y**	**y**	**y**
[redacted]	2018	B3.3 Relative	Basamid: Determination	Y	KST	**y**	**y**	**y**

		density (liquids) Also B3.1.1. Physical state B3.1.2. Colour B3.2 Acidity/Alkalinity B3.4.1.1. Accelerated storage test B3.5.6. Particle size distribution, content of dust/fines, attrition, friability	of accelerated storage stability Envigo Research Ltd, Derbyshire, UK Report No.: LR24DP Document No: -- GLP, unpublished					
[redacted]	2019b	B3.3 Relative density (liquids) and bulk, tap density (solids)	Determination of physico-chemical properties Bulk and tap density before and after storage (CIPAC MT 186) Consilab Gesellschaft für Anlagensicherheit mbH, Frankfurt/Main, Germany Report No.: CSL-19-0586.03 Document No.: -- GLP, not published	Y	KST	**y**	**y**	**y**
[redacted]	2019b	B3.3 Relative density (liquids) and bulk, tap density (solids)	Determination of physico-chemical properties Bulk and tap density before and after storage (CIPAC MT 186) Consilab Gesellschaft für Anlagensicherheit mbH,	Y	KST	**y**	**y**	**y**

			Frankfurt/Main, Germany Report No.: CSL-19-0586.03 Document No.: -- GLP, not published					
[redacted]	2000b	B3.4.1.1. Accelerated storage test Also B3.1.1. Physical state B3.1.2. Colour B3.1.3. Odour B3.2 Acidity/Alkalinity B3.3 Relative density (liquids) and bulk, tap density (solids) B3.5.6. Particle size distribution, content of dust/fines, attrition, friability B3.5.8. Flowability/Pourability/Dustability	Physical and chemical properties of BAS 002 01 N, BASF AG, BASF DocID 2000/1013123, GLP, unpublished	N	KST	**y**	**y**	**y**
[redacted]	2018	B3.4.1.1. Accelerated storage test Also B3.1.1. Physical state B3.1.2. Colour B3.2	Basamid: Determination of accelerated storage stability Envigo Research Ltd, Derbyshire, UK Report No.: LR24DP Document No: -- GLP, unpublished	Y	KST	**y**	**y**	**y**

		Acidity/Alkalinity B3.3 Relative density (liquids) B3.5.6. Particle size distribution, content of dust/fines, attrition, friability						
[redacted]	2002	B3.4.1.2. Long term storage at ambient temperature	Shelf Life in Original Container (Paper-Bag) at 20 °C and 30 °C of the Formulation BAS 002 01 N, 24 Month Storage - Analytical Results, Study Code PCF02163, Jun 25, 2002 BASF AG, Agricultural Center Limburgerhof, Germany BASF DocID 2002/1007108 GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2002	B3.4.1.2. Long term storage at ambient temperature Also B3.1.1. Physical state B3.1.2. Colour B3.5.6. Particle size distribution, content of dust/fines, attrition, friability	Shelf Life in Original Container of the Formulation BAS 002 01 N, 24 Month Storage - Physical Properties, Study Code PCF02167, Jun 25, 2002 BASF AG, Agricultural Center Limburgerhof, Germany BASF DocID 2002/1007106 GLP / Unpublished	N	KST	**y**	**y**	**y**

[redacted]	2020	B3.4.1.2. Long term storage at ambient temperature Also B3.1.1. Physical state B3.1.2. Colour B3.2 Acidity/Alkalinity B3.5.6. Particle size distribution, content of dust/fines, attrition, friability	Basamid: Long-term storage stability summary – Convance, Derbyshire, UK Report No.: GL31DY Document No.: -- GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	1987	B3.4.2.1. Light	The photolysis of 14C-Dazomet in water HRC, Report No. 1987/0396, unpublished	N	KST	**y**	**y**	**y**
[redacted]	2000b	B3.5.6. Particle size distribution, content of dust/fines, attrition, friability Also B3.1.1. Physical state B3.1.2. Colour B3.1.3. Odour B3.2 Acidity/Alkalinity B3.3 Relative density (liquids) and bulk, tap density (solids) B3.4.1.1. Accelerated storage test	Physical and chemical properties of BAS 002 01 N, BASF AG, BASF DocID 2000/1013123, GLP, unpublished	N	KST	**y**	**y**	**y**

		B3.5.8. Flowability/Pourability/Dustability						
[redacted]	2002		Shelf Life in Original Container of the Formulation BAS 002 01 N, 24 Month Storage - Physical Properties, Study Code PCF02167, Jun 25, 2002 BASF AG, Agricultural Center Limburgerhof, Germany BASF DocID 2002/1007106 GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2018		Basamid: Determination of accelerated storage stability Envigo Research Ltd, Derbyshire, UK Report No.: LR24DP Document No: -- GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2019a	B3.5.6. Particle size distribution, content of dust/fines, attrition, friability	Determination of physico-chemical properties Particle Size Distribution before and after storage (CIPAC MT 46.3, CIPAC MT 170) Consilab Gesellschaft für Anlagensicherheit mbH, Frankfurt/Main, Germany Report No.: CSL-19-0586.01 Document No.: --	Y	KST	**y**	**y**	**y**

			GLP, not published					
[redacted]	2020	B3.5.6. Particle size distribution, content of dust/fines, attrition, friability Also B3.1.1. Physical state B3.1.2. Colour B3.2 Acidity/Alkalinity B3.4.1.2. Long term storage at ambient temperature	Basamid: Long-term storage stability summary – Convance, Derbyshire, UK Report No.: GL31DY Document No.: -- GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2000b	B3.5.6. Particle size distribution, content of dust/fines, attrition, friability Also B3.1.1. Physical state B3.1.2. Colour B3.1.3. Odour B3.2 Acidity/Alkalinity B3.3 Relative density (liquids) and bulk, tap density (solids) B3.4.1.1. Accelerated storage test B3.5.8. Flowability/Pourability/Dustability	Physical and chemical properties of BAS 002 01 N, BASF AG, BASF DocID 2000/1013123, GLP, unpublished	N	KST	**y**	**y**	**y**

[redacted]	2002	B3.5.6. Particle size distribution, content of dust/fines, attrition, friability Also B3.1.1. Physical state B3.1.2. Colour B3.4.1.2. Long term storage at ambient temperature	Shelf Life in Original Container of the Formulation BAS 002 01 N, 24 Month Storage - Physical Properties, Study Code PCF02167, Jun 25, 2002 BASF AG, Agricultural Center Limburgerhof, Germany BASF DocID 2002/1007106 GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2018	B3.5.6. Particle size distribution, content of dust/fines, attrition, friability Also B3.1.1. Physical state B3.1.2. Colour B3.2 Acidity/Alkalinity B3.3 Relative density (liquids) B3.4.1.1. Accelerated storage test	Basamid: Determination of accelerated storage stability Envigo Research Ltd, Derbyshire, UK Report No.: LR24DP Document No: -- GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2019c	B3.5.6. Particle size distribution, content of dust/fines, attrition, friability	Determination of physico-chemical properties Dustiness before and after storage (CIPAC MT 171) Consilab Gesellschaft für Anlagensicherheit mbH,	Y	KST	**y**	**y**	**y**

			Frankfurt/Main, Germany Report No.: CSL-19-0586.02 GLP, not published					
[redacted]	2020	B3.5.6. Particle size distribution, content of dust/fines, attrition, friability Also B3.1.1. Physical state B3.1.2. Colour B3.2 Acidity/Alkalinity B3.4.1.2. Long term storage at ambient temperature	Basamid: Long-term storage stability summary – Convance, Derbyshire, UK Report No.: GL31DY Document No.: -- GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2000b	B3.5.6. Particle size distribution, content of dust/fines, attrition, friability Also B3.1.1. Physical state B3.1.2. Colour B3.1.3. Odour B3.2 Acidity/Alkalinity B3.3 Relative density (liquids) and bulk, tap density (solids) B3.4.1.1. Accelerated storage test	Physical and chemical properties of BAS 002 01 N, BASF AG, BASF DocID 2000/1013123, GLP, unpublished	N	KST	**y**	**y**	**y**

		B3.5.8. Flowability/Pourability/Dustability						
[redacted]	2002	B3.5.6. Particle size distribution, content of dust/fines, attrition, friability Also B3.1.1. Physical state B3.1.2. Colour B3.4.1.2. Long term storage at ambient temperature	Shelf Life in Original Container of the Formulation BAS 002 01 N, 24 Month Storage - Physical Properties, Study Code PCF02167, Jun 25, 2002 BASF AG, Agricultural Center Limburgerhof, Germany BASF DocID 2002/1007106 GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2018	B3.5.6. Particle size distribution, content of dust/fines, attrition, friability Also B3.1.1. Physical state B3.1.2. Colour B3.2 Acidity/Alkalinity B3.3 Relative density (liquids) B3.4.1.1. Accelerated storage test	Basamid: Determination of accelerated storage stability Envigo Research Ltd, Derbyshire, UK Report No.: LR24DP Document No: -- GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2020	B3.5.6. Particle size distribution, content of dust/fines, attrition, friability	Basamid: Long-term storage stability summary – Convance, Derbyshire,	Y	KST	**y**	**y**	**y**

		Also B3.1.1. Physical state B3.1.2. Colour B3.2 Acidity/Alkalinity B3.4.1.2. Long term storage at ambient temperature	UK Report No.: GL31DY Document No.: -- GLP, unpublished					
[redacted]	2000b	B3.5.8. Flowability/Pourability/Dustability Also B3.1.1. Physical state B3.1.2. Colour B3.1.3. Odour B3.2 Acidity/Alkalinity B3.3 Relative density (liquids) and bulk, tap density (solids) B3.4.1.1. Accelerated storage test B3.5.6. Particle size distribution, content of dust/fines, attrition, friability	Physical and chemical properties of BAS 002 01 N, BASF AG, BASF DocID 2000/1013123, GLP, unpublished	N	KST	**y**	**y**	**y**
[redacted]	2000a	B3.8. Surface tension	Surface Tension of BAS 002 01 N, Study Code PCF02242,	N	KST	**y**	**y**	**y**

			Dec 12, 2000, BASF AG, Agricultural Center Limburgerhof, Germany, BASF DocID 2000/1018765, GLP / Unpublished					
[redacted]	2000	B4.1. Explosives Also A4.1. Explosives liquids A4.6. B4.6. Flammable A4.7. B4.7. Flammable solids A4.8. B4.8. Self-reactive substances and mixtures A4.11. B4.11. Self-heating substances and mixtures A4.14. B4.14. Oxidising solids A4.17.2. B4.17.2. Relative self-ignition temperature for solids	Evaluation of Safety Characteristics (A9 - A17), SIK-No. 00/0778, Apr. 13, 2000, BASF AG, Safety Engineering, Ludwigshafen, Germany, BASF DocID 2000/1013166, GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	1999	B4.1. Explosives	Expert judgement - Absence of explosive and oxidizing properties	**N**		**y**	**y**	**y**

