CLH report

Proposal for Harmonised Classification and Labelling

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

Substance Name:

Butanone Oxime

EC Number: **202-496-6**

CAS Number: **96-29-7**

Index Number: **616-014-00-0**

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CONTENTS

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING 4

1.1 SUBSTANCE 4
1.2 HARMONISED CLASSIFICATION AND LABELLING PROPOSAL 4
[1] CONVERTED ACUTE TOXICITY POINT ESTIMATE FROM TABLE 3.1.2 OF CLP 4
1.3 PROPOSED HARMONISED CLASSIFICATION AND LABELLING BASED ON CLP REGULATION 5

2 BACKGROUND TO THE CLH PROPOSAL 7

2.1 HISTORY OF THE PREVIOUS CLASSIFICATION AND LABELLING 7
2.2 SHORT SUMMARY OF THE SCIENTIFIC JUSTIFICATION FOR THE CLH PROPOSAL 7
2.3 CURRENT HARMONISED CLASSIFICATION AND LABELLING 10
2.4 CURRENT SELF-CLASSIFICATION AND LABELLING 10

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL 11

Part B.

SCIENTIFIC EVALUATION OF THE DATA 12

1 IDENTITY OF THE SUBSTANCE 12

1.1 NAME AND OTHER IDENTIFIERS OF THE SUBSTANCE 12
1.2 COMPOSITION OF THE SUBSTANCE 13
1.2.1 Composition of test material 13
1.3 PHYSICO-CHEMICAL PROPERTIES 14

2 MANUFACTURE AND USES 15

2.1 MANUFACTURE 15
2.2 IDENTIFIED USES 15

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES 15

4 HUMAN HEALTH HAZARD ASSESSMENT 16

4.1 TOXICOKINETICS (ABSORPTION, METABOLISM, DISTRIBUTION AND ELIMINATION) 16
4.1.1 Non-human information 16
4.1.2 Human information 17
4.1.3 Summary and discussion on toxicokinetics 17
4.2 ACUTE TOXICITY 19
4.2.1 Non-human information 19
4.2.2 Human information 22
4.2.3 Summary and discussion of acute toxicity 22
4.2.4 Comparison with criteria 24
4.2.5 Conclusions on classification and labelling 25
4.3 SPECIFIC TARGET ORGAN TOXICITY – SINGLE EXPOSURE (STOT SE) 25
4.3.1 Summary and discussion of Specific target organ toxicity – single exposure 27
4.3.2 Comparison with criteria 28
4.3.3 Conclusions on classification and labelling 29
4.4 IRRITATION 29
4.4.1 Skin irritation 29
4.4.2 Eye irritation 31
4.4.3 Respiratory tract irritation 33
4.5 CORROSIVITY 33
4.6 SENSITISATION 34
4.6.1 Skin sensititsation 34

4.6.2 Respiratory sensitisation ... *37*
4.7 REPEATED DOSE TOXICITY ... 38
4.7.1 Non-human information ... *41*
4.8 SPECIFIC TARGET ORGAN TOXICITY (CLP REGULATION) – REPEATED EXPOSURE (STOT-RE) ... 49
4.8.1 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT-RE according to CLP Regulation ... *49*
4.8.2 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT-RE ... *51*
4.8.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT-RE ... *53*
4.9 GERM CELL MUTAGENICITY (MUTAGENICITY) ... 54
4.9.1 Non-human information ... *56*
4.9.2 Human information ... *57*
4.9.3 Other relevant information ... *57*
4.9.4 Summary and discussion of mutagenicity ... *57*
4.9.5 Comparison with criteria ... *58*
4.9.6 Conclusions on classification and labelling ... *59*
4.10 CARCINOGENICITY ... 60
4.10.1 Non-human information ... *61*
4.10.2 Human information ... *66*
4.10.3 Other relevant information ... *66*
4.10.4 Summary and discussion of carcinogenicity ... *66*
4.10.5 Comparison with criteria ... *69*
4.10.6 Conclusions on classification and labelling ... *71*
4.11 TOXICITY FOR REPRODUCTION ... 72
4.11.1 Effects on fertility ... *73*
4.11.2 Developmental toxicity ... *76*
4.11.3 Other relevant information ... *76*
4.11.4 Summary and discussion of reproductive toxicity ... *76*
4.11.5 Comparison with criteria ... *77*
4.11.6 Conclusions on classification and labelling ... *79*
4.12 OTHER EFFECTS ... 80
5 ENVIRONMENTAL HAZARD ASSESSMENT ... 80
6 OTHER INFORMATION ... 80
7 REFERENCES ... 81
8 ANNEXES ... 85

Part A.

1 PROPOSAL FOR HARMONISED CLASSIFICATION AND LABELLING

1.1 Substance

Table 1: Substance identity

Substance name:	***butanone oxime***
EC number:	***202-496-6***
CAS number:	***96-29-7***
Annex VI Index number:	***616-014-00-0***
Degree of purity:	**-**
Impurities:	**-**

1.2 Harmonised classification and labelling proposal

Table 2: The current Annex VI entry and the proposed harmonised classification

	Classification		SCL/ATE/M-Factor
Current entry in Annex VI, CLP Regulation	Acute Tox. 4* Skin Sens. 1 Eye Dam. 1 Carc. 2	H312 H317 H318 H351	
Current proposal for consideration by RAC	Acute Tox. 3 Acute Tox. 4 Skin Sens. 1B Eye Dam. 1 Carc. 1B STOT SE 3	H301 H312 H317 H318 H350 H336	Oral: ATE = 100 mg/kg bw[1] Dermal: ATE = 1848 mg/kg bw[2]
Resulting harmonised classification (future entry in Annex VI, CLP Regulation)	Acute Tox. 3 Acute Tox. 4 Skin Sens. 1B Eye Dam. 1 Carc. 1B STOT SE 3	H301 H312 H317 H318 H350 H336	Oral: ATE = 100 mg/kg bw[1] Dermal: ATE = 1848 mg/kg bw[2]

[1] Converted acute toxicity point estimate from Table 3.1.2 of CLP
[2] LD_{50} value for the dermal route

1.3 Proposed harmonised classification and labelling based on CLP Regulation

Table 3: Proposed classification according to the CLP Regulation

CLP Annex I ref	Hazard class	Proposed classification	Proposed SCLs and/or M-factors	Current classification [1)]	Reason for no classification [2)]
2.1.	Explosives	None		None	Not assessed in this dossier
2.2.	Flammable gases	None		None	Not assessed in this dossier
2.3.	Flammable aerosols	None		None	Not assessed in this dossier
2.4.	Oxidising gases	None		None	Not assessed in this dossier
2.5.	Gases under pressure	None		None	Not assessed in this dossier
2.6.	Flammable liquids	None		None	Not assessed in this dossier
2.7.	Flammable solids	None		None	Not assessed in this dossier
2.8.	Self-reactive substances and mixtures	None		None	Not assessed in this dossier
2.9.	Pyrophoric liquids	None		None	Not assessed in this dossier
2.10.	Pyrophoric solids	None		None	Not assessed in this dossier
2.11.	Self-heating substances and mixtures	None		None	Not assessed in this dossier
2.12.	Substances and mixtures which in contact with water emit flammable gases	None		None	Not assessed in this dossier
2.13.	Oxidising liquids	None		None	Not assessed in this dossier
2.14.	Oxidising solids	None		None	Not assessed in this dossier
2.15.	Organic peroxides	None		None	Not assessed in this dossier
2.16.	Substance and mixtures corrosive to metals	None		None	Not assessed in this dossier
3.1.	**Acute toxicity - oral**	**Acute Tox. 3**	ATE = 100 mg/kg bw[3]	**None**	**Harmonized classification proposed**
	Acute toxicity - dermal	**Acute Tox. 4**	ATE = 1848 mg/kg bw[4]	**Acute Tox. 4***	**Harmonized classification proposed**
	Acute toxicity - inhalation	None		None	Data conclusive but not sufficient

					for classification
3.2.	Skin corrosion / irritation	None		None	Data conclusive but not sufficient for classification
3.3.	**Serious eye damage / eye irritation**	**Eye Dam. 1**		**Eye Dam. 1**	**Harmonized classification proposed**
3.4.	Respiratory sensitisation	None		None	Data lacking
3.4.	**Skin sensitisation**	**Skin Sens. 1B**		**Skin Sens. 1**	**Harmonized classification proposed**
3.5.	Germ cell mutagenicity	None		None	Data conclusive but not sufficient for classification
3.6.	**Carcinogenicity**	**Carc. 1B**		**Carc. 2**	**Harmonized classification proposed**
3.7.	Reproductive toxicity	None		None	Data conclusive but not sufficient for classification
3.8.	**Specific target organ toxicity –single exposure**	**STOT SE 3**		**None**	**Harmonized classification proposed**
3.9.	Specific target organ toxicity – repeated exposure	None		None	Data conclusive but not sufficient for classification
3.10.	Aspiration hazard	None		None	Not assessed in this dossier
4.1.	Hazardous to the aquatic environment	None		None	Not assessed in this dossier
5.1.	Hazardous to the ozone layer	None		None	Not assessed in this dossier

[1)] Including specific concentration limits (SCLs) and M-factors
[2)] Data lacking, inconclusive, or conclusive but not sufficient for classification
[3)] Converted acute toxicity point estimate from Table 3.1.2 of CLP
[4)] LD_{50} value for the dermal route

Table 4: Proposed labelling based according to the CLP Regulation

	Labelling	Wording
Pictograms	GHS08 GHS06 GHS05	Health hazard Skull and crossbones Corrosion
Signal Word	Dgr	Danger
Hazard statements	H350 H301 H312 H318 H317 H336	May cause cancer Toxic if swallowed Harmful in contact with skin Causes serious eye damage May cause an allergic skin reaction May cause drowsiness or dizziness

Proposed notes assigned to an entry: None

2 BACKGROUND TO THE CLH PROPOSAL

2.1 History of the previous classification and labelling

Butanone oxime was previously discussed by the Technical Committee for Classification and Labelling (TC C&L) according to Directive 67/548/EEC. The Working Group on the Classification and Labelling of Dangerous Substances ECB in Ispra agreed on 19-21 January 2000 that butanone oxime should be classified with Carc. Cat. 3; R40 - Xn; R21 - Xi; R41 - R43, and agreed that classification for toxicity to reproduction is not warranted. Further it was decided that symbol Xn; R-phrases 21-40-41-43; and S-phrases (2-) 13-23-26-36/37/39 shall be added, but no Nota or specific concentration limits shall be set. This agreement was considered final and the proposal was sent to the European Commission, and was enacted by the Technical Progress Committee (TPC) for possible inclusion in a future ATP (amendments on technical progress).

