CLH report

Proposal for Harmonised Classification and Labelling

Based on Regulation (EC) No 1272/2008 (CLP Regulation), Annex VI, Part 2

International Chemical Identification:

2,2-dimethylpropan-1-ol, tribromo derivative; 3-bromo-2,2-bis(bromomethyl)propan-1-ol (TBNPA)

EC Number: 253-057-0

CAS Number: 36483-57-5 and 1522-92-5

Index Number: 603-RST-VW-Y

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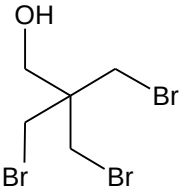
CONTENTS

1 IDENTITY OF THE SUBSTANCE

1.1 Name and other identifiers of the substance

Table 1: Substance identity and information related to molecular and structural formula of the substance. Taken from ECHA´s dissemination site if no other source is given

Name(s) in the IUPAC nomenclature or other international chemical name(s)	2,2-dimethylpropan-1-ol, tribromo derivative; 3-bromo-2,2-bis(bromomethyl)propan-1-ol
Other names (usual name, trade name, abbreviation)	TBNPA, FR-513
ISO common name (if available and appropriate)	-
EC number (if available and appropriate)	253-057-0
EC name (if available and appropriate)	2,2-dimethylpropan-1-ol, tribromo derivative
CAS number (if available)	36483-57-5;1522-92-5
Other identity code (if available)	-
Molecular formula	$C_5H_9Br_3O$
Structural formula	
SMILES notation (if available)	BrCC(CBr)(CBr)CO
Molecular weight or molecular weight range	324.838 g/mol (from PubChem)
Information on optical activity and typical ratio of (stereo) isomers (if applicable and appropriate)	-
Description of the manufacturing process and identity of the source (for UVCB substances only)	-
Degree of purity (%) (if relevant for the entry in Annex VI)	-

1.2 Composition of the substance

Table 2: Constituents (non-confidential information)

Constituent (Name and numerical identifier)	**Concentration range (% w/w minimum and maximum in multi-constituent substances)**	**Current CLH in Annex VI Table 3.1 (CLP)**	**Current self-classification and labelling (CLP)**
TBNPA (CAS no. 36483-57-5; 1522-92-5)	≥ 97% (w/w)	-	Aquatic chronic 3 H412 Eye Irrit. 2 H319 Acute Tox. 4 H302 Muta. 2 H341 Muta. 1B H340 Carc. 1B H350 Not classified

2 PROPOSED HARMONISED CLASSIFICATION AND LABELLING

2.1 Proposed harmonised classification and labelling according to the CLP criteria

Table 3: Proposed CLH

	Index No	International Chemical Identification	EC No	CAS No	Classification		Labelling			Specific Conc. Limits, M-factors	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	-										
Dossier submitters proposal		2,2-dimethylpropan-1-ol, tribromo derivative; 3-bromo-2,2-bis(bromomethyl)propan-1-ol	253-057-0	36483-57-5; 1522-92-5	Muta. 1B Carc. 1B	H340 H350	GHS08, Dgr	H340 H350			
Resulting Annex VI entry if agreed by RAC and COM		2,2-dimethylpropan-1-ol, tribromo derivative; 3-bromo-2,2-bis(bromomethyl)propan-1-ol	253-057-0	36483-57-5; 1522-92-5	Muta. 1B Carc. 1B	H340 H350	GHS08, Dgr	H340 H350			

Table 4: Reason for not proposing harmonised classification and status under public consultation

Hazard class	Reason for no classification	Within the scope of public consultation
Explosives	Hazard class not assessed in this dossier	No
Flammable gases (including chemically unstable gases)	Hazard class not assessed in this dossier	No
Oxidising gases	Hazard class not assessed in this dossier	No
Gases under pressure	Hazard class not assessed in this dossier	No
Flammable liquids	Hazard class not assessed in this dossier	No
Flammable solids	Hazard class not assessed in this dossier	No
Self-reactive substances	Hazard class not assessed in this dossier	No
Pyrophoric liquids	Hazard class not assessed in this dossier	No
Pyrophoric solids	Hazard class not assessed in this dossier	No
Self-heating substances	Hazard class not assessed in this dossier	No
Substances which in contact with water emit flammable gases	Hazard class not assessed in this dossier	No
Oxidising liquids	Hazard class not assessed in this dossier	No
Oxidising solids	Hazard class not assessed in this dossier	No
Organic peroxides	Hazard class not assessed in this dossier	No
Corrosive to metals	Hazard class not assessed in this dossier	No
Acute toxicity via oral route	Hazard class not assessed in this dossier	No
Acute toxicity via dermal route	Hazard class not assessed in this dossier	No
Acute toxicity via inhalation route	Hazard class not assessed in this dossier	No
Skin corrosion/irritation	Hazard class not assessed in this dossier	No
Serious eye damage/eye irritation	Hazard class not assessed in this dossier	No
Respiratory sensitisation	Hazard class not assessed in this dossier	No
Skin sensitisation	Hazard class not assessed in this dossier	No
Germ cell mutagenicity	**Harmonised classification proposed**	**Yes**
Carcinogenicity	**Harmonised classification proposed**	**Yes**
Reproductive toxicity	**Data inconclusive**	**Yes**
Specific target organ toxicity-single exposure	Hazard class not assessed in this dossier	No
Specific target organ toxicity-repeated exposure	**Data inconclusive**	**Yes**
Aspiration hazard	Hazard class not assessed in this dossier	No
Hazardous to the aquatic environment	Hazard class not assessed in this dossier	No
Hazardous to the ozone layer	Hazard class not assessed in this dossier	No

3 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING

The substance has no previous harmonised classification and labelling

4 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

There is no requirement for justification that action is needed at Community level.

5 IDENTIFIED USES

According to the information published on the ECHA dissemination site, this substance is used in the manufacture of polymers, plastic products and chemicals and as an intermediate.

TBNPA is used as a reactive flame retardant in polymers synthesis (100-1000 tpa) for the manufacture of plastic products and chemicals. It is used in industrial, professional and consumer settings in formulation and use of commercial mixture(s).