		Also A4.1. Explosives A4.14. B4.14. Oxidising solids	of dazomet, Internal notice, 16.12.1999 BASF AG, Research Safety Engineering, Ludwigshafen/Rhein, Germany BASF DocID 1999/1007916 No GLP / Unpublished					
[redacted]	2003	B4.1. Explosives Also A4.1. Explosives A4.14. B4.14. Oxidising solids	Expert Judgement: Absence of Explosive and Oxidizing - Properties of Methylisothiocyanate, Internal notice, 16.12.2003 BASF AG, Research Safety Engineering, Ludwigshafen/Rhein, Germany BASF DocID 2003/1022774 No GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2000	B4.7. Flammable solids Also A4.7. Flammable solids A4.1. B4.1. Explosives A4.6. B4.6. Flammable liquids A4.8.	Evaluation of Safety Characteristics (A9 - A17), SIK-No. 00/0778, Apr. 13, 2000, BASF AG, Safety Engineering, Ludwigshafen, Germany, BASF DocID 2000/1013166, GLP / Unpublished	N	KST	**y**	**y**	**y**

		B4.8. Self-reactive substances and mixtures A4.11. B4.11. Self-heating substances and mixtures A4.14. B4.14. Oxidising solids A4.17.2. B4.17.2. Relative self-ignition temperature for solids						
[redacted]	2000	B4.14. Oxidising solids Also A4.14. Oxidising solids A4.1. B4.1. Explosives A4.6. B4.6. Flammable liquids A4.7. B4.7. Flammable solids A4.8. B4.8. Self-reactive substances and mixtures A4.11. B4.11. Self-heating substances and mixtures	Evaluation of Safety Characteristics (A9 - A17), SIK-No. 00/0778, Apr. 13, 2000, BASF AG, Safety Engineering, Ludwigshafen, Germany, BASF DocID 2000/1013166, GLP / Unpublished	N	KST	**y**	**y**	**y**

		A4.17.2. B4.17.2. Relative self-ignition temperature for solids						
[redacted]	1999	B4.14. Oxidising solids Also A4.14. Oxidising solids A4.1. B4.1. Explosives	Expert judgement - Absence of explosive and oxidizing properties of dazomet, Internal notice, 16.12.1999 BASF AG, Research Safety Engineering, Ludwigshafen/Rhein, Germany BASF DocID 1999/1007916 No GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2003	B4.14. Oxidising solids Also A4.14. Oxidising solids A4.1. B4.1. Explosives	Expert Judgement: Absence of Explosive and Oxidizing Properties of Methylisothiocyanate, Internal notice, 16.12.2003 BASF AG, Research Safety Engineering, Ludwigshafen/Rhein, Germany BASF DocID 2003/1022774 No GLP / Unpublished	N	KST	**y**	**y**	**y**
[redacted]	2000	B4.6. Flammable liquids Also A4.6. Flammable liquids A4.1.	Evaluation of Safety Characteristics (A9 - A17), SIK-No. 00/0778, Apr. 13, 2000, BASF AG, Safety Engineering,	N	KST	**y**	**y**	**y**

		B4.1. Explosives A4.7. B4.7. Flammable solids A4.8. B4.8. Self-reactive substances and mixtures A4.11. B4.11. Self-heating substances and mixtures A4.14. B4.14. Oxidising solids A4.17.2. B4.17.2. Relative self-ignition temperature for solids.	Ludwigshafen, Germany, BASF DocID 2000/1013166, GLP / Unpublished					
[redacted]	2002	B4.6. Flammable liquids Also A4.6. Flammable liquids	Merkblätter Gefährliche Arbeitsstoffe, M 045, Supplement 151, July 2002 BASF DocID 2002/1017610 No GLP / Published	N	-	**y**	**y**	**y**
[redacted]	2000	B4.8. Self-reactive substances and mixtures Also A4.8. Self-reactive substances and mixtures A4.1. B4.1. Explosives	Evaluation of Safety Characteristics (A9 - A17), SIK-No. 00/0778, Apr. 13, 2000, BASF AG, Safety Engineering, Ludwigshafen, Germany,	N	KST	**y**	**y**	**y**

		A4.6. B4.6. Flammable liquids A4.7. B4.7. Flammable solids A4.11. B4.11. Self-heating substances and mixtures A4.14. B4.14. Oxidising solids A4.17.2. B4.17.2. Relative self-ignition temperature for solids	BASF DocID 2000/1013166, GLP / Unpublished					
[redacted]	2020	B4.17.3. Dust explosion hazard Also A4.17.3. Dust explosion hazard B3.1.1. Physical state B3.1.2. Colour B3.2 Acidity/Alkalinity B3.4.1.2. Long term storage at ambient temperature B3.5.6. Particle size distribution, content of dust/fines, attrition, friability	Basamid: Long-term storage stability summary – Convance, Derbyshire, UK Report No.: GL31DY Document No.: -- GLP, unpublished	Y	KST	**y**	**y**	**y**

[redacted]	2021a	B4.10. Pyrophoric solids Also A4.10. Pyrophoric solids	Basamid® Determination of physico-chemical properties Pyrophoric properties of solids (EC A.13. and UN Test N.2). Consilab Gesellschaft für Anlagensicherheit mbH, Frankfurt/Main, Germany Report No.: CSL-19-0586.05 Document No.: -- GLP, Unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2000	B4.11. Self-heating substances and mixtures Also A4.11. Self-heating substances and mixtures A4.1. B4.1. Explosives A4.6. B4.6. Flammable liquids A4.7. B4.7. Flammable solids A4.8. B4.8. Self-reactive substances and mixtures A4.14. B4.14. Oxidising solids A4.17.2.	Evaluation of Safety Characteristics (A9 - A17), SIK-No. 00/0778, Apr. 13, 2000, BASF AG, Safety Engineering, Ludwigshafen, Germany, BASF DocID 2000/1013166, GLP / Unpublished	N	KST	**y**	**y**	**y**

		B4.17.2. Relative self-ignition temperature for solids						
[redacted]	2021b	B4.12. Substances and mixtures which in contact with water emit flammable gases Also A4.12. Substances and mixtures which in contact with water emit flammable gases	Dazomet Determination of physico-chemical properties Emission of flammable gases at contact with water (EC A.12. and UN Test N.5) Consilab Gesellschaft für Anlagensicherheit mbH, Frankfurt/Main, Germany Report No.: CSL-19-0586.06 Document No.: -- GLP, Unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2000	B4.17.2. Relative self-ignition temperature for solids Also A4.17.2. Relative self-ignition temperature for solids A4.1. B4.1. Explosives A4.6. B4.6. Flammable liquids A4.7. B4.7. Flammable solids A4.8.	Evaluation of Safety Characteristics (A9 - A17), SIK-No. 00/0778, Apr. 13, 2000, BASF AG, Safety Engineering, Ludwigshafen, Germany, BASF DocID 2000/1013166, GLP / Unpublished	N	KST	**y**	**y**	**y**

		B4.8. Self-reactive substances and mixtures A4.11. B4.11. Self-heating substances and mixtures A4.14. B4.14. Oxidising solids						
[redacted]	2015-2016	B5.1. Active substance determination Also A5.1. Active substance determination	Report Amendment No. 1 Determination of Dazomet and its Impurities in Five Batches of Dazomet technical granules Report No.: 14K07078-01-5B Document No.: -- GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2016	B5.1. Active substance determination Also A5.1. Active substance determination	Report Amendment No. 2 Determination of Dazomet and its Impurities in Five Batches of Dazomet Technical Chemisches Institut Pforzheim GmbH (CIP), Germany Report No.: 16K09234-01-5B Document No.: -- GLP, unpublished CONFIDENTIAL information	Y	KST	**y**	**y**	**y**
[redacted]	2014	B5.2.1. Monitoring in soil (MITC) Also	MITC (Methyl Isothiocyanate): Validation of a residue analytical method for	Y	KST	**y**	**y**	**y**

		A5.2.1. Monitoring in soil (MITC)	soil. examination of short-term stability on frozen storage of MITC in Soil PTRL Europe, Germany Report No.: P 2157 G Document No.: -- GLP, unpublished					
[redacted]	2003	B5.2.2. Monitoring in air Also A5.2.2. Monitoring in air	Validation of Analytical Method 532 – Determination of Dazomet (BAS 002 N) in Air by C-MS BASF AG, Limburgerhof, Germany Report No.: 133606 Document No.: 436-002 BASF ID No.: 2003/1000992 GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2004	B5.2.2. Monitoring in air Also A5.2.2. Monitoring in air	Report Amendment No. 1 to Final Report - Validation of Analytical Method 532 - Determination of Dazomet (BAS 002 N) in Air by C-MS BASF AG, Limburgerhof, Germany Report No.: 133606 Document No.: 436-004 BASF ID No.: 2004/1009151 GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2012	B5.2.2. Monitoring in air (MITC)	MITC (Methyl Isothiocyanate): Validation of an Analytical Method for the Determination of MITC in	Y	KST	**y**	**y**	**y**

		Also A5.2.2. Monitoring in air (MITC)	Air PTRL Europe GmbH, Ulm, Germany Report No.: P 2158 G Document No: -- GLP, unpublished					
[redacted]	2020b	B5.2.3. Monitoring in water (MITC) Also A5.2.3. Monitoring in water (MITC)	MITC (methyl isothiocyanate): Independent laboratory validation for water EAG Laboratories GmbH, Germany Report No.: S20-06897 Document No.: -- GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	2019	B5.2.4. Monitoring in body fluids and tissues (N-Acetyl-S-(N-methylthiocarbamoyl)-L-cysteine) Also A5.2.4. Monitoring in body fluids and tissues (N-Acetyl-S-(N-methylthiocarbamoyl)-L-cysteine	Development and Validation of a Method for the Determination of N-Acetyl-S-(N-methylthiocarbamoyl)-L-cysteine in Blood and Liver Matrix EAG Laboratories GmbH, Ulm, Germany Report No.: P 5075 G Document No.: -- GLP, unpublished	Y	KST	**y**	**y**	**y**
[redacted]	1998a	B5.3. Monitoring in plants Also A5.3. Monitoring in plants	Raw Agricultural Commodity (RAC) residue trials of Basamid-Granular soil fumigant on strawberries, NPC Inc., Sterling, VA,	N	KST	**y**	**y**	**y**