Butanone oxime is listed by Index number 616-014-00-0 in Annex VI, Part 3, and Table 3.1 (list of harmonised classification and labelling of hazardous substances) of CLP. To date butanone oxime is legally classified as: Acute Tox. 4*, H312: Harmful in contact with skin; Skin Sens. 1, H317: May cause an allergic skin reaction; Eye Dam. 1, H318: Causes serious eye damage; and Carc. 2, H351: Suspected of causing cancer.

In July 2012 butanone oxime was proposed for substance evaluation (SEV) in compliance with Article 44(1) of the REACH Regulation. Butanone oxime is a high production volume chemical (> 1000 t/a) and is widely used with high exposure for workers. The SEV led to the conclusion that the existing harmonised classification and labelling of butanone oxime in CLP Annex VI should be revised with regard to carcinogenicity. The existing information on the toxicity of butanone oxime indicates that butanone oxime also meets the criteria for classification and labelling for acute oral toxicity and for narcotic effects according to CLP. Moreover, the results from skin sensitisation testing are sufficient for the allocation of butanone oxime into a sub-category.

For the purposes of this dossier all registrations available in October 2016 have been taken into account.

2.2 Short summary of the scientific justification for the CLH proposal

This proposal aims of an update of the existing harmonized classification and labelling of butanone oxime and of new entries with respect to human health hazards in CLP Annex VI.

Carcinogenicity

Butanone oxime is legally classified as carcinogen Category 2 according to CLP. The evaluation of the available data has verified the concern that a more severe classification regarding carcinogenicity is needed. The available data for carcinogenicity of butanone oxime do not comply with the legal classification of butanone oxime as carcinogen Category 2. In combined chronic toxicity/carcinogenicity studies in rats and mice exposed by inhalation to butanone oxime sufficient evidence of animal carcinogenicity was demonstrated. Two animal experiments using two species (rats and mice) resulted in clear evidence for carcinogenicity. A causal relationship has been established between butanone oxime and a statistically significant increased incidence of benign and malignant tumours. Being similar to OECD TG 453/EU B.33 both studies are well conducted and do not cast doubts about the relevance of the results. Tumour development was noted in rats

and mice exposed to relatively low concentrations of butanone oxime by inhalation for a period of up to two years.

Butanone oxime is thus considered to meet the criteria for classification and labelling as carcinogen Category 1B, H350 but not as Category 2, H351 according to CLP.

Acute toxicity - oral

The data from a preliminary dose range-finding study to a developmental toxicity study in rabbits have shown that butanone oxime induces lethality in this species (as assumed to haemolytic anaemia). In females (5/5) treated with 80 mg/kg bw butanone oxime starting on gestation day (GD) 6 mortalities were observed on GD8 until GD10. First deaths (2/5 females) occurred shortly after less than 48 hours after two dosages (cumulative 160 mg/kg bw). All 5 females were found dead until GD10. Taken together, from single dose studies in rats and from repeated dose studies in rabbits, rabbits appear to be more sensitive than rats to the acute toxic effects of butanone oxime. According to the Guidance on the application of the CLP-criteria, classification should be based on the lowest acute toxicity estimates (ATE) value available i.e. the lowest ATE in the most sensitive appropriate species tested. As specified in the guidance on haemolytic anaemia mortalities during days 0-3 in a repeated dose study should be considered for acute toxicity. Therefore, based on the LD_{50} value of ≤ 160 mg/kg bw and thus the ATE of 100 mg/kg bw (converted acute toxicity point estimate from table 3.1.2 of CLP) observed in a developmental toxicity study in rabbits, butanone oxime fulfils the criteria for classification as Acute Tox. 3, H301: Toxic if swallowed according to CLP (Annex I, Part 3, Table 3.1 Acute toxicity: 50 < Category 3 ≤ 300 mg/kg).

Acute toxicity - dermal

Based on the review of the available experimental data for acute dermal toxicity of butanone oxime, it is concluded that butanone oxime meets the criteria for classification and labelling as Acute Tox. 4, H312 (CLP) and the reference indicating minimum classification "(*)" is no longer necessary. The legal classification of butanone oxime is confirmed for Acute Tox. 4, H312 (Harmful in contact with skin).

Skin sensitisation

Butanone oxime has shown a clear evidence of skin sensitisation in guinea pigs (GPMT and Buehler assay). The results of a mouse ear swelling test (MEST) with butanone oxime have shown a sensitising response of 40 % and a swelling rate of 120 % for the mouse ear. Based on this animal model system a moderate potency for skin sensitisation is determined for butanone oxime. Based on available data, butanone oxime is classified as skin sensitizer category 1 (legal classification).

In comparison to the given criteria for the hazard category and sub-categories for skin sensitisation according to CLP butanone oxime fulfils the criteria for classification in the hazard class as skin sensitizer sub-category 1B, H317: May cause an allergic skin reaction, because a skin sensitisation response of ≥ 30 % at > 1.0 % i.d. induction dose was observed in the adjuvant type test method (GPMT); and of ≥ 15 % at > 20 % topical induction dose in the non-adjuvant type test method (Buehler assay).

Serious eye damage / eye irritation

The available data on serious eye damage/eye irritation do fulfil the criteria laid down in CLP, and the legal classification as 'Irreversible effects on the eye' Category 1, H318 is warranted.

Specific target organ toxicity – single exposure

Further the evaluation of data has verified the concern that butanone oxime caused transient target organ effects. There were changes in neurobehavioral function including narcotic effects. In acute oral, inhalation and dermal toxicity studies and also in studies with repeated exposure to butanone oxime in different animal species, transient and reversible changes in neurobehavioral function consistent with central nervous system depression, but no evidence of cumulative neurotoxicity was detected. Based on these data there is reasonable concern and butanone oxime should be classified additionally due to its narcotic effects according to CLP.

In rats single oral doses of ≥ 300 mg/kg bw butanone oxime administered by gavage produced narcotic effects. In the acute inhalation toxicity study with rats a strong transient narcotic effect occurred in both sexes at 4.83 mg/L/4h. In a dermal acute toxicity study in rabbits butanone oxime produced significant effects on the central nervous system (CNS) at single doses of 185 mg/kg bw and higher, and transient narcosis occurring during the first 48 hours following exposure at the low dose level of 18 mg/kg bw. Also in specific investigations transient and reversible functional disturbances in nervous system function consistent with CNS depression were observed in rats after single or repeated oral application of butanone oxime. Based on these data, butanone oxime meets the criteria for classification and labelling as a specific target organ toxicant (single exposure) of Category 3 for narcotic effects (STOT SE 3, H336: May cause drowsiness or dizziness) according to CLP (Annex I, Part 3.8.2.2.2).

In Table 5 the following hazard classes for butanone oxime are proposed.

Table 5: Proposed classification and labelling of butanone oxime according to CLP

Hazard Class and Category Code(s)	Hazard Statement Code(s)	Pictograms, Signal Word
Acute Tox. 3	H301: Toxic if swallowed	GHS06: Skull and crossbones, Danger
Acute Tox. 4	H312: Harmful in contact with skin	GHS07: Exclamation mark, Warning
Eye Dam. 1	H318: Causes serious eye damage	GHS05: Corrosion, Danger
Skin Sens. 1B	H317: May cause an allergic skin reaction	GHS07: Exclamation mark, Warning
Carc. 1B	H350: May cause cancer	GHS08: Health hazard, Danger
STOT SE 3	H336: May cause drowsiness or dizziness	GHS07: Exclamation mark, Warning

2.3 Current harmonised classification and labelling

Table 6: Entry in Annex VI of CLP

Classification		Labelling			Specific Concentration limits, M-Factors	Notes
Hazard Class and Category Code(s)	Hazard Statement Code(s)	Hazard Statement Code(s)	Supplementary Hazard Statement Code(s)	Pictograms, Signal Word Code(s)		
Acute Tox. 4*	H312	H312		GHS07		
Skin Sens. 1	H317	H317		GHS05		
Eye Dam. 1	H318	H318		GHS08		
Carc. 2	H351	H351		Dgr		