6 DATA SOURCES

- Report: Category approach for selected brominated flame retardants (Wedebye et al., 2016)
- RAC-opinion, CLH-report/annex and Risk Management Option Analysis for similar substance 2,2-bis(bromomethyl)propane-1,3-diol (BMP), CAS no. 3296-90-0
- REACH registration via ECHA´s dissemination site
- CSR in the REACH registration via ECHA´s Remote access portal/IUCLID
- Internet resources:

  eChemPortal

  Toxnet/Toxline/Pubmed/PubChem

  Search engine Google –www.google.com

Date of search: The period from initiation of the work until submission (large parts of 2018).

7 PHYSICOCHEMICAL PROPERTIES

Table 5: Summary of physicochemical properties of TBNPA

Property	Value	Reference	Comment (e.g. measured or estimated)
Physical state at 20°C and 101,3 kPa	Solid, white to off-white flakes	ECHA[1]	
Melting/freezing point	Melting / freezing point at 101 325 Pa: 68.96°C	"	
Boiling point	N.A.[2]	"	
Relative density	Relative density at 20C:2.286	"	

[1] ECHA dissemination site

[2] N.A. Not available

Property	Value	Reference	Comment (e.g. measured or estimated)
Vapour pressure	0 Pa at 25°C	"	
Surface tension	N.A.	"	
Water solubility	1.93 g/L at 20.1°C	"	
Partition coefficient n-octanol/water	Log Kow (Log Pow):2.6 at 22.5°C	"	
Flash point	N.A.	"	
Flammability	N.A.	"	
Explosive properties	N.A.	"	
Self-ignition temperature	N.A.	"	
Oxidising properties	N.A.	"	
Granulometry	N.A.	"	
Stability in organic solvents and identity of relevant degradation products	No change was found in the concentration of 2,2-dimethylpropan-1-ol, tribromo derivative (TBNPA) over 14 days, within the method's precision capability.	"	
Dissociation constant	N.A.		
Viscosity	N.A.		

8 EVALUATION OF PHYSICAL HAZARDS

Not evaluated in this dossier.

9 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION)

No data available

10 EVALUATION OF HEALTH HAZARDS

Acute toxicity/Skin corrosion/Irritation/Eye damage/Sensitisation

Not evaluated in this dossier.

10.1 Germ cell mutagenicity

Table 3: Summary table of mutagenicity/genotoxicity tests in vitro

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
In vitro	TBNPA	Based on range finding	**TBNPA was found to be clastogenic**	Study report

Method, guideline, deviations if any	Test substance,	Relevant information about the study including rationale for dose selection (as applicable)	Observations	Reference
cytogenicity / chromosome aberration study in mammalian cells (lymphocytes: Peripheral human lymphocytes) OECD TG 473	(CAS no. 36483-57-5) Purity 97%	study, the doses in the main studies ranged from 100 to 2000 µg/ml with and without metabolic activation (S-9 mix). Positive control was MMC, Negative control (solvent only) was DMSO 3hr exposure, 24 hr fixation.	in the presence of metabolic activation, and at the highest test substance concentration (1000 microgram/ml) in the absence of metabolic activation. Cytotoxicity seen as low as at 100 µg/ml, with metabolic activation. TBNPA has the **potential to disturb mitotic processes and cell cycle progression,**	unnamed, 2004
Mammalian cell gene mutation assay (Mouse lymphoma L5178Y cells, gene mutation) following OECD TG 476	TBNPA (CAS no. 36483-57-5) Purity 97%	Following a range finding test, in the main studies, concentrations varied from 10 to 535 µg/ml, and up to 8 dose groups pluss two solvent controls, e.g. 10, 50, 100, 200, 300, 400, 500 µg/ml in experiment 1 (without metabolic activation). Positive control methyl methane sulfonate/cyclophosphamide	TBNPA was **mutagenic** in the test system with incubations in the presence of metabolic activation (S9-mix). Cytotoxicity was seen atconcentration of 333 µg/plate and above	Study report unnamed, 2004
Bacterial reverse mutation assay: In vitro gene mutation study in bacteria (Ames test) OECD TG 471	TBNPA Purity 98%	The Ames test was done with S. typhimurium TA 1535, TA 1537, TA 98 and TA 100 (with and without metabolic activation from rodent S-9 mix). Following a preliminary test with 5000 µg/plate, the maximum concentration was 1500 µg/plate in the main test.	Cytotoxicity was seen at 5000 µg/plate. **Mutagenicity was seen** in both mutation tests with strains TA 1535 and TA 100 at concentrations between 15 and 500 µg/plate, but only with metabolic activation.	Study report unnamed, 1996

Table 4: Summary table of mutagenicity/genotoxicity tests in mammalian somatic or germ cells in vivo

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
Unscheduled DNA Synthesis (UDS) test with rat liver cells (hepatocytes) *in vivo*. GLP and OECD TG 486	TBNPA Purity not given	Sprague-Dawley rats (CD (Ctr;CD (SD) IGS BR) strain) *No. of animals per sex per dose:* 2 range finder studies: (1 male; 1 female) and (2 males 0 females); 2 main tests: study 1: 4 per dose (males); study 2: 4 per dose (males) All animals were dosed once. In the range finding tests the dose was 2000 mg/kg. In the main studies the dose was 670 and 2000 mg/kg bw. Administration: . oral by gavage. Treatment: 16 hr (experiment 1); 2 hr (experiment 2). Negative control: number of animals not given Positive control 2-Acetamididofluorene (2AAF) at 50 mg/kg bw, and Sym-Dimethylhydrazine dihydrochloride (NDHC) at 40 mg/kg bw.	Negative result: The test material did not induce any marked or toxcologiacally significant increases in the incidence of cells undergoing DNA synthesisin isolated rat hepatocytes following in vivo exposure for 2 or 16 hr. Therefore **the test material was considered to be non-genotoxic under the conditions of the study.** Concurrent positive control data: Both positive controls produced marked increases in the incidence of cells in repair and the vehicle control groups gave **acceptable values for net nuclear grain counts.** Administration of the test substance in the range finding study produced **toxicity in the dosed animals manifested as ataxia, lethargy, red colored urine** (no deaths). Lethargy and ataxia was also seen in the main studies.	Study report unnamed (2007a)
In vivo mammalian somatic cell study: cytogenicity / erythrocyte micronucleus OECD test guideline 474 is relevant, but the study was done prior to the guideline. No major deviations from the guideline. Reliability score made by the registrant: 1	TBNPA Degree of purity: 98.1%	NMRI mice / male and female No. of animals per sex per dose: In total 81 animals (45 males and 36 females). Ten animals (5 males, 5 females) per dose. Preliminary test: 2000, 1500, 1000, 500,400, 300 (mg/kg b.w) main test: 300, 150, 75 (mg/kg bw. On the day of the experiment, the test item was formulated in DMSO+corn oil (30%-70%). The vehicle was chosen to its relative non-toxicity for the animals. All animals received a single standard volume of 10 mL/kg body weight orally. Negative controls: "valid" (no more information available)	**TBNPA did not induce micronuclei as determined by this micronucleus test** with femur bone marrow cells of the mouse. The % micronuclei was 0.085, 0.110 and 0.125 at dose 75, 150, 300 mg/kg bw 24 hours post-treatment.	Study report unnamed (2007b)