			USA, BASF DocID 1998/5038 GLP / Unpublished					
[redacted]	1998b	B5.3. Monitoring in plants Also A5.3. Monitoring in plants	Raw Agricultural Commodity (RAC) residue trials of Basamid-Granular soil fumigant on tomatoes, NPC Inc., Sterling, VA, USA, BASF DocID 1998/5037 GLP / Unpublished	N	KST	**y**	**y**	**y**

2. Human Health part:

Data protection from the first approval *- 01/08/2012 - 31/01/2025*

Author(s)	Year	Section No / Reference No	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner	Data Identified as 'relevant' by the eCA[19] (Yes/No)	Applicability	
							CAR/ RAR	CLH
[redacted]	1992	A8.1.1-001 Also B8.1.1-001	Primary skin irritation/corrosion study with Dazomet in the rabbit, RCC NOTOX B.V., Hertogenbosch, The Netherlands, unpublished report 067308 (BASF Project 14H0111/919012), BASF DocID 1992/10417, 28 Apr 1992 (sponsored by BASF AG, Ludwigshafen/Rhein, Germany) GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1986a	A8.1.1-002	Report on the acute dermal irritation/corrosivity to the intact dorsal skin of the white rabbit based on OECD and EPA (FIFRA) of	N	KST	Yes		

[19] Only relevant for the renewal of an active substance. Remove column for active substance approval and CLH process.
For the identification of the relevant data, please see CA-Sept20-Doc.7.1.b - Relevant Renewal Data under Article 95_FINAL

			MITC, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 1986/319, BASF DocID 1986/319, 24 Oct 1986 GLP, unpublished					
[redacted]	1985a	A8.2.1-001 Also B8.1.2-001	Report on the acute irritation to the eye of the white rabbit based on OECD and EPA (FIFRA) of Dazomet, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 85/318, BASF DocID 1985/389, 27 Nov 1985 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1985b	A8.3.1-001 Also B8.3.1-001	Report on the maximization test for the sensitizing potential of Dazomet in guinea pigs, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 30H318/85, BASF DocID 1985/399, 20 Dec 1985 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1986	A8.3.1-001	Amendment to the report on the maximization test for the sensitizing potential of Dazomet in guinea pigs, BASF AG, Department of Toxicology,	N	KST	Yes	**Y**	**Y**

			Ludwigshafen/Rhein, Germany, unpublished report 30H318/85 dated 20 Dec 1985, BASF DocID 1986/196, 29 Jul 1986 GLP, unpublished					
[redacted]	1986b	A8.3.1-002	Report on the maximization test for the sensitizing potential of MITC in guinea pigs, BASF AG, Ludwigshafen/Rhein, Germany, unpublished report 30H231/85, BASF DocID 1986/374, 02 Dec 1986 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1980a	A8.5.4-001	N-512 mutagenicity evaluation in Salmonella typhimurium, Stauffer Chemical Company, USA, unpublished report T-10044, BASF DocID 1980/0217, 09 Jun 1980 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1986	A8.5.4-002	Report on the study of Methylisothiocyanate (ZNT test substance No.: 85/231) in the AMES test (standard plate test with Salmonella typhimurium), BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 40/1M0231/85, BASF DocID 1986/010, 28 Jan 1986 GLP, unpublished	N	KST	Yes	**Y**	**Y**

[redacted]	1987	A8.5.4-003	Mutagenicity evaluation of Dazomet in the rec-assay with Bacillus subtilis, Hazleton Biotechnologies Corporation, PE Veenendaal, Netherlands, unpublished report E-9583, BASF DocID 1987/029, Jan 1987 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1989	A8.5.4-004	Mutagenicity test on 85/231 MITC in the recombination assays with Bacillus subtilius strains H17 (rec+) and M45 (rec-), Hazleton Laboratories America Inc., Kensington, USA, unpublished report HLA 10538-0-404 (BASF project 70M0231/859186), BASF DocID 1989/0098, 13 Mar 1989 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1989	A8.5.4-005	*In vitro* cytogenetic investigations of Dazomet in human lymphocytes, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 30M0318/854174, BASF DocID 1989/0094, 04 Apr 1989 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1989	A8.5.4-005	Amendment to the report of April 4, 1989 on the *in vitro* cytogenetic	N	KST	Yes	**Y**	**Y**

			investigations of Dazomet (ZST test substance No.: 85/318) in human lymphocytes, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 30M0318/854174 dated 04 Apr 1989, BASF DocID 1989/0247, 03 Jul 1989 GLP, unpublished					
[redacted]	1987	A8.5.4-006	*In vitro* cytogenetic investigations in human lymphocytes with Methylisothiocyanate, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 30M0231/8575, BASF DocID 1987/0184, 26 May 1987 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1980b	A8.5.4-007	N-512 mutagenicity evaluation in mouse lymphoma multiple endpoint test, Stauffer Chemical Company, USA, unpublished report T-10136, BASF DocID 1980/0218, 20 Nov 1980 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1979	A8.5.4-008	Mutagenicity evaluation of N-521 in an *in vitro* cytogenetic assay measuring sister chromatid exchange and	N	KST	No	**N**	**N**

			chromosome aberrations, Litton Bionetics, Inc., Kensington, USA, unpublished report LBI 20990, BASF DocID 1979/0167, Mar 1979 Not GLP, unpublished					
[redacted]	1990	A8.5.4-009 Also A8.5.4-010 A8.5.4-018 A8.5.5-001 A8.9.5.3 -002 A8.9.5.1 -007 A8.9.5.1 -008 A8.9.5.1 -009 A8.9.5.2 -003 A8.9.5.1 -014 A8.9.5.1 -015 A8.10.2-002 A8.11-003 A8.11-004	Summary of toxicity data on Methyl Isothiocyanate (MITC), Agrochemical Division, Nihon Schering K.K. and Agrochemical & Animal Health Products Development, Shionogi & Co., Ltd., published data, J. Pesticide Sci. 15, 297-304, BASF DocID 1990/0571, 1990 Not GLP, published	N	-	Yes	**Y**	**Y**
[redacted]	1986	A8.5.4-011	Report on a point mutation test carried out on CHO cells (HGPRT locus) with the test substance Dazomet (substance No. 84/198), BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 84/198, BASF DocID 1986/215, 18 Aug 1986	N	KST	Yes	**Y**	**Y**

			GLP, unpublished					
[redacted]	1985	A8.5.4-012	Evaluation of Dazomet in the rat primary hepatocyte unscheduled DNA synthesis assay, Litton Bionetics, Inc., Kensington, USA, unpublished report LBI20991, BASF DocID 1985/217, Jun 1985 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1990	A8.5.4-018 Also A8.5.4-009 A8.5.4-010 A8.5.5-001 A8.9.5.3 -002 A8.9.5.1 -007 A8.9.5.1 -008 A8.9.5.1 -009 A8.9.5.2 -003 A8.9.5.1 -014 A8.9.5.1 -015 A8.10.2-002 A8.11-003 A8.11-004	Summary of toxicity data on Methyl Isothiocyanate (MITC), Agrochemical Division, Nihon Schering K.K. and Agrochemical & Animal Health Products Development, Shionogi & Co., Ltd., published data, J. Pesticide Sci. 15, 297-304, BASF DocID 1990/0571, 1990 Not GLP, published	N	KST	Yes	**Y**	**Y**
[redacted]	1990	A8.5.5-001 Also A8.5.4-009 A8.5.4-010 A8.5.4-018 A8.9.5.3 -002 A8.9.5.1 -007	Summary of toxicity data on Methyl Isothiocyanate (MITC), Agrochemical Division, Nihon Schering K.K. and Agrochemical & Animal Health Products Development, Shionogi & Co., Ltd., published data,	N	KST	Yes	**Y**	**Y**

		A8.9.5.1 -008 A8.9.5.1 -009 A8.9.5.2 -003 A8.9.5.1 -014 A8.9.5.1 -015 A8.10.2-002 A8.11-003 A8.11-004	J. Pesticide Sci. 15, 297-304, BASF DocID 1990/0571, 1990 Not GLP, published					
[redacted]	1985	A8.5.5-002	Cytogenetic investigations in NMRI mice after a single oral administration of Dazomet - Micronucleus test, BASF AG, Ludwigshafen/Rhein, Germany, unpublished report 26M0198/8421, BASF Doc ID 1985/154, 24 May 1985 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1979	A8.5.5-003	Mutagenicity evaluation of N-521 in the rat bone marrow cytogenetic assay, Litton Bionetics, Inc., Kensington, USA, unpublished report 21092, BASF DocID 1979/0168, Jul 1979 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1998	A8.5.5-004	*In vivo* studies on genotoxicity of a soil fumigant, Dazomet, Environmental and Molecular Mutagenesis 32: 179-184, BASF DocID 1998/1000828, 1998 Not GLP, unpublished	N	KST	N	**N**	**N**

[redacted]	1986	A8.5.5-005	Evaluation of Dazomet techn. (99.3 %) CH.03584, 84/198 in the *in vivo*/*in vitro* rat hepatocyte unscheduled DNA synthesis assay, Hazleton Biotechnologies Company (alt), Kensington, USA, unpublished report HBC20991, BASF DocID 1986/249, Sep 1986 GLP, unpublished	N	KST	N	**N**	**N**
[redacted]	1985	A8.5.5-006	Report on the study of chromosome aberrations in Chinese hamster spermatogonia with Dazomet, Laboratorium für Mutagenitätsprüfung, TH Darmstadt, Darmstadt, Germany, unpublished report LMP 103, BASF DocID 1985/375, 14 Nov 1985 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1979	A8.5.5-007	Mutagenicity evaluation of N-521 technical, batch #149, in the sex-linked recessive lethal test in Drosophila melanogaster, Litton Bionetics, Inc., Kensington, USA, unpublished report LBI 21093, BASF DocID 1979/0166, Jul 1979 GLP, unpublished	N	KST	N	**N**	**N**
[redacted]	1983	A8.7.1-001	Report on the study of the acute oral toxicity of	N	KST	Yes	**Y**	**Y**