2.4 Current self-classification and labelling

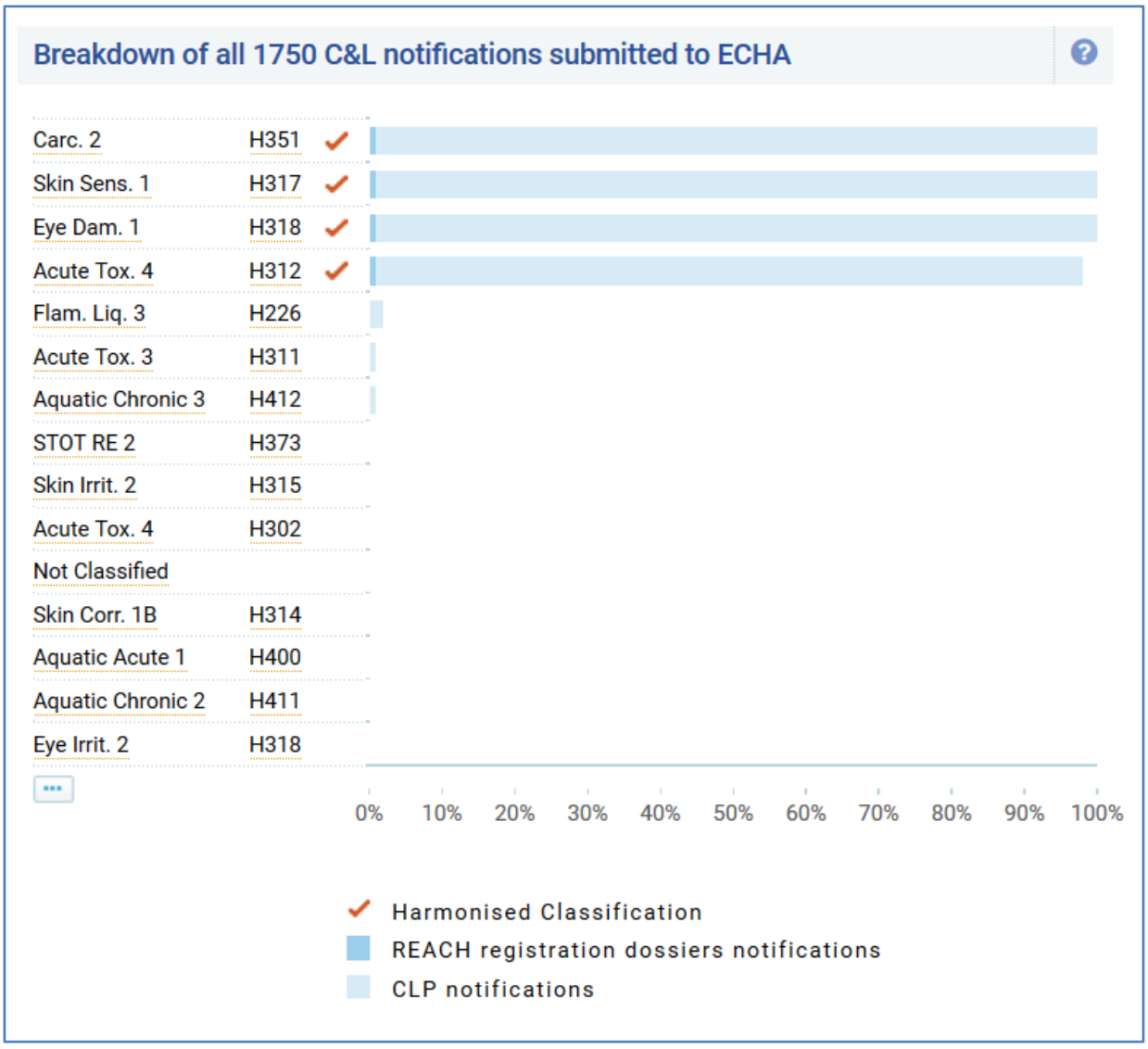


Figure 1: C&L notifications submitted to ECHA (www.echa.eu, May 2017)

3 JUSTIFICATION THAT ACTION IS NEEDED AT COMMUNITY LEVEL

In July 2012 butanone oxime was proposed for substance evaluation (SEV) in compliance with Article 44(1) of the REACH Regulation. The SEV led to the conclusion that the existing harmonised classification and labelling of butanone oxime in CLP Annex VI should be revised with regard to carcinogenicity. The existing information on the toxicity of butanone oxime further indicated that butanone oxime also meets the criteria for classification and labelling for acute oral toxicity and for narcotic effects according to CLP. Moreover, the results from skin sensitisation testing are sufficient for the allocation of butanone oxime into a sub-category.

Butanone oxime has CMR properties, thus a harmonized classification and labelling of this hazard class according to Article 36 of CLP is justified. Furthermore, a harmonized classification of the other proposed non-CMR hazard classes is also justified, since new hazard information was available suggesting that a change in harmonised classification is necessary. The self-classification of a substantial number of C&L notifiers is, moreover, diverging (16 different aggregated notifications in the C&L inventory), which also justifies the proposal for harmonised classification of the non-CMR hazard classes, especially regarding butanone oxime being a high production volume chemical (> 1000 t/a), which is widely used with high exposure for workers.

Part B.

SCIENTIFIC EVALUATION OF THE DATA

1 IDENTITY OF THE SUBSTANCE

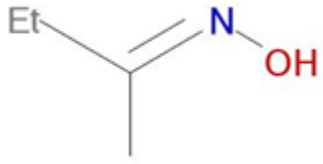
1.1 Name and other identifiers of the substance

Table 7: Substance identity

EC number:	202-496-6
EC name:	butanone oxime
CAS number (EC inventory):	96-29-7
CAS number:	96-29-7
CAS name:	2-Butanone, oxime
IUPAC name:	butan-2-one oxime
CLP Annex VI Index number:	616-014-00-0
Molecular formula:	C_4H_9NO
Molecular weight range:	87.12 g/mol

Structural formula:

There is only one major isomer for butanone oxime (MEKO), which is trans/anti.



1.2 Composition of the substance

Table 8: Constituents (non-confidential information)

Constituent	Typical concentration	Concentration range	Remarks
Butanone oxime EC-No.: 202-496-6	Please see confidential annex or technical dossier		

Current Annex VI entry:

Table 9: Impurities (non-confidential information)

Impurity	Typical concentration	Concentration range	Remarks
none			

Current Annex VI entry:

Table 10: Additives (non-confidential information)

Additive	Function	Typical concentration	Concentration range	Remarks
none				

Current Annex VI entry:

1.2.1 Composition of test material

Please see 'Confidential Annex' or technical dossier

1.3 Physico-chemical properties

Table 11: Summary of physico - chemical properties

Property	Value	Reference	Comment (e.g. measured or estimated)
State of the substance at 20°C and 101,3 kPa	*clear colourless liquid of organic origin*	*experimental result* *ASTM D 1209*	*CONDEA Servo BV 1995*
Melting/freezing point	*-29.5°C*	*OECD Guideline 102*	*Timmermans, 1921*
Boiling point	*> 152°C at 1013 kPa*	*OECD Guideline 103*	*Quitzsch et al. 1965*
Relative density	0.92 at 20°C		*CRC Handbook of Data on Organic Compounds 1985*
Vapour pressure	*1.07 kPa at 20°C* *0.14 kPa at 20°C*	*equivalent or similar to* *OECD Guideline 104*	*Wypych 2008* *NTP 1999*
Surface tension		*In accordance with Column 2 of REACH Annex VII, the study does not need to be conducted, as surface activity is not expected based on the structure of the substance; nor is it a desired substance property.*	
Water solubility	*100000 mg/L at 25°C and pH 7*	*OECD Guideline 105*	*Handbook of environmental data on organic chemicals 1983*
Partition coefficient n-octanol/water	*0.63 at 25°C*	*equivalent or similar to* *OECD Guideline 117 (Partition Coefficient (n-octanol / water), HPLC Method)*	*EPIWIN Systpro Database 1992*
Flash point			
Flammability			
Explosive properties			
Self-ignition temperature			
Oxidising properties			

Granulometry	-	*In accordance with Column 2 of REACH Annex VII, the study does not need to be conducted, as the substance (a liquid) is manufactured and marketed in a non-solid form.*	
Stability in organic solvents and identity of relevant degradation products	*Butanone oxime is stable and miscible in alcohol, diethyl ether, CClF4, CCl2F2, CH2Cl2,*		*Copley et al. 1938*
Dissociation constant	*pKa: 12.45 at 25°C*	*equivalent or similar to OECD Guideline 112*	*King and Marion 1944*
Viscosity	*15 mPa s at 20°C*	*experimental result ASTM D 2196*	*OECD 2003*

The vapour pressure data show inconsistencies as a coefficient of 10 is between the given values. However, only few data are given in the technical dossier. For the value of 1.07 kPa a guideline is stated which is "equivalent or similar to OECD Guideline 104" However the exact method is not known. For the second value of 0.14 kPa no further information is stated in the technical dossier. However it is cited in studies of the US EPA and of the Canadian Environment. Therefore it could be assumed that this value should also be valid.

2 MANUFACTURE AND USES

2.1 Manufacture

Not relevant for this dossier.

2.2 Identified uses

By virtue of its anti-skinning properties butanone oxime is used in formulations of alkyd paints, primers, varnishes and coatings both for workers and consumers.

3 CLASSIFICATION FOR PHYSICO-CHEMICAL PROPERTIES

Not evaluated in the scope of this dossier.

4 HUMAN HEALTH HAZARD ASSESSMENT

4.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

4.1.1 Non-human information

For basic toxicokinetics results from four experimental studies are available. For dermal absorption one study is available. In all studies butanone oxime was used as test material.

Basic toxicokinetics

In the studies of Burka et al. (1998) and NTP (1999) the extent of absorption was estimated. The disposition of ^{14}C-butanone oxime (purity: ~ 96 %) was determined in the male F344 rat following a single intravenous injection of 2.7 mg/kg bw butanone oxime. After administration, tissues and excreta of rats were collected and analysed for radioactivity. ^{14}C-butanone oxime was primarily excreted as CO_2 (48.8 %), via urine (21.4 %), and as exhaled volatiles (11.4 %). About 7 % of the administered radioactivity remained in the tissues after 72 hours. No tissue showed any marked accumulation of radioactivity.

The effect of dose on the rate and route of excretion of butanone oxime was also examined by Burka et al. (1998) and NTP (1999). The disposition of ^{14}C-butanone oxime was determined in the male F344 rat following single oral (gavage) administration of 2.7, 27, and 270 mg/kg bw. After administration, tissues and excreta of rats in each group were analysed for radioactivity. ^{14}C-butanone oxime was readily absorbed from the gastrointestinal tract and was extensively metabolized to CO_2 (50-70 %), mostly in the first 24 h after dosing. Excretion in urine increased with increasing dose and ranged from about 13 % (2.7 mg/kg bw) to 26 % (270 mg/kg bw). Respiratory excretion as volatiles was 5-18 % (increased as the dose increased). As excretion in CO_2 decreased with dose, excretion in urine and as volatiles increased. Excretion in faeces was less than 2 % for each dose. Total recoveries of radioactivity were approximately 90 % for each dose. Accumulation of radioactivity in the tissues was 5-7 % after 72 hours of dosing, with no tissue demonstrating any marked accumulation of radioactivity.

Metabolite profile in urine, 0-8 h after dosing of 270 mg/kg bw butanone oxime: 5 polar metabolites were identified that could only be partially resolved by anion exchange chromatography (CO_2, methyl ethyl ketone (MEK), glucurunides, and other polar metabolites). Incubation with glucuronidase, but not sulphatase, changed the urinary metabolic profile. MEK was a major component in the volatiles. The glucuronide conjugates of butanone oxime and its metabolites or other polar metabolites were primarily excreted in urine (Burka et al. 1998).