Method, guideline, deviations if any	Test substance,	Relevant information about the study (as applicable)	Observations	Reference
		Positive control substance(s): CPA; Cyclophosphamide (>98%); Dosing: 40 mg/kg b.w ; volume administration: 10 mL/kg b.w		

10.1.1 Short summary and overall relevance of the provided information on germ cell mutagenicity

In vitro studies:
In the OECD TG 473 *In vitro* cytogenicity / chromosome aberration study in mammalian cells TBNPA was found to be clastogenic in the presence of metabolic activation and at the highest test substance concentration (1000 microgram/ml) in the absence of metabolic activation. TBNPA has the potential to disturb mitotic processes and cell cycle progression (Study report unnamed, 2004).

The OECD TG 476 Mammalian cell gene mutation assay was positive. TBNPA was mutagenic in the test system with incubations in the presence of metabolic activation. The presence of S9-mix in both tests resulted an increase in mutation frequencies more than threefold and outside the labs historical data (no more detailed information about historical data is available in the registration). The increases were considered biologically relevant and TBNPA is considered mutagenic in vitro (Study report unnamed, 2004).

In the *in vitro* assays one Ames test was included. In the presence of hamster S-9 mix however, there were clear evidence of mutagenic activity between 500 and 15 µg/plate with strains TA 1535 and TA 100. The test showed no evidence of mutagenic activity in the absence or presence of rat S-9 mix (Study report unnamed, 1996).

In vivo studies: In the *in vivo* mammalian somatic cell study TBNPA did not induce micronuclei as determined by the micronucleus test with bone marrow cells of the mouse. Therefore TBNPA can be considered to be non-mutagenic in this test (Study report, unnamed, 2007b).

In the OECD TG 486 Unscheduled DNA Synthesis (UDS) test with rat liver cells (liver hepatocytes) *in vivo* TBNPA did not induce any marked or toxicologically significant increases in the incidence of cells undergoing unscheduled DNA synthesis in isolated rat hepatocytes following in vivo exposure for 2 or 16 hr. Therefore, the test material was considered to be non-genotoxic under the conditions of the study (Study report, 2007a).

10.1.2 Other relevant information

TBNPA belongs to a small category of brominated substances and an analogue read-across approach is proposed for mutagenicity and carcinogenicity, see section 10.2.1 below.

10.1.3 Comparison with the CLP criteria for mutagenicity

Category 1: "Substances known to induce heritable mutations or to be regarded as if they induce heritable mutations in the germ cells of humans. Substances known to induce heritable mutations in the germ cells of humans."

Category 1A: "The classification in Category 1A is based on positive evidence from human epidemiological studies. Substances to be regarded as if they induce heritable mutations in the germ cells of humans."

No epidemiological studies are available so Cat. 1A is not justified

Category 1B: According to CLP to classify a compound as Cat. 1B the following criteria must be fulfilled: "The classification in Category 1B is based on: – positive result(s) from in vivo heritable germ cell mutagenicity tests in mammals; or – positive result(s) from in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells.."

Category 2: Classification criteria for category 2, from CLP: "Substances which cause concern for humans owing to the possibility that they may induce heritable mutations in the germ cells of humans. The classification in Category 2 is based on: – Positive evidence obtained from experiments in mammals and/or in some cases from in vitro experiments, obtained from: – Somatic cell mutagenicity tests in vivo, in mammals; or – Other in vivo somatic cell genotoxicity tests which are supported by positive results from in vitro mutagenicity assays"

Rationale for proposal for classification in Cat. 1B:

TBNPA was clastogenic in human lymphocytes in vitro in the presence of metabolic activation and at the highest test concentration without metabolic activation, and mutagenic in mouse lymphoma cells in vitro in the presence of metabolic activation. In bacterial reverse mutation assays, mutagenicity was seen. Two in vivo tests with TBNPA were negative: a) in rat hepatocytes (UDS test) and b) micronucleus test in femur bone marrow cells of the mouse. We have no reproductive toxicity studies that indicate that TBNPA reaches the germ cells. The database is limited to a single prenatal developmental toxicity study. However, as described above, we propose to read across from the source substance BMP to the target substance TBNPA, see section 10.2.1 and table 10 (Data matrix for studies relevant for assessing germ cell mutagenicity, Analogue Approach). RAC states in the recent RAC-opinion for BMP that "there is positive evidence of somatic cell mutagenicity for BMP from in vitro/in vivo studies and evidence from the reproductive toxicity studies and that this supports that BMP reaches the (female) germ cells". According to RAC "both facts in combination are sufficient to give 'some' evidence that the substance has the potential to cause mutations to germ cells". RAC agreed that BMP should be classified as a germ cell mutagen, Cat. 1B; H340. We propose the same classification for TBNPA.

10.1.4 Conclusion on classification and labelling for mutagenicity

TBNPA should be classified as Muta. 1B, H340

10.2 Carcinogenicity

No data available.

10.2.1 Read-across for mutagenicity and carcinogenicity

10.2.1.1 Hypothesis for the analogue approach

The read-across is based on the report "Category approach for selected brominated flame retardants - preliminary structural grouping of brominated flame retardants" (Wedebye et al., 2016). The subtitle of the report reflects the preliminary structural grouping of all the brominated flame retardants on the Danish market, plus some additional common ones, in total 67. The authors then chose the group of small brominated alkyl alcohols (SBAA) for further investigation, so the main title of the report "Category approach…" refers to the work done on this group while the subtitle "preliminary…" refers to the bigger group initially investigated.