		Also B8.5.1-001	"Dazomet" in the rat, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 80/46, BASF DocID 1984/073, 07 Nov 1983 (translation, original report in German from 10 Dec 1980) Not GLP, unpublished					
[redacted]	1994a	A8.7.1-002 Also A8.13.2-003	Dazomet – Acute oral neurotoxicity study in Wistar rats, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 20C0062/92044, BASF DocID 1994/10800, 16 Sep 1994 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1986c	A8.7.1-003	Report on the study of acute toxicity on the rat based on OECD and EPA (FIFRA) of MITC, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 1986/281, BASF DocID 1986/281, 14 Oct 1986 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1987a	A8.7.1-004	Report on the study of acute oral toxicity on the mouse based on OECD and EPA (FIFRA) of MITC, BASF AG, Department of	N	KST	Yes	**Y**	**Y**

			Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 1987/055, BASF DocID 1987/055, 4 Feb 1987 GLP, unpublished					
[redacted]	1986	A8.7.2-001 Also B8.5.2-001	Acute inhalation toxicity LC50 4 hours (rat) - dust study of Dazomet, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 13I0318/85, BASF DocID 1986/289, 23 Oct 1986 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1975	A8.7.2-002	Acute inhalation toxicity (inhalation danger) of Basamid granular to the rat, BASF AG, Ludwigshafen/Rhein, Germany, unpublished report XVI/1,BASF DocID 1975/0041, 27 Aug 1975 Not GLP, unpublished	N	KST	No	**N**	**N**
[redacted]	1981	A8.7.2-003	Methyl Isothiocyanate - Acute inhalation toxicity in rats - 4 hour exposure, Huntingdon Research Centre, Huntingdon, United Kingdom, unpublished report BSF 378/801109, BASF DocID 1981/082, 09 Apr 1981 GLP, unpublished	N	KST	Yes	**Y**	**Y**

[redacted]	1992	A8.7.3-001 Also B8.5.3-001	Study on the acute dermal toxicity of Dazomet techn. in rats, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 11A0111/911011, BASF DocID 1992/10412, 06 May 1992 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1987b	A8.7.3-002	Report on the study of acute dermal toxicity on the rat based on OECD and EPA (FIFRA) of MITC, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 85/231, BASF DocID 1987/014 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1992	A8.8.1-001	Distribution and metabolism of 14C-Dazomet in rats, Huntingdon Research Centre, Huntingdon, United Kingdom, unpublished report HRC/BSF 487/921420, BASF DocID 1992/11478, 01 Dec 1992 (sponsored by BASF AG, Limburgerhof, Germany) GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1993	A8.8.1-001	Amendment No. 1 to “Distribution and metabolism of 14C-Dazomet in rats”,	N	KST	Yes	**Y**	**Y**

			Huntingdon Research Centre, Huntingdon, United Kingdom, unpublished report HRC/BSF 487/921420 dated 01 Dec 1992, BASF Doc ID1993/10354, 25 Mar 1993 GLP, unpublished					
[redacted]	1987b	A8.8.1-002	The biokinetics and metabolism of 14C-Dazomet in the rat, Huntingdon Research Centre, Huntingdon, United Kingdom, unpublished report HRC/BSF 455/87954, BASF DocID 1987/0469, 12 Nov 1987 (sponsored by BASF AG, Limburgerhof, Germany) GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1988a	A8.8.1-002	1st Amendment to HRC/BSF 455/87954 - The biokinetics and metabolism of 14C-Dazomet in the rat, Huntingdon Research Centre, Huntingdon, United Kingdom, unpublished report HRC/BSF 455/87954 dated 12 Nov 1987, BASF DocID 1988/0096, 02 Feb 1988 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1985	A8.8.1-003	The absorption and disposition of 14C-	N	KST	Yes	**Y**	**Y**

			Dazomet in rats, Huntingdon Research Centre, Huntingdon, United Kingdom, unpublished report HRC/BSF 423/85945, BASF DocID 1985/0455 GLP, unpublished					
[redacted]	1987a	A8.8.1-004	The biokinetics and metabolism of methyl isothiocyanate-14C in the rat, Huntingdon Research Centre, Huntingdon, United Kingdom, unpublished report HRC/BSF 456/87983, BASF DocID 1987/0463, 19 Sep 1987 (sponsored by BASF AG, Limburgerhof, Germany), GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1988b	A8.8.1-004	1st Amendment to HRC/BSF 456/87983 - The biokinetics and metabolism of methyl isothiocyanate-14C in the rat, Huntingdon Research Centre, Huntingdon, United Kingdom, unpublished report HRC/BSF 456/87983 dated 19 Sep 1987, BASF DocID 1988/0095, 1988 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	2004	A8.8.2-001 Also B8.6-001	C-BAS 002 N (Dazomet) - Study of the Dermal Absorption in Rats BASF AG, Germany	N	KST	Yes	**Y**	**Y**

			Document No.: -- BASF Doc ID 2004/1021174 Report No.: 01B0357/036007 GLP, unpublished					
[redacted]	1989d	A8.9.5.1-001	Study on the oral toxicity of Dazomet in rats - Dietary administration for 4 weeks (range-finding study), BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 20C0318/8527, BASF DocID 1989/0089, 21 Mar 1989 (translation, original report in German dated 28 Dec 1988) GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1966	A8.9.5.1-002 Also A8.9.5.1-012 A8.12.1-015	Toxicologic studies on 3,5-Dimethyltetrahydro-1,3,5,2H-thiadiazine-2-thione, a soil fungicide and slimicide, Toxicology and Applied Pharmacology 9, 521-527, BASF DocID 1966/10071, 1966 Not GLP, published	N	_	No	**N**	**N**
[redacted]	1987	A8.9.5.3-001	21-Day dermal toxicity study in rabbits, Hazleton Laboratories America, Inc., Madison, Wisconsin, USA, unpublished report HLA 6220-100, BASF DocID 1987/5141, 17 Jun 1987, (sponsored by Dazomet Task Force	N	KST	Yes	**Y**	**Y**

			Consortium Submitter No. 54662-Q) GLP, unpublished					
[redacted]	1990	A8.9.5.3-002 Also A8.5.4-009 A8.5.4-010 A8.5.4-018 A8.5.5-001 A8.9.5.1 -007 A8.9.5.1 -008 A8.9.5.1 -009 A8.9.5.2 -003 A8.9.5.1 -014 A8.9.5.1 -015 A8.10.2-002 A8.11-003 A8.11-004	Summary of toxicity data on Methyl Isothiocyanate (MITC), Agrochemical Division, Nihon Schering K.K. and Agrochemical & Animal Health Products Development, Shionogi & Co., Ltd., published data, J. Pesticide Sci. 15, 297-304, BASF DocID 1990/0571, 1990 Not GLP, published	N	_	No	**N**	**N**
[redacted]	1976	A8.9.5.2-001	Basamid Granular - Inhalation study in rats (repeated exposure for 3 weeks), Huntingdon Research Centre, Huntingdon, UK, unpublished report BSF169/76115, BASF DocID 1976/0040, 11 Oct 1976 (sponsored by BASF AG) Not GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1987	A8.9.5.2-002	Study on the subchronic inhalation toxicity of Methyl Isothiocyanate in Wistar rats (4-week study), Department of	N	KST	Yes	**Y**	**Y**

			Toxicology, BASF AG, Ludwigshafen/Rhein, Germany, unpublished Report No. 40I0231/8539, BASF DocID 1987/0244, 29 Jan 1987 GLP, unpublished					
[redacted]	1987a	A8.9.5.1-003	Report on the study of the oral toxicity of Dazomet in rats after 3-month administration in the diet, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 30C0318/8544, BASF DocID 1987/0448, 17 Dec 1987 (translation, original report in German dated 11 Dec 1987) GLP, unpublished	N	KST	Y	**Y**	**Y**
[redacted]	1994b	A8.9.5.1-004 Also A8.13.2-004	Dazomet - Subchronic oral neurotoxicity study in Wistar rats, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 50C0062/92068, BASF DocID 1994/10799, 23 Sep 1994 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1989a	A8.9.5.1-005	Report on the study of the oral toxicity of Dazomet in mice, dietary administration for 4 weeks (prolonged to 91 days), (range-finding study),	N	KST	Yes	**Y**	**Y**

			BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 25C0318/8530, BASF DocID1989/0053, 07 Feb 1989 (translation, original report in German dated 03 Feb 1988) GLP, unpublished					
[redacted]	1987b	A8.9.5.1-006 Also A8.13.4-004	Report on the study of the toxicity of Dazomet in Beagle dogs after 3-month administration via the diet, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 31D0318/8533, BASF DocID1987/ 0456, 21 Dec 1987 (translation, original report in German dated 09 Sep 1987) GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1990	A8.9.5.1-007 Also A8.5.4-009 A8.5.4-010 A8.5.4-018 A8.5.5-001 A8.9.5.3 -002 A8.9.5.1 -008 A8.9.5.1 -009 A8.9.5.2 -003 A8.9.5.1 -014 A8.9.5.1 -015 A8.10.2-002	Summary of toxicity data on Methyl Isothiocyanate (MITC), Agrochemical Division, Nihon Schering K.K. and Agrochemical & Animal Health Products Development, Shionogi & Co., Ltd., published data, J. Pesticide Sci. 15, 297-304, BASF DocID 1990/0571, 1990 Not GLP, published	N	_	No	**N**	**N**

		A8.11-003 A8.11-004						
[redacted]	1990	A8.9.5.1-008 Also A8.5.4-009 A8.5.4-010 A8.5.4-018 A8.5.5-001 A8.9.5.1-007 A8.9.5.3 -002 A8.9.5.1 -009 A8.9.5.2 -003 A8.9.5.1 -014 A8.9.5.1 -015 A8.10.2-002 A8.11-003 A8.11-004	Summary of toxicity data on Methyl Isothiocyanate (MITC), Agrochemical Division, Nihon Schering K.K. and Agrochemical & Animal Health Products Development, Shionogi & Co., Ltd., published data, J. Pesticide Sci. 15, 297-304, BASF DocID 1990/0571, 1990 Not GLP, published	N	_	No	**N**	**N**
[redacted]	1990	A8.9.5.1-009 Also A8.5.4-009 A8.5.4-010 A8.5.4-018 A8.5.5-001 A8.9.5.3 -002 A8.9.5.1-007 A8.9.5.1-008 A8.9.5.2 -003 A8.9.5.1 -014 A8.9.5.1 -015 A8.10.2-002 A8.11-003 A8.11-004	Report on the study of the oral toxicity of Dazomet in rats after 24-month administration in the diet, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 70C0318/8583, BASF DocID 1989/0276, 31 Jul 1989 GLP, unpublished	N	_	No	**N**	**N**