The biotransformation of butanone oxime (purity: 99.5 %) in comparison to acetoxime (CAS 127-06-0) in vivo and in vitro was evaluated and the capacity to catalyse these reactions was compared in different animal species and humans (Völkel et al. 1999; TL 22, 2000, unpublished study report, confidential). The biotransformation of butanone oxime was studied in liver microsomes and cytosol from male and female rats, mice and several human liver samples. The chemical reactivity of the postulated butanone oxime-metabolites was characterised. Butanone oxime was found to be oxidized to butane-2 nitronate by microsomal monooxygenases but at very low rates. No sex differences in the rates of microsomal oxidation of butanone oxime to butane 2-nitronate were noted. The hypothesized biosynthesis of methyl ethyl ketoxime *O*-sulfate or acetoxime *O*-sulfate in liver sub-cellular fractions from corresponding nitronates or oximes did not occur at all or occurred

at very low rates since formation of the stable *O*-sulfate could not be demonstrated using acetoxime and butanone oxime or propane 2-nitrate and butane 2-nitronate as substrates in the presence of appropriate cofactors.

Additionally, the ability of butanone oxime to induce DNA and RNA-modifications was studied in male and female rats exposed to butanone oxime by inhalation. No increase in modifications was detected in DNA isolated from rats exposed to butanone oxime of 1000 ppm (3.6 mg/L) for 6 hours. An increase in 8-aminoguanosine was observed in liver RNA from rats exposed to butanone oxime to a greater extent in males than in females.

The toxicokinetic studies demonstrated the existence of two and suggested a possible third metabolic pathway for butanone oxime in the rat, the major pathway being the hydrolysis of butanone oxime to MEK. One of the minor pathways appears to be a P450 mediated oxidation of butanone oxime to butane-2 nitronate and the second a reduction of butanone oxime. No quantitative sex differences in these pathways were identified.

The disposition of butanone oxime in Swiss Webster pregnant mice, which received a single oral dose of ^{14}C-butanone oxime on GD14 (Gestation day 14), was evaluated by autoradiography at selected time points: 20 minutes, 1, 3, 9 and 24 hours (TL 15, 1981, unpublished study report, confidential). Nasal epithelium and the liver had the highest concentrations of radioactivity. The nasal epithelium showed a remarkably rapid and persistent affinity for the material, high concentrations were found at all time intervals studied. Tissues which showed an increasing relative concentration with time were bone marrow, spleen, seromucous and salivary glands, Harder's gland, intestinal wall, mammary ducts, and foetus. The concentration in the pancreas peaked after 3 hours and then declined. There was apparent absorption of the compound and/or metabolites by the liver and kidney. Urine and bile contained considerable radioactivity throughout the course of the study. There was minimal radioactivity in the contents of the intestine.

Dermal absorption

The dermal absorption and disposition of ^{14}C-butanone oxime was determined in male F344 rats following single dermal administration of 2.7 and 270 mg/kg bw butanone oxime. Dose sites were protected from grooming by a non-occlusive foam appliance with a cloth cover and a metal shield. After administration, tissues, including application site and excreta of rats in each group were analysed for radioactivity (Burka et al. 1998; NTP 1999). In the 72 hours after dermal application of ^{14}C-butanone oxime, 13 % of the 2.7 mg/kg bw dose and 26 % of the 270 mg/kg bw dose were absorbed. No tissue demonstrated marked accumulations of radioactivity.

4.1.2 Human information

No information is available on absorption, distribution, metabolism, or excretion studies of butanone oxime in humans.

4.1.3 Summary and discussion on toxicokinetics

Data on the toxicokinetics of butanone oxime was obtained from animal testing. No data were found on the toxicokinetics of butanone oxime after exposure by inhalation. No information is available on the toxicokinetics of butanone oxime in humans.

Absorption

After a single oral (gavage) administration of 2.7, 27, or 270 mg/kg bw, ^{14}C-butanone oxime was readily absorbed (about 100 %) from the gastrointestinal tract and was primarily converted to CO_2 (71 %), mostly in the first 24 hours after dosing. During 72 hours of exposure, 13 % of a 2.7 mg/kg bw dose and 26 % of a 270 mg/kg dose were absorbed when administered dermally.

Distribution

Distribution of oral and intravenous administered dose of 2.7 mg/kg bw butanone oxime to rats were strikingly different, with less conversion to CO_2 in the intravenous application than by the oral administration, 49 % or 71 %, respectively. The decrease in excretion as CO_2 following intravenous administration was offset by increases in excretion in urine and as volatiles. A comparison of dermal and intravenous data indicates that the relative distribution of the absorbed doses in the dermal studies into urine, CO_2 and tissues was similar to those of the intravenous doses. After a single intravenous injection of 2.7 mg/kg bw butanone oxime to male F344 rats, about 7 % of the administered radioactivity remained in the tissues after 72 hours. The distribution of radioactivity into individual tissues was also similar to that found after intravenous administration. Radioactivity was detected in all examined tissues (adipose, blood, kidney, liver, muscle, skin and testis) 72 hours post-dosing. About 5-7 % of the administered radioactivity remained in the major tissues after 72 hours. None of the tissue demonstrated any marked accumulation of radioactivity. Therefore it can be concluded that butanone oxime does not accumulate in tissues.

In a further study the distribution of butanone oxime in Swiss Webster pregnant mice receiving a single oral dose of ^{14}C-butanone oxime on GD14 was evaluated. The highest concentrations of radioactivity were detected in the nasal epithelium and the liver. The nasal epithelium showed a rapid and persistent affinity for the material, and high concentrations were found at all-time intervals studied. Organs and tissues which showed an increasing relative concentration with time were bone marrow, spleen, seromucous and salivary glands, Harder's gland, intestinal wall, mammary ducts, and foetuses.

Metabolism

Butanone oxime is extensively metabolized, yielding CO_2, MEK, glucuronides, and other polar metabolites, and does not accumulate in tissues. The toxicokinetic studies of butanone oxime demonstrated the existence of two metabolic pathways and the possibility of a third one (based on acute oral, dermal and intravenous doses only). The major pathway is the hydrolysis of butanone oxime to MEK, and the second pathway is the oxidation of butanone oxime to butane 2-nitronate by microsomal monooxygenases, but this occurs at very low rates. No sex differences in the capacity to oxidize butanone oxime were observed in the species examined.

Excretion

Single oral doses of butanone oxime given at 2.7, 27 and 270 mg/kg bw to rats were extensively converted to CO_2 (~ 50-70 %), mostly in the first 24 hours post-dosing. Excretion in urine increased with increasing dose, and ranged from 13 % of the low dose to 26 % of the high dose. Excretion as volatiles was only 5-7 % of the dose for the two lower doses, but comprised an average of 18 % for the high dose. CO_2 remained the major metabolite as the dose increased, less of the administered

dose was excreted as CO_2 and relatively more was excreted in urine and as volatiles. Excretion in the faeces was < 2 % for each dose level.

Overall, ^{14}C-butanone oxime was readily absorbed from the gastrointestinal tract and the skin, underwent widespread uptake, was distributed over the entire body, was extensively metabolized to CO_2 and MEK, which were excreted via the lungs, and glucuronide conjugates of butanone oxime and its metabolites or other polar metabolites, which were excreted in urine and bile, and was not accumulate in tissues. Distribution of butanone oxime was clearly different following intravenous application compared with oral administration, particularly in the first few hours. Nearly twice as much radioactivity was eliminated by the first time point following oral administration of 2.7 mg/kg bw compared with intravenous application at the same dose, suggesting that a substantial portion of butanone oxime undergoes first-pass metabolism following oral administration. Following dermal administration, significantly greater amounts of volatiles were excreted than after gavage or intravenous administration. Butanone oxime and its metabolites were primary excreted via urine.

Butanone oxime biotransformation appears to be complex. The first activating step (likely P450 dependent oxidation) may have only a minor and dose-dependent contribution to the overall biotransformation of butanone oxime. The results indicate that nitronate formation alone is not sufficient to explain the carcinogenicity of butanone oxime.

4.2 Acute toxicity

4.2.1 Non-human information

4.2.1.1 Acute toxicity: oral

For the acute oral toxicity of butanone oxime results from 4 experimental studies in rats are used for evaluation. Additionally, mortalities observed in repeated dose toxicity studies during days 0-3 were considered relevant for assessing the acute toxicity of a compound. For that reason, the data from a developmental toxicity study (range-finding and main study) in rabbits (oral, gavage) (TL19, 1990b, unpublished study report, confidential; Derelanko et al. 2003) are discussed as deaths in animals were observed in these studies within 48 hours after first administration. In all studies butanone oxime was used as test material.

The results of all available experimental studies on acute toxicity after oral administration of butanone oxime are summarised in Table 12.

Table 12: Butanone oxime: Studies on acute oral toxicity (gavage)

Reference Species; strain; sex; method	LD_{50} / Results
TL8 (1991), unpublished study report, confidential; Schulze and Derelanko (1993) **Rat**; Sprague-Dawley; male, female (10/sex/dose) acute neurotoxicity study, GLP compliant Test substance:	**$LD_{50, rat\ m/f}$ > 900 mg/kg bw** Doses tested: 0, 100, 300 and 900 mg/kg bw 900 mg/kg bw (highest dose): no mortality; decreased activity 30-60 min after exposure LOEL = 300 mg/kg bw: based on transient neurobehavioral effects (impaired gait, disturbed aerial righting reflex, reversible within 24h); suggested a transient narcoleptic response