Scientific hypothesis and justification of read-across by characterisation of the analogue approach (according to the ECHA Read-Across Assessment Framework, RAAF scenario 2).

The scientific hypothesis for the read-across is that the chemical structure of TBNPA (CAS-no. 36483-57-5/1522-92-5), BrCC(CBr)(CBr)CO is very similar to BMP that is already classified as Muta. 1B and Carc. 1B (CAS no. 3296-90-0, C(C(CO)(CBr)CBr)O). The structural similarity was recognized by the Danish Environment Protection Agency (DEPA) and published in a report by Wedebye et al. 2016 when **BMP and TBNPA were found to belong to the same (Q)SAR-based clusters for genotoxicity and carcinogenicity**, and described to belong to the group of SBAA. The last member of the group, 2,3-DBPA, is classified with Carc. 1B and Repr. 2. However, this substance does not belong to the same clusters for genotoxicity and carcinogenicity as BMP and TBNPA. For reproductive toxicity the three substances are in separate clusters.

All members of the SBAA group were predicted by a number of (Q)SAR models including the OECD (Q)SAR Toolbox to be positive for carcinogenic and genotoxic properties indicating that they have a carcinogenic potential with a possible mutagenic/genotoxic mode of action (see chapter 3 in Wedebye et al. 2016 for more details on the (Q)SAR predictions).

There are several alerts for mutagenicity and carcinogenicity for SBAAs in the (Q)SAR models applied. For example "aliphatic halogen" is an alert for *in vitro* and *in vivo* mutagenicity and carcinogenicity in the OECD (Q)SAR Toolbox (according to Wedeby et al. (2016), it does not seem that there is one single mechanistic interpretation of this alert in relation to mutagenicity and cancer).

For details on the grouping, see Wedebye et al., 2016.

Table 8: The members of the small brominated alkyl alcohols (SBAA) group:

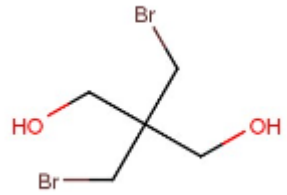
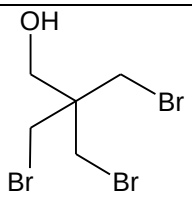
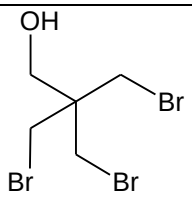
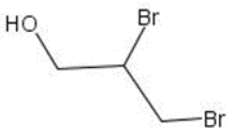
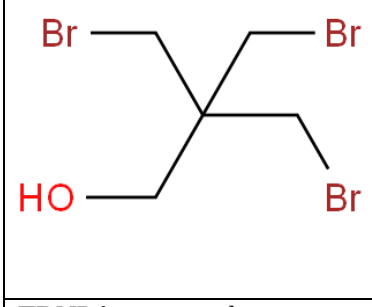
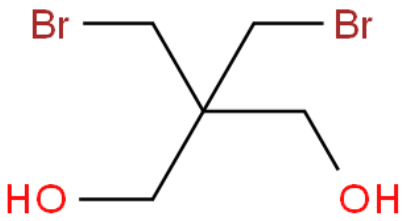
Chemical name	Synonyms	EC no.	CAS no.	Harmonized classification, CMR	Structural formula
2,2-bis(bromomethyl)propane-1,3-diol (BMP)	Dibromoneopentyl glycol (DBNPG) 2,2-bis-(bromomethyl)-1,3-propanediol Dinol FR-522	221-967-7	3296-90-0	Muta. 1B, H340 Carc. 1B, H350	
2,2-dimethylpropan-1-ol, tribromo derivative (TBNPA)	2,2-dimethylpropan-1-ol, tribromo derivative, tribromoneopentyl alcohol, 3,3,3-tribromo-2,2-dimethyl-propan-1-ol, FR-513	253-057-0	36483-57-5	-	
3-bromo-2,2-bis(bromomethyl)-1-propanol	3-bromo-2,2-bis(bromomethyl)propan-1-ol Pentaerythritol Tribromide	-	1522-92-5	-	
2,3-dibromo-1-propanol (2,3-DBPA)	2,3-dibromopropan-1-ol 2,3-dibromopropyl alcohol DBP	202-480-9	96-13-9	Carc. 1B, H350 Repr. 2, H361f	

Table 9: Target substance and source substance, Moleculare structures of TBNPA and BMP (Source Danish (Q)SAR database)

	
TBNPA, target substance	BMP, source substance

The Danish report (Wedebye et al., 2016) states that according to (Q)SAR-based clusterings, BMP and TBNPA (the 6,9% impurity in BMP) are in the same (Q)SAR-based clusters for carcinogenicity and genotoxicity. There are genotoxicity study results revealing almost identical properties for BMP and TBNPA.

Table 10: Data matrix for studies relevant for assessing germ cell mutagenicity, Analogue Approach

CAS #	**36483-57-5**	**3296-90-0**
	Target chemical	**Source chemical**
Chemical name	**TBNPA**	**BMP**
Gene mutation in bacteria:		
Bacterial Reverse Mutation Assay (Ames test)		Negative in tested Salmonella strains TA98/100/1535/1537 with and without rat and hamster S9 (Mortelmans et al., 1986; NTP, 1996)
	Positive: Tested in Salmonella strains 1535, TA 1537, TA 98 and TA 100 with and without rat and hamster S9. Positive in TA 1535 and TA 100 with S9 (study report unnamed, 1996)	Positive: Tested in TA98/100/1535/1537 Positive in TA1535/100 with hamster S9 Negative with rat S9 Negative without S9 (Unnamed author, 1996b; Zeiger et al., 1992; NTP, 1996)
Gene mutation in mammalian cells:		
Mammalian cell gene mutation test, *in vitro*	Positive: Mutagenicity was seen in mouse lymphoma L5178Y cells with rat S9 (study report unnamed, 2004)	
Mammalian cytogenetic assays, *in vitro*:		
In vitro cytogenicity / Chromosome aberration study in mammalian cells	Positive: Clastogenic chromosomal aberrations in peripheral human lymphocytes with rat S9 (study report unnamed, 2004)	Positive: Chromosomal aberration in Chinese hamster ovary cells with rat S9 (Galloway et al., 1987; NTP, 1996)
Sister Chromatid Exchange Assay		Equivocal: Slight increases in Chinese hamster ovary at toxic levels with S9 (Galloway et al., 1987; NTP, 1996)