[redacted]	1989a	A8.9.5.1-011	Amendment to the report of July 31, 1989 on the study of oral toxicity of Dazomet in rats after 24-month administration in the diet, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 70C0318/8583 dated 31 Jul 1989, BASF DocID 1989/0470, 20 Oct 1989 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1989	A8.9.5.1-011	24 months chronic toxicity (feeding) study with Dazomet in the rat (BASF report 70C0318/8583), Pathology report, RCC, Itingen, Switzerland, unpublished report 200384, BASF DocID 1989/0276, 19 Jun 1989 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1989a	A8.9.5.1-011	Toxicologic studies on 3,5-Dimethyltetrahydro-1,3,5,2H-thiadiazine-2-thione, a soil fungicide and slimicide, Toxicology and Applied Pharmacology 9, 521-527, BASF DocID 1966/10071, 1966 Not GLP, published	N	KST	Yes	**Y**	**Y**
[redacted]	1966	A8.9.5.1-012 Also A8.9.5.1-002 A8.12.1-015	Interim report on the toxicity of CRAG mylone fungicide (fungicide 974), Mellon Institute of Industrial Research,	N	_	No	**N**	**N**

			University of Pittsburgh, USA, unpublished report 23-3, BASF DocID 1960/10010, 13 Jan 1960 Not GLP, unpublished					
[redacted]	1960	A8.9.5.1-012	Report on the study of the toxicity of Dazomet in Beagle dogs, administration via the diet over 12 months, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 33D0318/85118, BASF DocID1989/0050, 24 Feb 1989 GLP, unpublished	N	–	No	**N**	**N**
[redacted]	1989c	A8.9.5.1-013	Pathology report on the study of the toxicity of Dazomet in Beagle dogs, administration via the diet over 12 months, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 33D0318/85118, BASF DocID 1989/0050, 24 Feb 1989 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1989a	A8.9.5.1-013	Summary of toxicity data on Methyl Isothiocyanate (MITC), Agrochemical Division, Nihon Schering K.K. and Agrochemical & Animal Health Products Development, Shionogi &	N	KST	Yes	**Y**	**Y**

			Co., Ltd., published data, J. Pesticide Sci. 15, 297-304, BASF DocID 1990/0571, 1990 Not GLP, published					
[redacted]	1990	A8.9.5.1-014 Also A8.5.4-009 A8.5.4-010 A8.5.4-018 A8.5.5-001 A8.9.5.3 -002 A8.9.5.1-007 A8.9.5.1-008 A8.9.5.2 -003 A8.9.5.1-009 A8.9.5.1 -015 A8.10.2-002 A8.11-003 A8.11-004	Summary of toxicity data on Methyl Isothiocyanate (MITC), Agrochemical Division, Nihon Schering K.K. and Agrochemical & Animal Health Products Development, Shionogi & Co., Ltd., published data, J. Pesticide Sci. 15, 297-304, BASF DocID 1990/0571, 1990 Not GLP, published	N	_	No	**N**	**N**
[redacted]	1990	A8.9.5.1-015 Also A8.5.4-009 A8.5.4-010 A8.5.4-018 A8.5.5-001 A8.9.5.3 -002 A8.9.5.1-007 A8.9.5.1-008 A8.9.5.2 -003 A8.9.5.1-009 A8.9.5.1-014 A8.10.2-002 A8.11-003 A8.11-004	Summary of toxicity data on Methyl Isothiocyanate (MITC), Agrochemical Division, Nihon Schering K.K. and Agrochemical & Animal Health Products Development, Shionogi & Co., Ltd., published data, J. Pesticide Sci. 15, 297-304, BASF DocID 1990/0571, 1990 Not GLP, published	N	_	No	**N**	**N**

[redacted]	1990	A8.9.5.2-003 Also A8.5.4-009 A8.5.4-010 A8.5.4-018 A8.5.5-001 A8.9.5.3 - 002 A8.9.5.1-007 A8.9.5.1-008 A8.9.5.1-009 A8.9.5.1-014 A8.9.5.1-015 A8.10.2-002 A8.11-003 A8.11-004	Report on the study of the prenatal toxicity of Dazomet in rats after oral administration (gavage), BASF AG, Ludwigshafen/Rhein, Germany, unpublished report 34R0318/8564, BASF DocID 1987/0457, 29 Dec 1987 GLP, unpublished	N	_	Yes	**Y**	**Y**
[redacted]	1987a	A8.10.1-001	Report on the study of the oral toxicity of Dazomet in rats after 24-month administration in the diet, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 70C0318/8583, BASF DocID 1989/0276, 31 Jul 1989 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1987b	A8.10.1-003	Report on the study of the prenatal toxicity of MITC in rats after oral administration (gavage), Department of Toxicology, BASF AG, Ludwigshafen/Rhein, Germany, unpublished report 34R0231/8537,	N	KST	Yes	**Y**	**Y**

			BASF DocID 1987/0326, 2 Sep 1987 *GLP, unpublished*					
[redacted]	1993	A8.10.1-004	Study of the prenatal toxicity of Dazomet in rabbits after oral administration (gavage), BASF AG, Ludwigshafen/Rhein, Germany, unpublished report 40R0062/92058, BASF DocID 1993/10969, 17 Sep 1993 *GLP, unpublished*	N	KST	Yes	**Y**	**Y**
[redacted]	1986b	A8.10.1-005	Embryotoxicity (including teratogenicity) study with MITC, ZNT-No. 85/231-2 in the rabbit, Research & Consulting Company AG (RCC), Itingen, Switzerland, unpublished report 056687, BASF DocID 1986/395, 05 Sep 1986 *GLP, unpublished*	N	KST	Yes	**Y**	**Y**
[redacted]	1986a	A8.10.1-005	Dose-finding embryotoxicity (including teratogenicity) study with MITC, ZNT-No. 85/231-2 in the rabbit, Research & Consulting Company AG (RCC), Itingen, Switzerland, unpublished report056676, BASF DocID 1986/085, 17 Jan 1986 *GLP, unpublished*	N	KST	Yes	**Y**	**Y**

[redacted]	1989b	A8.10.2-001	Reproduction study with Dazomet in rats - Continuous dietary administration over 2 generations (2 litters in the first and 1 litter in the second generation), BASF AG, Ludwigshafen/Rhein, Germany, unpublished report 71R0318/8597, BASF DocID 1989/0051, 22 Feb 1989 *GLP, unpublished*	N	KST	Yes	**Y**	**Y**
[redacted]	1989b	A8.10.2-001	Pathology report, Reproduction study with Dazomet in rats - Continuous dietary administration over 2 generations (2 litters in the first and 1 litter in the second generation), BASF AG, Ludwigshafen/Rhein, Germany, unpublished report 71R0318/8597, BASF DocID 1989/0051, 22 Feb 1989 *GLP, unpublished*	N	KST	Yes	**Y**	**Y**
[redacted]	1990	A8.10.2-002 Also A8.5.4-009 A8.5.4-010 A8.5.4-018 A8.5.5-001 A8.9.5.3 - 002 A8.9.5.1-007 A8.9.5.1-008	Summary of toxicity data on Methyl Isothiocyanate (MITC), Agrochemical Division, Nihon Schering K.K. and Agrochemical & Animal Health Products Development, Shionogi & Co., Ltd., published data, J. Pesticide Sci. 15, 297-	N	_	Yes	**Y**	**Y**

		A8.9.5.1-009 A8.9.5.1-014 A8.9.5.1-015 A8.9.5.2-003 A8.11-003 A8.11-004	304, BASF DocID 1990/0571, 1990 *Not GLP, published*					
[redacted]	1989b	A8.11-001	Study of the oncogenic potential of Dazomet in rats after 24-month administration in the diet, BASF AG, Ludwigshafen/Rhein, Germany, unpublished report 70C0318/8584, BASF DocID 1989/0277, 31 Jul 1989 *GLP, unpublished*	N	KST	Yes	**Y**	**Y**
[redacted]	1989a	A8.11-001	Amendment No. 1 to the report of July 31, 1989 on the study of the oncogenic potential of Dazomet in rats after 24-month administration in the diet, BASF AG, Ludwigshafen/Rhein, Germany, unpublished report 70C0318/8584 dated 31 Jul 1989, BASF DocID 1989/0468, 20 Oct 1989 *GLP, unpublished*	N	KST	Yes	**Y**	**Y**
[redacted]	1989b	A8.11-001	Amendment No. 2 to the report of July 31, 1989 - Study of the oncogenic potential of Dazomet in	N	KST	Yes	**Y**	**Y**

			rats after 24-month administration in the diet, BASF AG, Ludwigshafen/Rhein, Germany, unpublished report 70C0318/8584 dated 31 Jul 1989, BASF DocID 1989/0469, 20 Oct 1989 *GLP, unpublished*					
[redacted]	1989b	A8.11-001	24 months oncogenicity (feedind) study with Dazomet in the rat, Pathology report part 1, RCC, Ittingen, Schwitzerland, unpublished report RCC project 200395 (BASF project 70C0318/8584), BASF DocID 1989/0277, 07 Jul 1989 GLP, unpublished	N	KST	Yes	**Y**	**Y**
[redacted]	1989c	A8.11-002	Report on the study of the oral toxicity of Dazomet in mice after 78-week administration in the diet, BASF AG, Ludwigshafen/Rhein, Germany, unpublished report 65C0318/8585, BASF DocID 1989/0341, 22 Sept 1989 *GLP, unpublished*	N	KST	Yes	**Y**	**Y**

[redacted]	1990	A8.11-002	Amendment No. 1 to the report of September 22 1989 on the study of the oral toxicity of Dazomet in mice after 78-week administration in the diet, BASF AG, Ludwigshafen/Rhein, Germany, unpublished report 65C0318/8585 dated 22 Sept 1989, BASF DocID1990/0036, 14 Feb 1990 *GLP, unpublished*	N	KST	Yes	**Y**	**Y**
[redacted]	1989	A8.11-002	Pathology report, study of the oncogenic potential of Dazomet in mice dietary administration for 78 weeks (BASF AG project 65C00318/8585), EPL Scientific Limited, Cambridge, U.K., unpublished report 102-002, 13 Mar 1989 (including photo documentation dated 15 Sep 1988, BASF DocID 1990/0036J) *GLP, unpublished*	N	KST	Yes	**Y**	**Y**
[redacted]	1989	A8.11-002	Amended Pathology report, study of the oncogenic potential of Dazomet in mice dietary administration for 78 weeks (BASF AG project 65C00318/8585), EPL Scientific Limited,	N	_	Yes	**Y**	**Y**