butanone oxime purity: confidential (> 98 %)	
TL1 (1978a), unpublished study report, confidential **Rat**; Sprague-Dawley; male, (> 9/dose) protocol similar to OECD TG 401/EU B.1, GLP compliant Test substance: butanone oxime purity: 99.5 %	**$LD_{50, male\ rat}$ ca. 2326 mg/kg bw** Doses tested: 0, 1500, 1908, 2427, 3089 and 4999 mg/kg bw 1500 mg/kg bw: no mortality; 1908 mg/kg bw: 22.2 % deaths 2427 mg/kg bw: 50 % deaths ≥ 3089 mg/kg bw: 100 % deaths. Mortality occurred within 48 hours.
TL3 (1971a), unpublished study report, confidential **Rat**; strain, sex and no. of animals not specified; in-house protocol, no GLP compliance Test substance: butanone oxime purity: confidential (> 98 %)	**$LD_{50, rat}$ ca. 2528 mg/kg bw** Doses tested and specific results not reported
TL5 (1982), unpublished study report, confidential **Rat**; Sherman-Wistar; male, female (5/sex/dose) method not specified, GLP compliant Test substance: butanone oxime purity: confidential (> 98 %)	**$LD_{50, male\ rat}$ ca. 930 mg/kg bw** (95 % confidence: 670 - 1310 mg/kg bw) **$LD_{50, female\ rat}$ ca. 1620 mg/kg bw** (95 % confidence: 1230 - 2140 mg/kg) Doses tested: 0, 250, 500, 1000, 2000 and 4000 mg/kg bw Most deaths occurred within a few hours. A very steep dose-response was seen in males as well as in females (mortality rate: m: 0 % at 500 mg/kg, and 80 % at 1000 mg/kg bw f: 0 % at 1000 mg/kg bw, and 80 % at 2000 mg/kg bw).
TL19 (1990b), unpublished study report, confidential; Derelanko et al. (2003) **Key study** **Rabbit;** New Zealand White; female; (5/group in preliminary study; 18/group in main study) According to OECD TG 414 / EU B.31 (Developmental toxicity study), GLP compliant	*Preliminary study (dose range-finding study):* 80 mg/kg bw/d for 2 days **(cumulative 160 mg/kg bw)** induced **mortality:** ≤ 48h in 2/5 females deaths between GD8-10 all 5/5 females Clinical signs: dark red or reddish-green coloured urine, enlarged spleen, brown discoloured lungs **$LD_{50, female\ rabbit}$ ≤ 160 mg/kg bw** 40 mg/kg bw/d for 4 days **(cumulative 160 mg/kg bw)**: induced mortality in 2/5 females (GD10-11) **$LD_{50, female\ rabbit}$ ≤ 160 mg/kg bw** According to the CLP Regulation (Annex I, Part 3, Table 3.1.2 Acute oral toxicity: 50 < Category 3 ≤ 300 mg/kg bw, converted acute toxicity point estimate/ATE =

Test substance: butanone oxime purity: confidential (> 98 %) Exposure duration: GDs 6-18 (daily)	100 mg/ kg bw) butanone oxime fulfils the criteria for classification as **Acute Tox. 3, H301: Toxic if swallowed** *Main study:* 40 mg/kg bw/d for 5 days **(cumulative 200 mg/kg bw)**: induced **mortality** in 8/18 females **(**GD11-24); clinical signs (decreased activity, wobbly gait, no faeces, greenish or reddish coloured fluid in the cage/tray, urine stains, emaciation, pale eyes and ears, and yellowish coloured crusty material in the nostrils); ↓: bw and food consumption; necropsy: fluid contents in the thoracic cavity, brown discoloration of the lungs, mucoid material attached to the mucosa of the stomach, pale liver, accentuated lobular markings on the liver, urinary bladder with dark red fluid contents and thickened mucosa **$LD_{50,\ female\ rabbit}$ ≤ 200 mg/kg bw** (estimate, not calculated)

4.2.1.2 Acute toxicity: inhalation

For the acute inhalation toxicity of butanone oxime results from two experimental studies in rats are used for evaluation. In both studies butanone oxime was used as test material. The results of experimental studies on acute inhalation toxicity to butanone oxime are summarised in Table 13.

Table 13: Butanone oxime: Studies on acute inhalation toxicity (vapour, whole body)

Reference **Species; strain; sex; method**	**LC_{50} / Results**
TL2 (1984a), unpublished study report, confidential **Rat**; F344; male, female (5/sex/group) protocol similar to OECD TG 403/EU B.2, GLP compliant Test substance: butanone oxime purity: confidential (> 98 %) Exposure duration: 4 h	**$LC_{50,\ rat}$ > 4.83 mg/L/4h** (analytical) (male/female); **no mortality** Concentrations tested: 0, 0.19, 1.45 and 4.83 mg/L LOAEC = 190 mg/m^3 based on statistically significant decreased bw gain in females in the observation period after exposure (14 days) LOAEC = 1450 mg/m^3 based on methaemoglobin formation LOAEC = 4800 mg/m^3 based on evidence of narcotic effects
TL3 (1971b), unpublished study report, confidential **Rat**; strain not specified; male, female (6/sex/group); in-house protocol, no GLP compliance Test substance: butanone oxime purity: confidential (> 98 %) Exposure duration: ca. 8 h	**$LC_{50,\ rat}$ > 13.2 mg/L/4h** (calculated, modified Haber's law: Cn * t = const, where C = concentration, t = exposure duration, and n = 3); no mortality at 10.5 mg/L (highest tested concentration; male/female)

4.2.1.3 Acute toxicity: dermal

For the acute dermal toxicity of butanone oxime results from two experimental studies in rabbits were used for evaluation. In both studies butanone oxime was used as test material. The results of experimental studies on acute toxicity after dermal exposure of butanone oxime are summarised in Table 14.

Table 14: Butanone oxime: Studies on acute dermal toxicity (occlusive coverage)

Reference Species; strain; sex; method	LD_{50} / Results
TL19 (1991), unpublished study report, confidential **Rabbit;** New Zealand White; male, female (5/sex/dose); protocol similar to OECD TG 402/EU B.3, GLP compliant Test substance: butanone oxime purity: confidential (> 98 %) Exposure duration: 24 h	**$LD_{50, rabbit, m/f}$ > 1000 mg/kg bw** (Limit Test) Doses tested: 1000 mg/kg bw no mortality within a 14 day period after dosing
TL2 (1984b), unpublished study report, confidential **Key study** **Rabbit**; New Zealand White; male, female (5/sex/dose); protocol similar to EPA OTS 798.1100 Guideline, GLP compliant Test substance: butanone oxime Purity: 99.5 % Exposure duration: 24 h	**$LD_{50, rabbit, m/f}$ = 1848 mg/kg bw** Doses tested: 0.02, 0.2 and 2.0 mL/kg bw (18, 185 and 1848 mg/kg bw) 2.0 mL/kg equivalent to 1848 mg/kg bw (calculation based on density of 0.924 g/mL); **mortality within 48h** LOAEL = 185 mg/kg bw, based on methaemoglobin formation, and splenic erythrophagocytosis LOEL = 18 mg/kg bw based on reversible narcotic effects According to the CLP Regulation (Annex I, Part 3, Table 3.1.1 and 3.1.2 Acute toxicity: 1000 < Category 4 ≤ 2000 mg/kg bw, LD50/ATE = 1848 mg/kg bw) butanone oxime fulfils the criteria for classification as **Acute Tox. 4, H312: Harmful in contact with skin**

4.2.1.4 Acute toxicity: other routes

No data were submitted.

4.2.2 Human information

No information is available on the acute toxicity of butanone oxime in humans.

4.2.3 Summary and discussion of acute toxicity

Data for acute toxicity of butanone oxime was obtained from animal testing. To evaluate the hazard class acute oral toxicity of butanone oxime, e.g. derivation of the LD_{50} value, data from a developmental study in rabbits were also considered. No information is available on the acute toxicity of butanone oxime in humans.

Acute oral toxicity studies with butanone oxime in rats resulted in the following LD_{50} values: > 900 mg/kg bw (male/female); approx. 2326 mg/kg bw (male); and approx. 2528 mg/kg bw (male/female). Lower values were reported from a fourth study: approx. 930 mg/kg bw in males and approx. 1620 mg/kg bw in females.

Taken together, comparing these LD_{50}-values from the rat with rabbit data, the rabbit appears to be more sensitive than the rat to the toxic effects of butanone oxime. Data from a developmental toxicity study in rabbits were included in the evaluation of the acute oral toxicity of butanone oxime indicating that acute mortalities were observed in female rabbits treated with butanone oxime during the gestation phase. In a preliminary dose range-finding study all 5 rabbits receiving doses of 80 mg/kg bw starting on GD6 were found dead between the GD8 to 10. First deaths (2/5 females) occurred extremely short after less than 48 hours after two dosages (cumulative 160 mg/kg bw). At necropsy animals showed dark red or reddish-green coloured urine, enlarged spleen, and brown discoloured lungs. The treatment with 40 mg/kg bw during the GD6 to 9 (four days) was fatal for 2/5 females. In the main study, the treatment with 40 mg/kg bw during the GD6 to 10, five days induced mortality in females starting on the GD11. A total of 8 from 18 females were found dead on GD24. Animals showed the following clinical signs: decreased activity, wobbly gait, no faeces, greenish or reddish coloured fluid in the cage/tray, urine stains, emaciation, pale eyes and ears, and yellowish coloured crusty material in the nostrils); decreases in body weight and food consumption; necropsy: fluid contents in the thoracic cavity, brown discoloration of the lungs, mucous material attached to the mucosa of the stomach, pale liver, accentuated lobular markings on the liver, urinary bladder with dark red fluid contents and thickened mucosa. Based on the available data it is concluded that butanone oxime is acutely toxic after oral application. The LD_{50} value for butanone oxime was not calculated but roughly estimated as being ≤ 160 mg/kg bw (2 x 80 mg/kg bw) based on 2/5 deaths until 48 hours after dosing and on lethality of all 5 females until 72 hours after dosing.

Acute inhalation toxicity: In the available studies the exact LC_{50} value for butanone oxime could not be established as no death in male and female rats occurred in these studies. In one study no lethality or signs of evident toxicity were noted at the highest vapour concentration tested of 4.83 mg/L following 4 hour whole body exposure. In another inhalation hazard test no mortality was observed after an 8 hour whole body exposure to the highest tested concentration of 10.5 mg/L butanone oxime as a vapour. The LC_{50} value was found to be > 10.5 mg/L/8h. This value was extrapolated to a 4 hour exposure by using the modified Haber's law ($C^n * t = const$, where C = concentration, t = exposure duration, and n = 3) for extrapolation from longer to shorter exposure durations. For a 4 hour exposure a LC_{50} value for butanone oxime of higher than 13.2 mg/L/4h was calculated. Because no mortalities were noted up to 13.2 mg/L/4h it is concluded that butanone oxime is not acutely toxic by inhalation.

Acute dermal toxicity: The dermal LD_{50} for rabbits was between 1000 and 1848 mg/kg bw butanone oxime. In one study no mortality was observed at 1000 mg/kg bw (Limit Test). After topically administration of a single dose of 185 mg/kg bw by an occlusive dressing for 24 hours methaemoglobin formation and splenic erythrophagocytosis was observed. At 2.0 mL/kg bw, equivalent to 1848 mg/kg bw (calculation based on density of 0.924 g/mL) all animals died within 48 hours after treatment. Based on the available data it is concluded that butanone oxime is acutely toxic after dermal administration.