Mammalian cytogenetic assays, *in vivo*:		
Micronucleus test (cytogenicity in-vivo).	Negative: TBNPA did not induce micronuclei in mouse femur bone marrow cells (study report unnamed, 2007b)	Positive: BMP was genotoxic in peripheral blood and bone marrow in both male and female mice in *in vivo* micronucleus tests with B6C3F1 mice (NTP, 1996)
DNA damage and repair assays:		
In vitro comet assays		Positive: BMP induced oxidative stress and induced DNA damage in the urothelial cell line of Urotsa cells in two tests (Kong et al., 2011; 2013)
		Negative: No DNA damage was seen in an *in vitro* comet assay with primary hepatocytes (non-target) isolated from male SD rats (Kong et al., 2013)
in vivo comet assay		Positive/Negative: BMP increased DNA damage in urine bladder, but not in liver in SD rats (Wada et al., 2014)
Unscheduled DNA synthesis (UDS) test *in vivo*	Negative: The test material did not induce any marked or toxicologically significant increases in the incidence of cells undergoing DNA synthesisin isolated rat hepatocytes (study report unnamed, 2007a)	
Reproductive toxicity studies:		
National Toxicology Program (NTP) Reproductive Assessment by Continuous Breeding bioassays (RACB)		Positive: BMP impaired fertility in female CD-I mice in both generations, no effect on reproductive organ weight or estrual cyclicity (Treinen et al., 1989)
Archived ovaries from NTP RACB bioassays		Positive: Dose-dependent decreased counts of small and/or growing follicles in CD-I mice (ovaries from the RACB study) (Bolon et al, 1997)
28-day oral repeat dose toxicity study	Negative: No effects on germ cells (Unnamed author, 2015)	

BMP (CAS no. 3296-90-0) showed no evidence of mutagenic activity in Ames´ tests with Salmonella strains TA98, TA100, TA1535 and TA1537, with or without activation from rat liver S9 (Mortelmans et al., 1986; NTP, 1996). There was however clear evidence of positive mutagenic activity from BMP in strains TA1535 and TA100 in the presence of Syrian hamster S9-mix (Unnamed author, 1996b; Zeiger et al., 1992; NTP, 1996). Chromosomal aberration was induced by BMP as breaks in the long arm of the X-chromosome in cultivated Chinese hamster ovary cells (CHO-W-B1) in the presence of metabolic activation (Galloway et al., 1987; NTP, 1996). BMP induced very slight increases in Chinese hamster ovary cells in the *in vitro* Sister Chromatid Exchange Assay at toxic levels with S9, and none withut metabolic activation (Galloway et al., 1987; NTP, 1996). In the two *in vitro* comet assays, BMP induced oxidative stress and induced DNA damage in the urothelial cell line of Urotsa cells (Kong et al., 2011; 2013). No DNA damage was seen in an

in vitro comet assay with primary hepatocytes (non-target) isolated from male SD rats (Kong et al., 2013). In an *in vivo* comet assay, BMP increased DNA damage in urine bladder, but not in liver in SD rats (Wada et al., 2014). BMP was genotoxic in peripheral blood and bone marrow in both male and female mice in *in vivo* micronucleus tests with B6C3F1 mice (NTP, 1996).

As described in the table above and further in detail in section 10.1 TBNPA was clastogenic in human lymphocytes in vitro and mutagenic in mouse lymphoma cells in vitro. In bacterial reverse mutation assays, mutagenicity was seen. Two in vivo tests with TBNPA were negative.

For BMP there are extensive reproduction toxicity studies indicating that the substance reaches the germ cells (Treinen et al., 1989; Bolon et al, 1997). For TBNPA, there is only a 28 days repeated dose toxicity study available where no effects were observed in germ cells.

For carcinogenicity there is only data for BMP. However it should be noted that TBNPA was a major impurity in the 2-year carcinogenicity study from NTP.

In the 2-year carcinogenicity study on BMP by National Toxicology Program (NTP) (1996) and also published by Dunnick et al. (1997), F-344 rats and B6C3F1 mice were given BMP orally through feed.

Male rats were given 100, 200 or 430 mg BMP/kg bw/day were as female rats were given 115, 230 or 460 mg BMP/kg bw/day, plus a stop exposure at 800 mg BMP/kg bw/day (3 months exposure). Clear exposure-related carcinogenic effects were observed at 17 sites in male rats (skin, subcutaneous tissue, mammary gland, Zymbal gland, oral cavity, esophagus, forestomach, small intestine, large intestine, mesothelium, kidney, urinary bladder, lung, thyroid gland, seminal vesicle, hematopoietic system, and pancreas) and at 4 sites in female rats (mammary gland, oral cavity, esophagus and thyroid gland). Dose response relationships between exposure and carcinogenicity were evident for several tumour types, and most cancer-sites are relevant for humans. Survival at the two highest doses in males and females and the male stop-exposure group was significantly lower than controls. Mean body weights of rats receiving the highest dose and the stopexposure group in males were lower than controls (5-15%). Food consumption was generally similar to that by controls, except from stop-exposure males (NTP, 1996).

Male mice were given 35, 70, or 140 mg BMP/kg/day whereas female mice were given 40, 80 or 170 mg BMP/kg/day.). A clear exposure related carcinogenic effects were also observed at 3 sites in the male (lung, kidney and Harderian gland) and female mice (subcutaneous tissue, lung and Harderian gland). Dose response relationships between exposure and carcinogenicity was evident for several tumour types and most sites of cancer are relevant for humans. Survival of the high dose males and females was significantly lower than that of the controls. Mean body weights of exposed male and female mice were similar to controls throughout the study. Final mean body weights were also generally similar to those of controls. Feed consumption by exposed male and female mice was similar to that by controls (NTP, 1996).

The test material in the study from the NTP, FR-1138®, contains 79% BMP and the following major impurities: 6,9% TBNPA (CAS no 36483-57-5/1522-92-5), 6,6% monobromoneopentyl triol (CAS no 19184-65-7) and other minor impurities (NTP, 1996).

Carcinogenicity was predicted for all the substances in the group small brominated alkyl alcohols when (Q)SAR models were applied (Wedebye et al., 2016).