			Cambridge, U.K., unpublished report 102-00 dated 13 Mar 1989, BASF DocID 1989/5210, 18 Sep 1989 *GLP, unpublished*					
[redacted]	1990	A8.11-003 Also A8.5.4-009 A8.5.4-010 A8.5.4-018 A8.5.5-001 A8.9.5.3 - 002 A8.9.5.1-007 A8.9.5.1-008 A8.9.5.1-009 A8.9.5.1-014 A8.9.5.1-015 A8.9.5.2-003 A8.10.2-002 A8.11-004	Summary of toxicity data on Methyl Isothiocyanate (MITC), Agrochemical Division, Nihon Schering K.K. and Agrochemical & Animal Health Products Development, Shionogi & Co., Ltd., published data, J. Pesticide Sci. 15, 297-304, BASF DocID 1990/0571, 1990 *Not GLP, published*	N	_	Yes	**Y**	**Y**
[redacted]	1990	A8.11-004 Also A8.5.4-009 A8.5.4-010 A8.5.4-018 A8.5.5-001 A8.9.5.3 - 002 A8.9.5.1-007 A8.9.5.1-008 A8.9.5.1-009 A8.9.5.1-014 A8.9.5.1-015 A8.9.5.2-003 A8.10.2-002	Summary of toxicity data on Methyl Isothiocyanate (MITC), Agrochemical Division, Nihon Schering K.K. and Agrochemical & Animal Health Products Development, Shionogi & Co., Ltd., published data, J. Pesticide Sci. 15, 297-304, BASF DocID 1990/0571, 1990 *Not GLP, published*	N	_	Yes	**Y**	**Y**

		A8.11-003						
[redacted]	1980	A8.11-005	Morphological transformation of BALB/3T3 cells Stauffer Chemical Company Report No.: T-10137; N-521 Document No.: 557-006 BASF Doc ID: 80/0219 *No GLP, unpublished*	N	KST	Yes	**Y**	**Y**
[redacted]	2000b	A8.12.1-001	BASF, Medical department (2000) personal communication, *Unpublished*	N	KST	Yes	**Y**	**Y**
[redacted]	1980	A8.12.1-002 Also A8.12.2-001	Allergic contact dermatitis from methylisothiocyanate in soil disinfectants, Contact Dermatitis, 6, 183-186, BASF DocID 1980/1000067 *Published*	N	_	Yes	**Y**	**Y**
[redacted]	1981	A8.12.2-002	Fatal poisoning with methyl isothiocyanate, British Medical Journal, 283, p 18 – 19, BASF DocID 1981/1000061, 1981 *Published*	N	_	Yes	**Y**	**Y**
[redacted]	1994	A8.12.1-003	Dose-assessment of airborne methyl isothiocyanate (MITC) following a Metam Sodium spill, Risk Analysis, 14 (2),	N	_	Yes	**Y**	**Y**

			p 191- 198, BASF DocID 1994/1000292, 1994 Published					
[redacted]	1994	A8.12.1-003	An epidemiological assessment of the Cantara Metam Sodium spill – acute health effects and methyl isothiocyanate exposure. In: Environmental Epidemiology: Effects of environmental chemicals on human health, Draper W M (ed), ACS Advances in Chemistry Series # 241, American Chemical Society, Washington, DC, BASF DocID 1994/1000291, 1994 Published	N	_	Yes	**Y**	**Y**
[redacted]	1993	A8.12.1-004	Pediatric consequences of methyl isothiocyanate exposure, Pulmonology, Abstract No. 2245, p 378A, BASF DocID 1993/1000270, 1993 Published	N	_	Yes	**Y**	**Y**
[redacted]	1998	A8.12.1-005	Test report: field operator exposure test with Basamid granular, Jai Research Foundation, JRF test number: 571, BASF DocID 1998/1003934, 1998 Unpublished	N	_	Yes	**Y**	**Y**
[redacted]	1982	A8.12.1-006	Allergische Reaktionen der Haut auf senfölabspaltende	N	_	Yes	**Y**	**Y**

			Verbindungen, Abh. Akad. Wiss. DDR, Abt. Math. Naturwiss. Tech., p 437 – 440, BASF DocID1980/1000065, 1980 Published					
[redacted]	1987	A8.12.1-007	Irritation and sensitization potential of pesticides, Contact dermatitis, 17, p 212 - 218, BASF DocID 1987/10369, 1987 Published	N	_			
[redacted]	1986	A8.12.1-007	A test series for pesticide dermatitis. Contact dermatitis 15, p 266 – 269, BASF DocID 1986/1001051, 1986 Published	N	_	Yes	**Y**	**Y**
[redacted]	1993	A8.12.1-008	Dermite de contact au dazomet: 7 cas, Arch. mal prof., 54 (8), p 649 – 651, BASF DocID 1993/1000208, 1993 Published	N	_	Yes	**Y**	**Y**
[redacted]	1992	A8.12.1-009	Allergic contact dermatitis from dazomet, Contact dermatitis, 26, p 135 – 136, BASF DocID 1992/1001897, 1992 Published	N	_	Yes	**Y**	**Y**
[redacted]	1993	A8.12.1-010	Phototoxic contact dermatitis with toxic hepatitis due to the percutaneous absorption of paraquat, Contact Dermatitis, 29, p 163 –	N	_	Yes	**Y**	**Y**

			164, BASF DocID 1993/1002143, 1993 Published					
[redacted]	1973	A8.12.1-011	Subject: dazomet and chloropicon, Contact Dermatitis, 7, p 410 - 411, BASF DocID 1973/1000101, 1973 Published	N	_	Yes	**Y**	**Y**
[redacted]	1970	A8.12.1-012	Berufliche Kontaktdermatitis durch Nematin (Vapam) in der Landwirtschaft, Dt. Gesundh.-Wesen, 25, p 495- 498, BASF DocID 1969/1000021, 1970 Published	N	_	Yes	**Y**	**Y**
[redacted]	1995	A8.12.1-013	Irritant dermatitis among workers cleaning up a pesticide spill: California 1991, Am. J. Ind. Med., 27, p 545 – 553, BASF DocID 1995/1000507, 1995 Published	N	_	Yes	**Y**	**Y**
[redacted]	1978	A8.12.1-014	Contact dermatitis to sodium N-methyldithiocarbamate, Contact dermatitis, 6, p 370 – 371, BASF DocID 1978/1000104, 1978 Published	N	_	Yes	**Y**	**Y**
[redacted]	1966	A8.12.1-015 Also A8.9.5.1-002 A8.9.5.1-012	Toxicologic studies on 3,5-Dimethyltetrahydro-1,3,5,2H-thiadiazine-2-thione, a soil fungicide and slimicide, Toxicology and Applied Pharmacology	N	_	Yes	**Y**	**Y**

			9, 521-527, BASF DocID 1966/10071, 1966 Not GLP, published					
[redacted]	1980	A8.12.2-001 Also A8.12.1-002	Allergic contact dermatitis from methylisothiocyanate in soil disinfectants, Contact Dermatitis, 6, 183-186, BASF DocID 1980/1000067 Published	N	_	Yes	**N**	**Y**
[redacted]	1996	A8.12.4-001	Cancer incidence among Icelandic pesticide users, Int. J. Epidemiol., 25 (6), p 1117 – 1124, BASF DocID 1996/1000408, 1996 Published	N	_	Yes	**N**	**Y**
[redacted]	1993	A8.12.4-002	Frequency of mircronuclei in lymphocytes from a group of floriculturists exposed to pesticides, Toxicol. Environ. Health, 40, 405-411, BASF DocID 1993/1000207, 1993 Published	N	_	Yes	**N**	**Y**
[redacted]	1995	A8.12.4-002	Genotoxic risk from occupational exposure to pesticides in floriculture, Clinical Chemistry, 41, 1919-1922, BASF DocID 1995/1002991, 1995 Published	N	_	Yes	**N**	**Y**
[redacted]	1985	A8.12.4-003	Sister-chromatid exchanges and chromosomal aberrations in a population exposed to pesticides. Mutation Research, 143 (4), p 237	N	_	Yes	**N**	**Y**

			-244, BASF DocID 1985/1000081, 1985 Published					
[redacted]	1991	A8.12.4-004	Cytogenetic biomonitoring of an Italian population exposed to pesticides: chromosome aberration and sister-chromatid exchange analysis in peripheral blood lymphocytes. Mutation Research, 260, p 105 - 113, BASF DocID 1991/1000317, 1991 Published	N	_	Yes	**N**	**Y**
[redacted]	1981	A8.12.2-002	Fatal poisoning with methyl isothiocyanate, British Medical Journal, 283, p 18 – 19, BASF DocID 1981/1000061, 1981 Published	N	_	Yes	**N**	**Y**
[redacted]	1994a	A8.13.2-003 Also A8.7.1-002	Dazomet – Acute oral neurotoxicity study in Wistar rats, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 20C0062/92044, BASF DocID 1994/10800, 16 Sep 1994 GLP, unpublished	N	**KST**	Yes	**Y**	**Y**
[redacted]	1994b	A8.13.2-004 Also A8.9.5.1 -004	Dazomet - Subchronic oral neurotoxicity study in Wistar rats, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished	N	**KST**	Yes	**Y**	**Y**

			report 50C0062/92068, BASF DocID 1994/10799, 23 Sep 1994 GLP, unpublished					
[redacted]	1987b	A8.13.4-004 Also A8.9.5.1 -006	Report on the study of the toxicity of Dazomet in Beagle dogs after 3-month administration via the diet, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 31D0318/8533, BASF DocID1987/ 0456, 21 Dec 1987 (translation, original report in German dated 09 Sep 1987) GLP, unpublished	N	KST	Yes	**Y**	**Y**

Data protection from this renewal *–(end ten years from the first day of the month following the date of the adoption of a decision in accordance with Article 14(4))*

Author(s)	Year	Section No / Reference No	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes / No)	Owner	Data Identified as 'relevant' by the eCA[20] (Yes / No)	Applicability	
							CAR / RAR	CLH
[redacted]	2019a	A8.5.4-013	Photo-Bacterial reverse mutation assay of Basamid	Y	KST	Yes	**Y**	**Y**

[20] Only relevant for the renewal of an active substance. Remove column for active substance approval and CLH process.
For the identification of the relevant data, please see CA-Sept20-Doc.7.1.b - Relevant Renewal Data under Article 95_FINAL