4.2.4 Comparison with criteria

Acute toxicity means those adverse effects occurring following oral or dermal administration of a single dose of a substance or a mixture, or multiple doses given within 24 hours, or an inhalation exposure of 4 hours. Acute toxicity relates to effects occurring after a single or relative brief exposure to a substance or mixture. Acute toxicity classification is generally assigned on the basis of evident lethality. The evidence for acute toxicity of butanone oxime is obtained from animal testing. Substances can be allocated to one of four toxicity categories based on acute toxicity by the oral, dermal or inhalation route according to the criteria shown in the Table 3.1.1 and 3.1.2 of Annex I, Part 3.

Since the Commission has recently proposed a notation for ATE values in Table 3.1 of CLP (10th ATP to CLP), introducing harmonised ATEs in the same column as the SCLs and M-factors, specific ATEs and/or converted acute toxicity point estimate values according to Table 3.1.2 of CLP have to be used for classification purposes.

Acute oral toxicity: The following applies for the classification as

'*Acute oral toxicity -50 < Category 3 ≤ 300 mg/kg bw'*

'Acute oral toxicity -300 < Category 4 ≤ 2000 mg/kg bw.'

Based on the lowest oral LD_{50} values (about 930 mg/kg bw for males, and 1620 mg/kg bw for females) from studies with rats, butanone oxime would fulfil the criteria for classification for acute oral toxicity Category 4. However, the data from a preliminary dose range-finding study to a developmental toxicity study in rabbits (TL19, 1990b, unpublished study report, confidential; Derelanko et al. 2003) have shown that butanone oxime induces acute lethality in this species at lower doses. In female rabbits treated with 80 mg/kg bw butanone oxime starting on GD6 mortalities were observed between the GD8-10. First deaths (2/5 females) occurred extremely shortly after less than 48 hours after two dosages (on GD6 and 7, cumulative 160 mg/kg bw), and the remaining 3/5 females were found dead up to GD10. These mortalities occurring within the first 48 hours after dosing are taken as relevant for the classification proposal on acute oral toxicity.

In the synopsis of the available data from single dose studies in rats and from repeated dose studies in rabbits, the rabbit appears to be more sensitive than the rat to the acute toxic effects of butanone oxime. According to the Guidance on the application of the CLP-criteria, classification should be based on the lowest ATE/LD_{50} value available i.e. the lowest ATE/LD_{50} in the most sensitive appropriate species tested. As specified in the guidance on haemolytic anaemia mortalities during days 0-3 in a repeated dose study should be considered for acute toxicity. Based on these data it is concluded that butanone oxime is acutely toxic by oral application (CLP Guidance, 3.9.2.5.2. Haematotoxicity).

For the oral route, the estimated ATE/LD_{50} is ≤ 160 mg/kg bw. Since there is no exact experimentally-derived LD_{50} value, the appropriate conversion from Table 3.1.2 of CLP (Annex I, Part 3) to a converted acute toxicity point estimate that relates to a classification category is used. According to Table 3.1.2 of CLP (50 < Category 3 ≤ 300 mg/kg bw), the converted acute toxicity point estimate and thus ATE for oral toxicity is 100 mg/kg bw. Based on this derived ATE, butanone oxime fulfils the criteria for classification as acute hazard Category 3 (Acute Tox. 3, H301: Toxic if swallowed).

Acute inhalation toxicity: The following applies in comparison to

'Acute inhalation toxicity (vapour): 10 < Category 4 ≤ 20.0 mg/L.'

No LC_{50} value could be established for butanone oxime as **no deaths** occurred in an inhalation hazard test up to a concentration of 10.5 mg/L/8h (corresponding to 13.2 mg/L/4h by using the modified Haber's law) butanone oxime as a vapour (TL3, 1971b, unpublished study report, confidential). At this highest tested concentration in the study no compound related signs of overt toxicity rather than lethality as indications of acute inhalation toxicity were observed. There are no data available that could justify a classification on acute inhalation toxicity according to CLP.

Acute dermal toxicity: The following applies for the classification as

'Acute dermal toxicity -1000 < Category 4 ≤ 2000 mg/kg bw.'

The current Annex VI entry for butanone oxime includes a classification for acute toxicity Category 4 with hazard statement H312 (Harmful in contact with skin) as a minimum classification as indicated by the reference '*' in the column "Classification" in Table 3.1. Based on the review of the available experimental data for acute dermal toxicity for butanone oxime, it is confirmed that butanone oxime meets the criteria for classification and labelling as Acute Tox. 4, H312 according to CLP and the reference indicating minimum classification (*) is no longer necessary. Reliable LD_{50} values for classification of butanone oxime were derived from acute dermal toxicity studies in rabbits. In the key study (TL19, 1991, unpublished study report, confidential), performed to a comparable protocol as OECD TG 402/EU B.3, no lethality was observed at the highest dose tested of 1000 mg/kg bw. In the second study (TL2, 1984b, unpublished study report, confidential), the dermal LD_{50} was found to be 1848 mg/kg bw. Based on this ATE/LD_{50} value, butanone oxime meets the criteria for classification as Acute Tox. 4, H312 according to CLP (Annex I, Part 3, Table 3.1.1 and 3.1.2 Acute toxicity (dermal): 1000 < Category 4 ≤ 2000 mg/kg bw).

4.2.5 Conclusions on classification and labelling

According to CLP butanone oxime has to be classified as:

Acute Tox. 3 for oral exposure and labelled with hazard statement H301: Toxic if swallowed.; with the pictogram "GHS06: Skull and crossbones", and with the signal word "Danger"; and

Acute Tox. 4 for dermal exposure and labelled with hazard statement H312: Harmful in contact with skin; with the pictogram "GHS07: Exclamation mark", and with the signal word "Warning".

Butanone oxime has not to be classified as acutely toxic by inhalation according to CLP.

4.3 Specific target organ toxicity – single exposure (STOT SE)

In acute oral, inhalation and dermal toxicity studies on butanone oxime, transient and reversible changes in neurobehavioral function consistent with central nervous system depression, but no evidence of cumulative neurotoxicity was detected. In repeated dose toxicity studies similar observations were noted after application of the test substance in different animal species. The results of experimental studies regarding narcotic effects of butanone oxime are summarised below.

Table 15: Butanone oxime: Narcotic effects observed in experimental animals

Reference Species; strain; sex; method	Study results / Narcotic effects
TL8 (1991), unpublished study report, confidential; Schulze and Derelanko (1993) **Rat**; Sprague-Dawley; male/female (10/sex/dose); **acute oral neurotoxicity study** (gavage), GLP compliant Test substance: butanone oxime purity: confidential (> 98 %) Doses tested: 0, 100, 300, 900 mg/kg bw	transient neurobehavioral effects (impaired gait; disturbed aerial righting reflex; reversible within 24h); suggested a transient narcoleptic response **LOEL $_{rat\ m/f}$ = 300 mg/kg bw** based on transient narcotic effects
TL2 (1984a), unpublished study report, confidential **Rat**; F344; male/female (5/sex/group); **acute inhalation toxicity study**, vapour, 4 h**;** protocol similar to OECD TG 403/EU B.2, GLP compliant Test substance: butanone oxime purity: confidential (> 98 %) Concentrations tested: 0, 0.19, 1.45, 4.83 mg/L	During exposure strong temporary narcotic effect in both sexes **LOAEC $_{rat\ f}$ = 4.83 mg/L** based on observation of narcotic effects
TL2 (1984b), unpublished study report, confidential **Rabbit**; New Zealand White; male/female (5/sex/dose); **acute dermal toxicity study**, occlusive, 24 h**;** protocol similar to EPA OTS 798.1100 Guideline, GLP compliant Test substance: butanone oxime purity: 99.5 % Doses tested: 0.02, 0.2, 2.0 mL/kg bw (18, 185, 1848 mg/kg bw)	**LOAEL$_{rabbit,\ m/f}$ = 185 mg/kg bw** based on significant effects on nervous system (narcosis) **LOEL$_{rabbit,\ m/f}$ = 18 mg/kg bw** based on reversible narcotic effects, occurring during 48 hours following exposure
TL9 (1991), unpublished study report, confidential; Schulze and Derelanko (1993) **Rat**; Sprague-Dawley; male/female (main study: 10/sex/dose; satellite groups: 4/sex/dose) **sub-chronic oral (gavage) toxicity study**, equivalent to OECD TG 408/EU B.26, GLP compliant Test substance: butanone oxime purity: > 99.8 % Doses tested: 0, 40, 125, 400 mg/kg bw/day, exposure duration: 5days/week, 13 weeks	**400 mg/kg bw/d (m/f):** clinical signs: changes (transient and reversible) in neurobehavioral function consistent with CNS depression (hypoactivity, ataxia, impaired aerial righting); dark-coloured urine **NOAEL$_{m/f}$ = 125 mg/kg bw/d** based on neurobehavioral effects
TL19 (1990b), unpublished study report,	**Preliminary study (dose range-finding study):** **≥ 40 mg/kg bw/d:** clinical signs: laboured breathing,

confidential; Derelanko et al. (2003) **Rabbit**; New Zealand White; female (18/dose); **developmental toxicity study, oral (gavage)**, according to OECD TG 414/ EU B.31, GLP compliant Test substance: butanone oxime purity: > 99 % Doses tested: 0, 8, 14, 24, 40 mg/kg bw, exposure duration: GD6-18 (daily)	decreased activity, few or no faeces **Main study: 40 mg/kg bw/d:** clinical signs: decreased activity, wobbly gait, no faeces, ↓: bw, food consumption; **$LOAEL_f$ = 40 mg/kg bw/d** based on neurobehavioral effects

Single oral doses of ≥ 300 mg/kg bw butanone oxime administered by gavage were found to produce transient and reversible changes in neurobehavioral function consistent with CNS depression, but no evidence of cumulative neurotoxicity was detected (TL8, 1991, unpublished study report, confidential; Schulze and Derelanko 1993). In the acute inhalation toxicity study a strong, transient narcotic effect occurred in both sexes at 4.83 mg/L/4h during the exposure (TL2, 1984a, unpublished study report, confidential). In a dermal acute toxicity study in rabbits butanone oxime produced narcosis at single doses of 185 mg/kg bw and higher. Narcosis was transient at the low dose level of 18 mg/kg bw and higher occurring during the first 48 hours following exposure.