TBNPA and BMP have almost identical structure, similar physicochemical properties (table 11) and almost similar genotoxicity test results. We assume that the target substance TBNPA and the source substance BMP share the same toxic mode of action for genotoxicity. BMP and other brominated chemicals have been shown to be genotoxic in a spectrum of tests. It is hypothesized that the carcinogenic activity of brominated chemicals is due to genotoxic mechanisms (NTP, 1996). This corresponds to the RAAF scenario 2.

Table 11: Summary of physicochemical properties for TBNPA and BMP

Property	**TBNPA Value** (ECHA dissemination site)	**BMP Value** (ECHA dissemination site)
Physical state at 20°C and 101,3 kPa	Solid, white to off-white flakes	Off white crystalline powder, odourless
Melting point	Melting / freezing point at 101 325 Pa: 68.96°C	Melting / freezing point at 101 325 Pa:109 °C
Boiling point	N.A.	Boiling point at 101 325 Pa:270 °C
Relative density	Relative density at 20C: 2.286	Relative density at 20C: 1.2
Vapour pressure	0 Pa at 25°C	0.002 Pa at 25 °C
Surface tension	N.A.	N.A.
Water solubility	1.93 g/L at 20.1°C	19.4 g/L at 20 °C
Partition coefficient n-octanol/water	Log Kow (Log Pow):2.6 at 22.5°C	Log Kow (Log Pow):1.08

Table 12: Analogue approach – assessment

Assessment element common to all analogue scenarios	**Assessment**	**Score (1-5)**
AE A.1 Source substance	The chemical structure of TBNPA is very similar to BMP	5
AE A.2 Links/differences	Structurally TBNPA and BMP have very similar molecular formulas, differing only in regard to that one of the OH-groups is substituted with Br in TBNPA	4
AE A.3 Source study	The source study is a NTP-study	5
AE A.4 Bias	TBNPA and BMP are in the same (Q)SAR-based clusters for carcinogenicity and genotoxicity	5

Table 13: Analogue approach – scenario 2

Scenario 2 assessment elements (AE): two different compounds with the same type of effect	**Assessment**	**Score (1-5)**
AE 2.1 Compounds	In the NTP 2-year study on BMP the purity was 78,6% Other constituents in the tested flame retardant FR- 1138: 6.9% TBNPA 6.6% 2,2-bis(hydroxymethyl)-1-bromo-3-hydroxypropane 0.2% pentaerythritol	5

	7.7% dimers and structural isomers	
AE 2.2 Underlying mechanism, qualitative aspects	The substances share the same genotoxic properties. We assume that the target substance TBNPA and the source substances (BMP) share the same toxic mode of action.	4
AE 2.3 Underlying mechanism, quantitative aspects	The genotoxic responses are similar.	4
AE 2.4 Other compounds	Glucuronidation is the sole route of metabolism of BMP in liver microsomes or primary liver cells of rodents, Rhesus monkey and human. The rate of BMP glucuronidation in rodent cells was 150-fold higher than in human hepatocytes. We assume that this is a detoxification route and that this is the same for TBNPA.	3
AE 2.5 Other effects	The mechanism of carcinogenicity for the source substance is not described beyond genotoxicity. However there is data demonstrating that BMP leads to the induction of oxidative DNA damage, which could be due to the release of bromine.	4

10.2.2 Comparison with the CLP criteria for carcinogenicity

Classification category 1: Known or presumed human carcinogens.

A substance is classified in Category 1 for carcinogenicity on the basis of epidemiological and/or animal data. A substance may be further distinguished as:

Category 1A, known to have carcinogenic potential for humans, classification is largely based on human evidence, or

No epidemiological studies are available so Cat. 1A is not justified

Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence.

The classification in Category 1A and 1B is based on strength of evidence together with additional considerations. Such evidence may be derived from: – human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or – animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity (presumed human carcinogen). In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals.

CATEGORY 2: Suspected human carcinogens. The placing of a substance in Category 2 is done on the basis of evidence obtained from human and/or animal studies, but which is not sufficiently convincing to place the substance in Category 1A or 1B, based on strength of evidence together with additional considerations. Such evidence may be derived either from limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.

Rationale for proposal for classification in Cat. 1B:

No carcinogenicity study is available for TBNPA. As described above, we propose to read across from the source substance BMP to the target substance TBNPA. RAC states in the recent RAC-opinion for BMP that it considers BMP to be a multi-site carcinogen in two species with tumours of human relevance. Therefore, RAC agreed to classify BMP as Carc. 1B; H350. We propose the same classification for TBNPA.

10.2.3 Conclusion on classification and labelling for carcinogenicity

TBNPA should be classified as Carc. 1B, H350

10.3 Reproductive toxicity

10.3.1 Adverse effects on sexual function and fertility

Effects on fertility have not been assessed as no relevant studies are available, except for a 28-day repeated dose toxicity study where no relevant effects were identified.

The study was waived by registrant based on a 28-day oral repeat dose toxicity study in rats with a 14 day recovery period where some relevant reproduction parameters were investigated (Unnamed author, 2015). The results showed no systemic toxicity effects and the No Observed Adverse Effect level (NOAEL) was determined as >500 mg/kg/day (highest dose tested). No treatment related changes in sperm count and motility were observed. Vaginal lavages which were taken early morning during the 3 week period from all females, prior to termination of the animals showed no treatment related changes in the oestrus cycle. In addition, there were no dose related changes in organ weight of ovaries, seminal vesicles, testis, ureter, uterus, vagina in comparison to control animals.