			Nucro-technics, Ontario, Canada Report No. Main Report: 349737 Document No.: -- GLP, unpublished					
[redacted]	2019b	A8.5.4-013	Photo-Bacterial reverse mutation assay of Basamid - Amendment I to 349737 Nucro-technics, Ontario, Canada Report No. 349737-1; Document No.: -- GLP, unpublished	Y	KST	Yes	**Y**	**Y**
[redacted]	2008	A8.5.4-014	Salmonella typhimurium reverse mutation assay with Dazomet TGAI RCC Cytotest Cell Research GmbH, Germany Report No.: SSC 295-007; RCC/CCR 1180900 Document No.: 557-017 GLP, unpublished	Y	KST	Yes	**Y**	**Y**
[redacted]	2019a	A8.5.4-015	Bacterial reverse mutation assay of methyl isothiocyanate Nucro-technics, Ontario, Canada Report No: 343657; Document No.: -- GLP, unpublished	Y	KST	Yes	**Y**	**Y**
[redacted]	2019b	A8.5.4-015	Bacterial reverse mutation assay of methyl isothiocyanate - Amendment I: Nucro-technics, Ontario,	Y	KST	Yes	**Y**	**Y**

			Canada Report No.: 343657-1 Document No.: -- GLP, unpublished					
[redacted]	2019c	A8.5.4-015	Bacterial reverse mutation assay of methyl isothiocyanate - Amendment II Nucro-technics, Ontario, Canada Report No.: 343657-2 Document No.: -- GLP, unpublished	Y	KST	Yes	**Y**	**Y**
[redacted]	2020a	A8.5.4-016	*In vitro* mammalian cell gene mutation test of Methyl Isothiocyanate Nucro-technics, Ontario, Canada Report No. 350543 Document No.: -- GLP, unpublished	Y	KST	Yes	**Y**	**Y**
[redacted]	2020b	A8.5.4-017	*In vitro* mammalian cell micronucleus test of Methyl Isothiocyanate in Chinese hamster ovary (CHO) cells Nucro-technics, Ontario, Canada Report No. 349112 Document No.: -- GLP, unpublished	Y	KST	Yes	**Y**	**Y**
[redacted]	2020	A8.5.5-008	Evaluation of *in vivo* micronucleus and DNA damage in female Sprague Dawley rats administered BASAMID (Basamid Granulat) ILS, Inc., Morrisville,	Y	KST	Yes	**Y**	**Y**

			USA Report No.: 55599.00702 Document No.: -- GLP, unpublished					
[redacted]	2020	A8.5.5-009 Also A8.13.2-001	MITC: Comet Assay in Rats IET, Japan Report No.: 20-0039 Document No.: GLP, unpublished	Y	KST	Yes	**Y**	**Y**
[redacted]	2020	A8.5.5-010 Also A8.13.2-002	[14C]MITC: Micronucleus Test in Rats IET, Japan Report No.: 20-0040 Document No.: GLP, unpublished	Y	KST	Yes	**Y**	**Y**
[redacted]	2020	A8.8.1-005	[Thiocarbonyl-2-14C]-dazomet: the metabolic stability and comparative metabolism of [thiocarbonyl-2-14C]-dazomet in hepatic microsomes from rat, dog and human. Charles River Report No.: 180069 Document No.: GLP, unpublished	Y	KST	Yes	**Y**	**Y**
[redacted]	2020	A8.9.5.1-010	Dazomet: Repeated Dose 90-Day Oral Toxicity Studies in Dogs Report No.: IET 20-0020 Document No.: GLP, unpublished	Y	KST	Yes	**Y**	**Y**

[redacted]	2020	A8.10.1-002	Dazomet – Re-evaluation of the incidence of runts in developmental toxicity studies with Dazomet and MITC DHD Consulting GmbH, Germany Report No.: KST-2020-03 Document No.: -- No GLP, unpublished	Y	KST	Yes	**Y**	**Y**
[redacted]	2019d	A8.13.1-001	Evaluation of *in vivo* micronucleus and DNA damage in female Sprague Dawley rats administered BASAMID (Basamid Granulat) ILS, Inc., Morrisville, USA Report No.: 55599.00702 Document No.: -- GLP, unpublished	Y	KST	Yes	**Y**	**Y**
[redacted]	2020	A8.13.2-001 Also A8.5.5-009	MITC: Comet Assay in Rats IET, Japan Report No.: 20-0039 Document No.: GLP, unpublished	Y	KST	Yes	**Y**	**Y**
[redacted]	2020	A8.13.2-002 Also A8.5.5-010	[14C]MITC: Micronucleus Test in Rats IET, Japan Report No.: 20-0040 Document No.: GLP, unpublished	Y	KST	Yes	**Y**	**Y**

[redacted]	2020	A8.8.1-005	[Thiocarbonyl-2-14C]-dazomet: the metabolic stability and comparative metabolism of [thiocarbonyl-2-14C]-dazomet in hepatic microsomes from rat, dog and human. Charles River Report No.: 180069 Document No.: GLP, unpublished	Y	KST	Yes	**Y**	**Y**
[redacted]	2020a	A8.13.2-005 Also A8.13.3-003	Basamid: Hershberger Bioassay in Wistar Male Rats Study Eurofins Advinus, India Report No.: ~~G19372~~ G19437 Document No.: -- GLP, unpublished	Y	KST	Yes	**Y**	**Y**
[redacted]	2020b	A8.13.2-006 Also A8.13.3-004	Basamid: Uterotrophic Bioassay in Wistar Female Rats Study Eurofins Advinus, India Report No.: G19532 Document No.: -- GLP, unpublished	Y	KST	Yes	**Y**	**Y**
[redacted]	2021c	A8.3.2-003	Dazomet-QSAR predicted profile from the Danish (Q)SAR Database http://qsar.food.dtu.dk/ No GLP, publicly available information	N	**-**	No	**N**	**N**
[redacted]	2021d	A8.3.2-004	MITC-QSAR predicted profile from the Danish (Q)SAR Database http://qsar.food.dtu.dk/	N	**-**	No	**N**	**N**

			No GLP, publicly available information					
[redacted]	2021e	A8.3.2-005	Dazomet-QSAR predictions for respiratory sensitization from the Danish (Q)SAR Models https://qsarmodels.food.dtu.dk/index.html No GLP, publicly available information	N	**-**	No	**N**	**N**
[redacted]	2021f	A8.3.2-006	MITC-QSAR predictions for respiratory sensitization from the Danish (Q)SAR Models https://qsarmodels.food.dtu.dk/index.html No GLP, publicly available information	N	-	No	**N**	**N**
[redacted]	2013	A8.12.2-003	Allergic Contact Dermatitis due to Dazomet Absorbed by Agricultural Rubber Boots Published in: Acta Dermato-Venereologica, Vol 93, pp 81-82 Report No.: - Document No.: - Non-GLP, published	N	-	Yes	**Y**	**Y**
[redacted]	2011	A8.12.4-005	Metam sodium intoxication: the specific role of degradation products – methyl isothiocyanate and carbon disulphide – as a function of exposure	N	-	Yes	**Y**	**Y**

			Published in: Clinical Toxicology, Vol 49, pp 416-422 Report No.: - Document No.: - Non-GLP, published					
[redacted]	2005	A8.13.4-003	Sodium Methyldithiocarbamate inhibits MAP Kinase activation through Toll-like Receptor 4, Alters Cytokine production by mouse peritoneal macrophages, and suppressed innate immunity Published in: Toxicological Sciences 87(1), 75-85 (2005) Report No.: -- Document No.: -- No GLP, published	N	-	Yes	**Y**	**Y**
[redacted]	1996	A8.13.4-001	Role of decomposition products in sodium methyldithiocarbamate – induced immunotoxicity Published in: Journal of Toxicology and Environmental Health, 47: 479-492, 1996 Report No.: -- Document No.: -- No GLP, published	N	-	Yes	**Y**	**Y**
[redacted]	1992	A8.13.4-002	Immunotoxicological Characteristics of Sodium Methyldithiocarbamate Published in:	N	-	Yes	**Y**	**Y**

			Fundamental and applied Toxicology 18, 40-47 (1992) Report No.: -- Document No.: -- No GLP, published					
[redacted]	2005	A8.13.4-003	Sodium Methyldithiocarbamate inhibits MAP Kinase activation through Toll-like Receptor 4, Alters Cytokine production by mouse peritoneal macrophages, and suppressed innate immunity Published in: Toxicological Sciences 87(1), 75-85 (2005) Report No.: -- Document No.: -- No GLP, published	N	-	Yes	**Y**	**Y**

3. Environmental part:

Data protection from the first approval *- 01/08/2012 - 31/01/2025*

Confidential (as per article 66) :

Author(s)	Year	Section No Reference No	Title. Source Company, Report No. GLP (Un)Published	Data Protection Claimed (Yes/No)	Owner	Data Identified as 'relevant' by the eCA[21] (Yes/No)	Applicability	
							RAR	CLH
[redacted]	2001	A.4.2.2 A9.1.5-001	Determination of the inhibition of the oxygen consumption by activated sludge in the activated sludge respiration inhibition test, [redacted] Department of Product Safety, Ludwigshafen/Rhein, Germany, BASF Doc ID 2001/1014685, 02 Oct 2001 GLP, Unpublished	N	KST	Y	Y	N
[redacted]	1988	A.4.2.2 A9.1.5-002	Influence of Dazomet on the growth of Pseudomonas putida, [redacted] Agricultural Research and Development Environmental Research, Ludwigshafen/Rhein, Germany, unpublished report No. 2560, BASF DocID 88/10116, 13 Jul 1988 GLP, Unpublished	N	KST	Y	Y	N
[redacted]	1999	A.4.2.2 A9.1.5-003	Determination of the inhibition of oxygen consumption by activated sludge by Methylisothiocyanat in the activated sludge respiration inhibition test, [redacted] Department of Ecology, Ludwigshafen /Rhein, Germany, unpublished report No. 99/0547/08/1, BASF DocID 2001/1010528, Dec 1999	N	KST	Y	Y	N

[21] Only relevant for the renewal of an active substance. Remove column for active substance approval and CLH process.
For the identification of the relevant data, please see CA-Sept20-Doc.7.1.b - Relevant Renewal Data under Article 95_FINAL