An acute neurotoxicity study and a sub-chronic study both in rats and with oral exposure by gavage revealed transient and reversible functional disturbances in nervous system function consistent with CNS depression. Single oral application of butanone oxime produced significant dose-related decreases in motor activity within one hour after exposure which reached statistically significance at 900 mg/kg bw. Increased ease of cage removal and handling were also noted. Repeated oral application of 300 mg/kg bw or higher for 13 weeks induced transient findings, i.e. impaired gait, aerial righting reflex, and flattened posture. No progressive long-term, irreversible neurotoxic changes were associated with repeated butanone oxime administration for 13 weeks at doses up to 400 mg/kg bw/d. Female rabbits (dams) treated with 40 mg/kg bw/d and higher during the GD6-18 exhibited neurological effects, e.g. decreased activity and unsteady wobbly gait.

4.3.1 Summary and discussion of Specific target organ toxicity – single exposure

The evidence for specific target organ toxicity through single exposure to butanone oxime was obtained from animal testing. In rats single oral doses of ≥ 300 mg/kg bw butanone oxime administered by gavage produced narcotic effects (TL8, 1991, unpublished study report, confidential; Schulze and Derelanko 1993). In the acute inhalation toxicity study a strong transient narcotic effect occurred in both sexes at 4.83 mg/L/4h (TL2, 1984a, unpublished study report, confidential). In a dermal acute toxicity study in rabbits butanone oxime produced significant defensive or narcotic effects on the CNS at single doses of 185 mg/kg bw and higher, and transient narcotic effects occurring during the first 48 hours following exposure at the low dose level of 18 mg/kg bw. Also in specific investigations transient and reversible functional disturbances in nervous system function consistent with CNS depression were observed in rats after single or repeated oral application of butanone oxime.

In a sub-chronic toxicity study in rats, transient neurobehavioral changes (on cage removal, handling, posture, gait, arousal, salivation, approach response, rearing responses, and aerial righting) were noted immediately after oral dosing with 400 mg/kg bw/d. These changes in neurobehavioral function were consistent with CNS depression, but no evidence of cumulative or

persistent neurotoxicity was detected. A dose of 125 mg/kg bw/d butanone oxime did not induce changes in neurobehavioral function or nervous system structure in rats. In a developmental toxicity study with oral application of butanone oxime, rabbits (dams) showed neurological effects, e.g., decreased activity, wobbly gait, at oral doses of 40 mg/kg bw/d and higher.

Information with respect to toxicity after single exposure, e.g. findings of narcosis, in humans are not available from case reports, epidemiological studies, medical surveillance or national poisons centres.

4.3.2 Comparison with criteria

Specific target organ toxicity, single exposure (STOT SE) is defined as specific, non-lethal target organ toxicity arising from a single exposure to a substance. These adverse effects produced by a single exposure include consistent and identifiable toxic effects in humans, or, in experimental animals, which have affected the function or morphology of a tissue/organ, or have produced serious changes to the biochemistry or haematology of the organism, and these changes are relevant for human health.

The following applies for the classification as

'STOT-SE Category 3: Transient target organ effects:'

This category only addresses narcotic effects and respiratory tract irritation. These are target organ effects for which a substance does not meet the criteria of Categories 1 or 2. Transient target organ effects of Category 3 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. Criteria for classification of substances for narcotic effects are defined in Annex I: 3.8.2.2.2 of CLP. Guidance values are not provided for Category 3 substances.

Classification in Category 3 is primarily based on human data, if available, animal data can be included in the evaluation.

'*The criteria for classifying substances as Category 3 for narcotic effects are:*

(a) Central nervous system depression including narcotic effects in humans such as drowsiness, narcosis, reduced alertness, loss of reflexes, lack of coordination, and vertigo are included. These effects can also be manifested as severe headache or nausea, and can lead to reduced judgement, dizziness, irritability, fatigue, impaired memory function, deficits in perception and coordination, reaction time, or sleepiness;

Criteria for narcotic effects observed in animal studies are defined under point

(b) narcotic effects observed in animal studies may include lethargy, lack of coordination, loss of righting reflex, and ataxia. If these effects are not transient in nature, then they shall be considered to support classification for Category 1 or 2 specific target organ toxicity single exposure.'

Narcotic effects were observed in several animal studies with different application routes immediately or shortly delayed after administration of butanone oxime. Data from acute oral, inhalation and dermal toxicity testing in rats and rabbits have shown a strong transient narcotic effect in both sexes following single exposure to butanone oxime. In rats significant dose-related decreases in motor activity were observed one hour after single oral dose of 300 mg/kg bw

butanone oxime which reached statistically significance at 900 mg/kg bw. In addition increased ease of cage removal and handling were seen. In rabbits transient narcotic effects occurred during the first 48 hours following exposure by skin at the low dose level of 18 mg/kg bw and higher. During a sub-chronic toxicity study in rats, transient neurobehavioral changes were noted immediately after oral dosing with 400 mg/kg bw/d. In a developmental toxicity study, rabbits (dams) showed neurological effects, e.g. decreased activity, wobbly gait, at the time immediately after application of oral doses of 40 mg/kg bw/d and higher.

The available data from acute oral, inhalation and dermal toxicity and also result from repeated dose toxicity studies have shown clear evidence of transient narcotic effects of butanone oxime in rats and rabbits. Based on these data, butanone oxime meets the criteria for classification and labelling as a specific target organ toxicant (single exposure) of Category 3 for narcotic effects according to CLP (Annex I: 3.8.2.2.2.).

4.3.3 Conclusions on classification and labelling

According to CLP butanone oxime has to be classified as:

STOT-SE 3 and labelled with hazard statement H336: May cause drowsiness or dizziness; with the pictogram “GHS07: Exclamation mark”, and with the signal word “Warning”.

4.4 Irritation

4.4.1 Skin irritation

Table 16: Summary table of relevant skin irritation studies

Method	Results	Remarks	Reference
no specific test method: exposure occlusive over 24 h; observation period: 72 h; 3 non-abraded and 3 abraded skin sites; undiluted test substance; GLP compliant **Rabbit**; New Zealand White (6 animals, sex not specified)	**slightly irritating** to non-abraded and abraded skin of rabbits; PDII (Primary dermal irritation index, according to US CPSC/US OSHA): ca. 1.5 (mean (erythema and oedema)), not fully reversible within 72h; scores reversible at the end of the observation period According to CLP **no classification for skin corrosion/irritation**	In vivo study, reliable with restrictions Test material: butanone oxime, purity: confidential (> 98 %)	TL1 (1978b), unpublished study report, confidential
equivalent to OECD TG 404/EU B.4; no GLP compliance; exposure semi-occlusive over 4h; undiluted test substance **Rabbit**; New Zealand White; sex and no. of animals not reported	**not irritating** following a 4 hour exposure under semi-occlusive conditions to shaved skin According to CLP **no classification for skin corrosion/irritation**	In vivo study, reliable with restrictions Test material: butanone oxime, purity: confidential (> 98 %)	TL3 (1971c), unpublished study report, confidential

4.4.1.1 Non-human information

There are results from two experimental studies in rabbits available. In one study performed by a protocol similar to OECD TG 404/EU B.4, no irritation was observed in rabbits following a 4 hour exposure to butanone oxime under semi-occlusive conditions to the shaved skin. In the other study butanone oxime has been shown to be slightly irritating to the skin of rabbits; the primary irritation index was 1.5. In the available studies butanone oxime was used as test material. The results of experimental studies on skin irritation are summarised in Table 16 (s. there).

4.4.1.2 Human information

No information is available on the skin irritation of butanone oxime in humans.

4.4.1.3 Summary and discussion of skin irritation

The assessment of skin irritation of butanone oxime is based on animal testing. There are no epidemiological studies, clinical studies or case reports available reporting on skin irritation of butanone oxime in humans.

Butanone oxime caused no irritation in rabbits after a 4-hour application time. Butanone oxime has been shown to be slightly irritating to the skin of rabbits after exposure over a period of 24 hours.

4.4.1.4 Comparison with criteria

Evaluation criteria for local effects on the skin are severity of the damage and reversibility. Skin irritation means the production of reversible damage to the skin following the application of a test substance for up to 4 hours. In a tiered approach, emphasis shall be placed upon existing human data, followed by existing animal data, followed by in vitro data and then other sources of information.

The following applies in comparison to

'Skin irritation category: Irritation (Category 2):

(1) Mean score of ≥ 2.3 and ≤ 4.0 for erythema/eschar or for oedema in at least 2 of 3 tested animals from gradings at 24, 48 and 72 hours after patch removal or, if reactions are delayed, from grades on 3 consecutive days after the onset of skin reactions; or

(2) Inflammation that persist to the end of the observation period normally 14 days in at least 2 animals, particularly taking into account alopecia (limited area), hyperkeratosis, hyperplasia, and scaling reactions; or

(3) In some cases where there is pronounced variability of response among animals, with very definite positive effects related to chemical exposure in a single animal but less than the criteria above.'

No sign of irritation was observed in a guideline-confirming study on rabbits following a 4-hour application time to butanone oxime. In another study the primary dermal irritation index was 1.5 after exposure over 24 hours, which is below the mean scores that may require classification.

4.4.1.5 Conclusions on classification and labelling

Based on the available data in animals and according to CLP, classification of butanone oxime as Skin Irrit. Cat. 2 is not warranted.

4.4.2 Eye irritation

Table 17: Summary table of relevant eye irritation study

Method	Results	Remarks	Reference
equivalent to OECD TG 405/EU B.5; GLP compliant undiluted test substance Observation period: 72 h **Rabbit**; New Zealand White; 6 animals, sex not specified	**irreversible effects on the eye** corneal opacity, irititis, conjunctively hyperaemia (score: ≥ 2) in 6/6 animals at 24, 48, and 72 h after exposure; necrosis of the conjunctivae in 2/6 animals, not reversible at the end of observation period According to CLP butanone oxime fulfils the criteria for classification as **Eye Cat 1, H318: Causes serious eye damage**	**Key study** In vivo study Test material: butanone oxime, purity: confidential (> 98 %)	TL1 (1978c), unpublished study report, confidential

4.4.2.1 Non-human information

There are results from an experimental study equivalent to OECD TG 405/EU B.5 performed in 6 rabbits. The test results showed that butanone oxime caused serious eye damage which was not fully reversible. In the available study butanone oxime was used as test material. The results of the experimental study on eye irritation are summarised in Table 17 (see there).