10.3.2 Adverse effects on development

Table 14: Summary table of animal studies on adverse effects on development

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
Oral, by gavage, OECD TG 414, SD rats, 20 females/dose	TBNPA 0, 100, 300, 500/(1000) mg/kg bw/d dosed on GD 6-19	In a Prenatal Developmental Toxicity Study in SD rats, the highest dose were reduced from 1000 to 500 mg/kg bw/day due to post dosing toxicity, and two animals were killed due to animal welfare reasons. Transient effects on body weight was seen in the high dose group, and some cases of minor abnormalities in the ossification of pelvic bones were observed in the medium and high dose groups, but in all cases within the historical controls from the test laboratory. Body weight at sacrifice and absolute and relative organ weight data for the parental animals: At 1000 / 500 mg/kg/day mean body weight loss (2%) was observed during Days 6-7 of gestation (after the first dose). On Days 6-9 dams in the high dose group had lower food consumption (4 g/day lower, stat.	Study report unnamed, 2016

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, dose levels duration of exposure	Results	Reference
		sign) and body weight gain compared to the controls. The body weight gain was 8, 10 and 6 g in the control, 500 mg/kg/day dose, 1000 mg/kg/day dose, respectively. This was due to both lower gravid uterine weight in the dosed animals and lower body weight gain when the maternal body weight was adjusted for the weight of the uterus. No effects was seen on maternal body weight in the low and medium dose groups. Mean number of live pups (litter size): Embryo-fetal survival was considered to have been unaffected by treatment at 100, 300 or 1000 / 500 mg/kg/day with mean numbers of implantations, resorptions, live young and percentages of sex ratio and pre- and post-implantation loss being similar to control values across all treated groups. Mean litter or pup weight by sex and with sexes combined: Mean placental, male, female and overall fetal weights / litter weight at 100, 300 or 1000 / 500 mg/kg/day were similar to controls and unaffected by treatment. External, soft tissue and skeletal malformations and other relevant: alterations: No dose-related major fetal abnormalities were found. In the medium dose group, there was a slightly increased incidence of the minor abnormalities delayed / incomplete ossification / unossified pelvic bones compared to concurrent control (11 fetuses from 7 litters; compared to 4 fetuses from 3 litters in the Controls and 15 fetuses from 12 litters in HCD). In the high dose group there was a slightly increased incidence of the minor abnormalities delayed / incomplete ossification / unossified pelvic bones compared to concurrent control in 12 fetuses from 8 litters. This was also within the concurrent Historical Control Data (HCD) range and was considered unrelated to treatment. At 1000 mg/kg/day there was a slightly increased incidence of other minor abnormalities compared to Controls, but all within the historical controls.	

10.3.3 Short summary and overall relevance of the provided information on adverse effects on development

In a prenatal developmental toxicity study in SD rats, the highest dose was reduced from 1000 to 500 mg/kg bw/day due to post dosing toxicity. Two animals were killed due to animal welfare reasons. No clear findings of developmental toxicity was observed. Minor effects on ossification in the medium and high dose groups were within the historical controls. More details in the studies have not been available to the dossier submitter and it was considered not necessary to request the full study report from the registrant.

10.3.4 Comparison with the CLP criteria

The data from the prenatal developmental toxicity study were not considered sufficiently severe to meet the criteria for classification.

10.3.5 Conclusion on classification and labelling for reproductive toxicity

The data for reproductive toxicity is inconclusive. The results from the repeated dose toxicity studies do not warrant classification. The results from the prenatal developmental toxicity study do not warrant classification.

10.4 Specific target organ toxicity-single exposure

Not evaluated in this dossier.

10.5 Specific target organ toxicity-repeated exposure

Table 15: Summary table of animal studies on STOT RE

Method, guideline, deviations if any, species, strain, sex, no/group	Test substance, route of exposure, dose levels, duration of exposure	Results	Reference

OECD TG 407 (Repeated Dose 28-Day Oral Toxicity in Rodents), GLP compliant.	TBNPA (97% pure), Oral by gavage. Corn oil vehicle Doses: 30, 150 or 500 mg/kg/day Dosed daily for 28 days 14 days recovery for the recovery group	Sprague-Dawley rats, male and female A test-article related response was evident in the liver (predominantly at ≥150 mg/kg/day) as indicated by increased organ weight and a correlative microscopic finding of slight minimal centrilobular hypertrophy. The effects were transient and minor changes to liver and kidney weight and salts in blood. Organ weights: A test-substance related response increased liver weight was evident (predominantly at ≥150 mg/kg/day), and a correlative microscopic finding of slight minimal centrilobular hypertrophy were reported. Full or partial recovery were seen at the end of the study. Slightly higher kidney weights were observed in females in the low dose group and in males in the medium dose group. All findings showed full recovery, with the exception of kidney weights which remained slightly high at the end of the recovery period for males in the top dose group. Clinical signs: In the top dose group, frequent incidences of chin rubbing and/or salivation (sometimes reported as excessive) was reported at some point from week 2 in all females and in the majority of males. In one female in the medium dose group, single incidences of chin rubbing and excessive salivation occurred on days 11 and 16, respectively. The signs were occurred following dosing and dissapeared 1-2 hours after. Females receiving 500 mg/kg/day displayed transient unsteady gait approximately 20 minutes after completion of dosing the group on Days 27 and 28 of treatment and one high dose female (No. 54) appeared to be less active than the other females within the group (on Day 28) at the same time. These were transient signs which had resolved by 1 to 2 hours after dosing. Clinical biochemistry findings: At the end of 4 weeks treatment, there was a transient and slightly low sodium concentration (0.98X Control) and slightly high potassium concentration (1.18X Control) in top dose males.	Study report unnamed, 2015 Key study 2 in the dissemination site
14 days oral dosing by gavage. Necropsy on day 15. No guidelines followed	TBNPA (98.4% pure). Oral by gavage. Corn oil vehicle Doses: 0, 100, 300 and 1000 mg/kg/day	Crj: CD(SD) rats, male and female Males receiving 1000 mg/kg/day were killed early on Day 4 of treatment for animal welfare reasons. Urine staining occurred in males and females in the top dose group.	Study report unnamed, 2011 Key study 1 in the dissemination site

30 days feeding study. No GLP/guidelines	TBNPA (98% pure). Given in feed. 0, 10, 30, 100 and 300 mg/kg bw/day nominal in feed	Sprague-Dawley rats, male and female Effects in male rats from 100 mg/kg bw/day included kidney damage and urine bladder hyperplasia. No effects in females.Treatment-related effects were: increase in serum urea nitrogen content in male rats receiving 300 mg/kg/day TBNPA in their diet, and renal tubular damage and generalized hyperplasia of the mucosal lining of urinary bladders of male rats reciving 300 and 100 mg/kg/day of FR-1360 in their diet. No changes were noted in any of the female rats in this study.	Study report unnamed, 1973 Supporting study 3 in the dissemination site

10.5.1 Short summary and overall relevance of the provided information on specific target organ toxicity – repeated exposure

Three studies are available, one of them is carried out in accordance with OECD TG 407 with exposure for 28 days followed by a 2 week recovery period (2015). Based on the available studies, the target organs seem to be liver, kidneys and urine bladder after exposure to TBNPA. The effects were mild and reversible, except for one of the studies (2011) where the high dose on day 4 lead to high acute toxicity making it necessary to kill animals for animal welfare reasons. No significant toxic effects were observed.