			GLP, Unpublished					
[redacted]	1986a	A.4.2.3.1 A9.1.1-001	Study of the acute toxicity of BAS 002 01 N in the Bluegill (Lepomis macrochirus RAF.), [redacted] Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished Report 84/198, BASF DocID 86/10319, 04 April 1986 Not GLP, Unpublished	N	KST	Y	Y	Y
[redacted]	1986b	A.4.2.3.1 A9.1.1-001	Study of the acute toxicity of BAS 002 01 N in the Bluegill (Lepomis macrochirus RAF.), [redacted] Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 84/198 (repetition), BASF DocID 1986/1001073, 30 May 1986 Not GLP, Unpublished	N	KST	Y	Y	Y
[redacted]	1982a	A.4.2.3.1 A9.1.1-004	Acute toxicity of N-521 to Rainbow trout (Salmo gairdneri) T-11045, [redacted] Beltsville, USA, unpublished report No. 82-E-1509R, BASF DocID 82/10070, Nov 1982 Not GLP, Unpublished	N	KST	Y	Y	Y
[redacted]	2002	A.4.2.3.1 A9.1.1-005	Methyl isothiocyanate (metabolite of BAS 002 N, dazomet) - Acute toxicity study on the Rainbow trout (Oncorhynchus mykiss) in a semi-static system over 96 hours, [redacted], Department of Product Safety, Ludwigshafen/Rhein, Germany, unpublished report 12F0722/015099, BASF DocID 2002/1006168, 25 Jun 2002 GLP, Unpublished	N	KST	Y	Y	Y
[redacted]	1982b	A.4.2.3.1 A9.1.2-001	The Acute Toxicity of N-521 to Daphnia magna Straus, [redacted] Beltsville, USA, unpublished report 82-E-1509D, BASF Doc.ID 82/10069, 29 Nov 1982 Not GLP, Unpublished	N	KST	Y	Y	Y
[redacted]	1980	A.4.2.3.1 9.1.2-006	Determination of the acute toxicity of BAS 002 01 N/Basamid Granulat (98% Dazomet) to the Waterflea Daphnia magna	N	KST	Y	Y	Y

			Straus, BASF AG, Department of Toxicology, Ludwigshafen/Rhein, Germany, unpublished report 4/80-1/0227/5/80-801-A 1/15, 04 September 1980, Not GLP, Unpublished					
[redacted]	2002	A.4.2.3.1 A9.1.2-003	Effect of Methyl-isothiocyanate (MITC) on the immobility of Daphnia magna Straus in a 48 hour semi-static, acute toxicity test, [redacted] Agricultural Center Limburgerhof, Germany, unpublished report No. 58330, BASF Doc ID 2002/1006188, 22 Jul 2002 GLP, Unpublished	N	KST	Y	Y	Y
[redacted]	1984	A.4.2.3.1 A9.1.3-001	Determination of the effects of BAS 002 01 N on the green alga Scenedesmus subspicatus 86.81 SAG in the growth inhibition test, [redacted] Department of Ecology, Ludwigshafen/Rhein, Germany, unpublished report No. 2/0018/2/84-98/84, BASF Doc ID 84/10212, 5 July 1984 Not GLP, Unpublished	N	KST	Y	Y	Y
[redacted]	1989	A.4.2.3.1 9.1.3-006	Effect of Dazomet on the growth of the green alga Ankistrodesmus bibraianus, [redacted] Agricultural Center Limburgerhof, Germany, unpublished report n° P88-E057, BASF DocID 1989/10259, Mar 1989 GLP, Unpublished	N	KST	Y	Y	Y
[redacted]	1998	A.4.2.3.1 A9.1.3-005	Effect of Methyl isothiocyanate on the growth of the green alga Pseudokirchneriella subcapitata, [redacted] Agricultural Center Limburgerhof, Germany, unpublished report No. 48881, BASF Doc ID 98/10767, Sep 1998 GLP, Unpublished	N	KST	Y	Y	Y
[redacted]	1990	A.4.2.3.1 A9.1.6.1-001	Sublethal toxic effects on Rainbow trout (Salmo gairdneri Rich. = Oncorhynchus mykiss) of Methylisothiocyanate (MITC), [redacted] Department of Toxicology,	N	KST	Y	Y	Y

			Ludwigshafen/Rhein, Germany, unpublished report 2F0761/895215, BASF Doc ID 90/10055, 23 Feb 1990 GLP, Unpublished					
[redacted]	2001	A.4.2.3.1 A9.1.6.2-001	Methyl isothiocyanate - Determination of the chronic effect on the reproduction of the water flea Daphnia magna STRAUS, [redacted] Department of Product Safety, Ludwigshafen/Rhein, Germany, unpublished report No. 99/0547/51/2, 30 Nov 2001 GLP, Unpublished	N	KST	Y	Y	Y

Data protection from this renewal *–(end ten years from the first day of the month following the date of the adoption of a decision in accordance with Article 14(4))*

Confidential (as per article 66) :

Author(s)	Year	Section No Reference No	Title. Source Company, Report No. GLP (Un)Published	Data Protection Claimed (Yes/No)	Owner	Data Identified as 'relevant' by the eCA[22] (Yes/No)	Applicability	
							RAR	CLH
[redacted]	2019a	A.4.2.3.1 A9.1.1-002	BASAMID® - Acute Toxicity to Rainbow trout (Oncorhynchus mykiss) in a 96-Hour Test, [redacted], unpublished report No. 20180135, May 23, 2019 GLP, Unpublished	Y	KST	Y	Y	Y
[redacted]	2019b	A.4.2.3.1 A9.1.1-003	Methyl isothiocyanate (MITC) - Acute Toxicity to Rainbow trout (Oncorhynchus mykiss) in a 96-Hour Test, [redacted], unpublished report No. 20180075, March	Y	KST	Y	Y	Y

[22] Only relevant for the renewal of an active substance. Remove column for active substance approval and CLH process.
For the identification of the relevant data, please see CA-Sept20-Doc.7.1.b - Relevant Renewal Data under Article 95_FINAL

			08, 2019 GLP, Unpublished					
[redacted]	2019c	A.4.2.3.1 A9.1.2-004	BASAMID® – Acute Toxicity to Daphnia magna in a 48-Hour Immobilization Test, Innovative Environmental Services (IES) Ltd, unpublished report 20180134, April 09, 2019 GLP, Unpublished	Y	KST	Y	Y	Y
[redacted]	2019d	A.4.2.3.1 A9.1.2-005	Methyl isothiocyanate (MITC) – Acute Toxicity to Daphnia magna in a 48-Hour Immobilization Test, [redacted] Ltd, unpublished report No. 20180074, March 08, 2019 GLP, Unpublished	Y	KST	Y	Y	Y
[redacted]	2019a	A.4.2.3.1 A9.1.3-003	BASAMID® – Effect on Pseudokirchneriella subcapitata in a 72-Hour Algal Growth Inhibition Test, [redacted], unpublished report No. 20180133, March 18, 2019 GLP, Unpublished	Y	KST	Y	Y	Y
[redacted]	2018a	A.4.2.3.1 A9.1.3-002	Methyl isothiocyanate (MITC) – Effect on Pseudokirchneriella subcapitata in a 72-Hour Algal Growth Inhibition Test, [redacted], unpublished report No. 20180073, November 23, 2018 GLP, Unpublished	Y	KST	Y	Y	Y
[redacted]	2019b	A.4.2.3.1 A9.1.3-004	Methyl isothiocyanate (MITC) – Effect on Anabaena flos-aquae in a 72-Hour Algal Growth Inhibition Test, [redacted], unpublished report No. 20180139, January 15, 2018 GLP, Unpublished	Y	KST	Y	Y	Y
[redacted]	2019e	A.4.2.3.1 A9.1.10-001	Methyl isothiocyanate (MITC) - Effect on the Aquatic Higher Plant Lemna gibba in a 7-Day Growth Inhibition Test under Flow-Through Conditions, [redacted], unpublished report No. 20180077,	Y	KST	Y	Y	Y

			November 25, 2019 GLP, Unpublished					
[redacted]	2015	A.4.2.3.1 A9.1.6.1-002	Methyl Isothiocyanate (MITC) : An Early Life-Stage Toxicity Test with the Fathead Minnow (Pimephales promelas), [redacted] unpublished report n° 246A-117, October 16, 2015 GLP, Unpublished	Y	KST	Y	Y	Y
[redacted]	2019f	A.4.2.3.1 A9.1.6.2-002	Methyl isothiocyanate (MITC) – Effect on Survival, Reproduction and Growth of Daphnia magna in a Flow-Through Test over Three Weeks, [redacted], unpublished report No. 20180076, October 16, 2019 GLP, Unpublished	Y	KST	Y	Y	Y
[redacted]	2020	A.4.2.3.1 A9.1.10-002	Methyl isothiocyanate (MITC) - Toxicity to the Aquatic Macrophyte Myriophyllum spicatum in a 14-Day Sediment-Free Growth Inhibition Test under Flow-Through Conditions, [redacted], unpublished report No. 20180078, July 21, 2020 GLP, Unpublished	Y	KST	Y	Y	Y
[redacted]	2018b	A.4.2.3.1 A9.1.2-002	Methyl isothiocyanate (MITC) – Effect on First-Instar Larvae of Chironomus riparius in a 48-Hour Immobilization Test, [redacted], unpublished report 20180117, October 11, 2018 GLP, Unpublished	Y	KST	Y	Y	Y

Not confidential (as per article 66):

Author(s)	Year	Section No / Reference No	Title. Source Company, Report No. GLP (Un)Published	Data Protection Claimed (Yes/No)	Owner	Data Identified as 'relevant' by the eCA[23] (Yes/No)	Applicability	
							RAR	CLH
Smith MS, Weeraratna CS	1975	A.4.2.4 A9.2.1-002	Influence of some biologically active compounds on microbial activity and on the availability of plant nutrients in soils. II. Nitrapyrin, dazomet, 2-chlorobenzamide and tributyl-3-chlorobenzylammonium bromide, Pesticide Science, 6: 605-615, Doc ID 1975/1000201 Not GLP, Published	N	Pesticide Science	Y	Y	N
Markert S, Kundler P	1975	A.4.2.4 A9.2.1-002	Modellversuche zum Einfluss von handelsüblichen Pflanzenschutzmitteln auf die Stickstoffumsetzzung im Boden, Arch. Acker- und Pflanzenbau und Bodenkunde 19: 487-497, BASF DocID 1975/1000221 Not GLP, Published	N	Arch. Acker- und Pflanzenbau und Bodenkunde	Y	Y	N
Hoeflich, G.	1977	A.4.2.4 A9.2.1-002	Einsatz von Bioziden zur Beeinflussung der Bodenmikroflora und deren Umsetzung (The effect of biocides on the microflora of soils and their degradation), Zbl. Bakt. II 132: 148-154, BASF DocID 1977/11187 Not GLP, published	N	Zbl. Bakt. II	Y	Y	N

[23] Only relevant for the renewal of an active substance. Remove column for active substance approval and CLH process. For the identification of the relevant data, please see CA-Sept20-Doc.7.1.b - Relevant Renewal Data under Article 95_FINAL

Appendix VI: Confidential information

See the Confidential Annex (separate document).

Appendix VII: Study summaries (relevant for the CLH proposal)

Study summaries are presented in the Annex I report (Confidential information, see separate document).