10.5.2 Comparison with the CLP criteria

The results from the repeated dose toxicity studies do not warrant classification, as there were no significant toxic effects observed. The observations in the repeated dose toxicity studies were not considered sufficiently severe to meet the criteria for classification.

10.5.3 Conclusion on classification and labelling for STOT RE

Based on the available data, no classification is warranted with regards to STOT-RE.

10.6 Aspiration hazard

Not evaluated in this dossier.

11 EVALUATION OF ENVIRONMENTAL HAZARDS

Not evaluated in thos dossier.

12 EVALUATION OF ADDITIONAL HAZARDS

Not evaluated in this dossier.

13 ADDITIONAL LABELLING

Not relevant

14 REFERENCES

Dunnick, J. K., Heath, J. E., Farnell, D. R., Prejean, J. D., Haseman, J. K. & Elwell, M. R. (1997). *Carcinogenic activity of the flame retardant , 2,2-bis(bromomethyl)-1,3-propanediol in rodents, and comparison with the carcinogenicity of other NTP brominated chemicals. Toxicologic Pathology* 25, 541-548.

Galloway, S. M., Armstrong, M. J., Reuben, C., Colman, S., Brown, B., Cannon, C., Bloom, A. D., Nakamura, F., Ahmed, M., Duk, S., Rimpo, J., Margolin, B. H., Resnick, M. A., Anderson, B. & Zeiger, E. (1987). *Chromosome aberrations and sister chromatid exchanges in chinese hamster ovary cells: evaluations of 108 chemicals. Environmental and Molecular Mutagenesis* **10**, 1-35.

Kong, W., Gu, P., Knudsen, G. A. & Sipes, I. G. (2013). *Comparison of 2,2-bis(bromomethyl)-1,3-propanediol inducedgenotoxicity in UROtsa cells and primary rat hepatocytes: Relevanceof metabolism and oxidative stress. Toxicology Letters* **222**, 273-279.

Kong, W., Kuester, R. K., Gallegos, A. & Sipes, I. G. (2011). *Induction of DNA damage in human urothelial cells by thebrominated flame retardant 2, 2-Bis (bromomethyl)-1, 3-propanediol: role of oxidative stress. Toxicology. 2011 December 18; 290(2-3): 272–278.*

Mortelmans, K., Haworth, S., Lawlor, T., Speck, W., Tainer, B. & Zeiger, E. (1986). *Salmonella mutagenicity tests: II. Results from the testing of 270 chemicals. Environmental Mutagenesis* **8**, 1-119.

National Toxicology Program (NTP) (1996). *Toxicology and carcinogenesis studies of 2,2-bis(bromomethyl)-1,3-propanediol (FR-1138 ®) (CAS NO. 3296-90-0) in F344/N rats and B6C3F1 mice (feed studies). Natl Toxicol Program Tech Rep Ser* **452**, 1-465.

Norwegian Environment Agency (2018). *Risk Management Option Analysis Conclusion Document 2,2-bis(bromomethyl)propane-1,3-diol (BMP) and structurally similar substances, small brominated alkylated alcohols (SBAA):* https://echa.europa.eu/rmoa/-/dislist/details/0b0236e1809bb18d

Norwegian Environment Agency (2017). *CLH-report 2,2-bis(bromomethyl)propane-1,3-diol:* https://echa.europa.eu/documents/10162/087072a8-71c4-26b5-98a2-2ef9bed6f176

Wada, K., Yoshida, T., Takahashi, N. & Matsumoto, K. (2014). *Effects of seven chemicals on DNA damage in the rat urinary bladder:A comet assay stud. Mutation research. Genetic toxicology and environmental mutagenesis* **769**, 1-6.

Wedebye et al. (2016). *Category approach for selected brominated flame retardants. The Danish Environmental Protection Agency. ISBN no. 978-87-93435-90-2*

Zeiger, E., Anderson, B., Haworth, S., Lawlor, T. & Mortelmans, K. (1992). *Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals*. *Environmental and Molecular Mutagenesis* **19**, 2-141.

Mutagenicity in vitro:

Unnamed author (2004), Study report, REACH registration: https://echa.europa.eu/registration-dossier/-/registered-dossier/6484/7/7/2

Unnamed author (2004), Study report, REACH registration: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/6484/7/7/2/?documentUUID=1de76583-e4ca-4077-803c-7bf6dc92ad76

Unnamed author (1996), Study report, REACH registration: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/6484/7/7/2/?documentUUID=e115ea71-ed77-449f-9943-6bca66b27e3a

Unnamed author (1996b), REACH registration: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/6484/7/7/2/?documentUUID=e115ea71-ed77-449f-9943-6bca66b27e3a

Mutagenicity in vivo:

Unnamed author (2007a), Study report, REACH registration: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/6484/7/7/3

Unnamed author (2007b), Study report, REACH registration: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/6484/7/7/3/?documentUUID=ca22dcb7-3231-4dd3-95f8-44fad85f4c68

Reproductive toxicity:
Unnamed author (2015), Study report, REACH registration:
https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/6484/7/6/2/?documentUUID=bdfdd675-2048-4263-be0c-16a9ce3e7a9b
Unnamed author (2016), Study report, REACH registration: https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/6484/7/9/3

STOT RE:
Unnamed author (2015), Study report, REACH registration:
https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/6484/7/6/2/?documentUUID=bdfdd675-2048-4263-be0c-16a9ce3e7a9b
Unnamed author (2011), Study report, REACH registration:
https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/6484/7/6/2/?documentUUID=bdfdd675-2048-4263-be0c-16a9ce3e7a9b
Unnamed author (1973), Study report, REACH registration:
https://www.echa.europa.eu/web/guest/registration-dossier/-/registered-dossier/6484/7/6/2/?documentUUID=ebb534b0-675a-410f-a02e-7827a8c45906

15 ANNEXES

ANNEX I to the CLH report