4.4.2.2 Human information

No information is available on serious eye damage/eye irritation of butanone oxime in humans.

4.4.2.3 Summary and discussion of eye irritation

The assessment of eye irritation of butanone oxime is based on animal testing.

The results from the available eye irritation study in rabbits have provided evidence that butanone oxime caused serious eye damage. Corneal opacity, irititis and hyperaemia of the conjunctivae were observed 24, 48, and 72 hours post exposure (average scores 2 or above) in 6/6 animals. Conjunctivae necrosis was observed in 2/6 rabbits which was not reversible at the end of the observation period. Based on these data it is concluded that butanone oxime has the potential to seriously damage the eyes.

Butanone oxime is classified in Annex VI of CLP as Eye Dam. 1, H318.

4.4.2.4 Comparison with criteria

Serious eye damage means the production of tissue damage in the eye, or serious physical decay of vision, following application of a test substance to the anterior surface of the eye, which is not fully reversible within 21 days of application. Eye irritation means the production of changes in the eye following the application of test substance to the anterior surface of the eye, which are fully reversible within 21 days of application. In a tiered approach, emphasis shall be placed upon existing human data, followed by existing animal data, followed by in vitro data and then other sources of information.

Evaluation criteria for local effects on the eye of rabbits are the nature, intensity (severity of the damage) and reversibility of responses. Evaluation takes place separately for cornea, iris and conjunctiva (erythema and swelling).

Substances are allocated to one of the categories within the hazard class, Category 1 (serious eye damage) or Category 2 (eye irritation) as follows:

(a) Category 1 (serious eye damage): substances that have the potential to seriously damage the eyes

(b) Category 2 (eye irritation): substances that have the potential to induce reversible eye irritation

The following applies for classification for substances based on standard animal test data as *'Serious eye damage (Category 1):* A substance that produces:

(a) in at least one animal effects on the cornea, iris or conjunctiva that are not expected to reverse or have not fully reversed within the observation period of normally 21 days; and/or

(b) in at least 2 of tested animals, a positive response of
(i) corneal opacity ≥ 3: and/or
(ii) iritis > 1.5

Calculated as the mean scores following grading at 24, 48 and 72 hours after instillation of the test material.'

The available eye irritation study in rabbits showed that butanone oxime caused serious damage to the eyes. Butanone oxime caused corneal opacity, irititis and hyperaemia of the conjunctivae. These lesions were observed 24, 48, and 72 hours post exposure (average scores 2 or above) in 6/6 animals. In addition, irreversible effects on the eye were observed in 2/6 rabbits. Conjunctival necrosis was observed in these rabbits which was not reversible at the end of observation period.

4.4.2.5 Conclusions on classification and labelling

Based on the available results, butanone oxime meets the criteria for classification and labelling as 'Irreversible effects on the eye' Category 1, H318 according to CLP, and the legal classification as Eye Dam. 1 is warranted.

According to CLP butanone oxime has to be classified as:

Eye Dam. 1 and labelled with hazard statement H318: Causes serious eye damage; with the pictogram “GHS05: Corrosion”, and with the signal word “Danger”. The legal classification of butanone oxime as ‘Eye Dam. 1’ is confirmed.

4.4.3 Respiratory tract irritation

There are no data on respiratory tract irritation in animals and humans.

4.5 Corrosivity

No information is available on skin corrosion from animal experiments.

4.6 Sensitisation

4.6.1 Skin sensitisation

Table 18: Summary table of relevant skin sensitisation studies

Method	Results	Remarks	Reference
GPMT according to OECD TG 406/EU B.6, GLP compliant **Guinea pig**; female; Hartley (10/dose)	**Skin sensitising** Induction: 3 % in propylene glycol i.d., 0.3 mL 100 % e.d.; Challenge: 0.2 mL 50 % in propylene glycol e.d. TG: 24h: 9/10, 90 %; 48h: 8/10, 80 % Negative Control: 24h/48h: 0/10 Reliability check: 0.1 % DNCB: 24h/48h: 10/10 According to CLP butanone oxime fulfils the criteria for classification as **Skin Sens. 1B, H317: May cause an allergic skin reaction**	**Key study** Test substance: butanone oxime, purity: confidential (> 98 %)	TL6 (1983), unpublished study report, confidential
Buehler assay according to OECD TG 406/EU B.6, GLP compliant **Guinea pig**; female; Hartley (10/dose; 5/control)	**Skin sensitising** Induction: 25 % in propylene e.d.; Challenge: 5 % in propylene glycol e.d. TG (1. challenge): 24h: 6/10, 60 %; 48h: 5/10, 50 % (2. challenge): 24h: 9/10, 90 %; 48h: 8/10, 80 % Negative Control: 24h/48h: 0/10 Reliability check: 0.1 % DNCB: 24h/48h: 10/10 According to CLP butanone oxime fulfils the criteria for classification as **Skin Sens. 1B, H317: May cause an allergic skin reaction**	**Key study** Test substance: butanone oxime, purity: confidential (> 98 %)	TL20 (1989), unpublished study report, confidential
GPMT according to OECD TG 406/EU B.6, GLP compliant **Guinea pig**; female; Hartley (10/dose)	**Skin sensitising** Induction: 4 % i.d., 100 % e.d.; Challenge: 50 % e.d. TG: 7/10, 70 % No more data According to CLP butanone oxime fulfils the criteria for classification as **Skin Sens. 1, H317: May cause an allergic skin reaction**	Supporting study Specifics not reported, summary results Test substance: butanone oxime, purity: confidential (> 98 %)	TL16 (1989), unpublished study report, confidential
MEST Mouse ear swelling test, no GLP compliance assumed **Mouse**; female; CF-1, (10/ test group, 5/control)	**Skin sensitising** Induction: 50 % in 70 % ethanol e.d.; Challenge: 50 % in 70 % ethanol e.d. TG: 40 % sensitised; 120 % swelling Reliability check: DNCB: 80 % sensitised; 130 % swelling According to CLP butanone oxime fulfils the criteria for classification as **Skin Sens. 1, H317: May cause an allergic skin reaction**	Supporting study Test substance: butanone oxime, purity: 99.98 %	Gad et al. (1986, 1988)
mLLNA according to	**Not sensitising** Vehicle: acetone/olive oil (4:1v/v); 50 %, 100 %	Supporting study	TL13 (2009), unpublished

OECD TG 429/EU B.42, GLP compliant **Mouse**; female; CBA (5/dose)	Stimulation index: 50 %: 1.3; 100 %: 1.0 Reliability check: hexyl cinnamic aldehyde (CAS 101-86-0) According to CLP **no classification for skin sensitisation**	Test substance: butanone oxime, purity: confidential (> 98 %)	study report, confidential

4.6.1.1 Non-human information

The skin sensitising potential of butanone oxime was investigated in guinea pigs and mice. Two guinea pig maximisation tests (GPMT) and one Buehler assay according to OECD TG 406/EU B.6 under GLP conditions are available, in addition a local lymph node assay in mice (mLLNA) according to OECD TG 429/EU B.42, and further a mouse ear swelling test (MEST). In the available studies butanone oxime was used as test material. The results of experimental studies on skin sensitisation are summarised in Table 18 (s. there).

Butanone oxime has shown a clear evidence of skin sensitisation in guinea pigs (GPMT and Buehler assay). The results of a mouse ear swelling test (MEST) with butanone oxime have shown a sensitising response of 40 % and a swelling rate of 120 % for the mouse ear. Based on this animal model system a moderate potency for skin sensitisation is determined for butanone oxime. In a standard LLNA in mice, performed under GLP butanone oxime has shown a negative result.

4.6.1.2 Human information

No human data on the sensitising potential of butanone oxime are available.

4.6.1.3 Summary and discussion of skin sensitisation

Data on skin sensitisation of butanone oxime were obtained from animal testing according to the existing testing guidelines.

In two GPMT, and a Buehler assay guinea pigs exhibited positive results. In a MEST a moderate potency for skin sensitisation was determined in mice for butanone oxime. In a standard LLNA in mice butanone oxime concentrations of 50 % and 100 % resulted in stimulation indices (SI) of 1.3 and 1.0, which indicate a negative result in this test system. However, as this result was contradictory to the available reliable assays in guinea pigs and in a test with another mouse strain, more weight was given on the positive tests.

To its allergenic potency and to its relevance to human health butanone oxime was justified as a ‘substance with a solid-based indication of a contact allergenic potential and a substance with the capacity of cross-reactions’ (listed in Category B) by a group of experts including dermatologists from universities, representatives from the chemical industry and from regulatory authorities in Germany (Schlede et al. 2003).

Butanone oxime is currently classified as skin sensitizer category 1 and is listed in Annex VI of CLP as Skin Sens. 1, H317.

4.6.1.4 Comparison with criteria

Skin sensitisers shall be classified in Category 1 where data are not sufficient for sub-categorisation. Where data are sufficient a refined evaluation according to section 3.4.2.2.1.3 allows the allocation of skin sensitisers into sub-category 1A, strong sensitisers, or sub-category 1B for other skin sensitisers.

Hazard category and sub-categories for skin sensitisers:

'Category 1: Substances shall be classified as skin sensitisers (Category 1) where data are not sufficient for sub-categorisation in accordance with the following criteria:

(a) if there is evidence in humans that the substance can lead to sensitisation by skin contact in a substantial number of persons; or

(b) if there are positive results from an appropriate animal test (see specific criteria).'

Based on the available data, butanone oxime is classified as skin sensitizer category 1 and is listed in Annex VI of CLP. The classification is based on positive results from appropriate animal tests: GPMT, Buehler assay, and MEST.

Classification into sub-categories is only allowed if data are sufficient. The available results from animal testing with butanone oxime are sufficient for a refined evaluation allowing the sub-categorisation.

'Sub-category 1A: Substances showing a high frequency of occurrence in humans and/or a high potency in animals can be presumed to have the potential to produce significant sensitisation in humans. Severity of reaction may also be considered.'

'Sub-category 1B: Substances showing a low to moderate frequency of occurrence in humans and/or a low to moderate potency in animals can be presumed to have the potential to produce sensitisation in humans. Severity of reaction may also be considered.'

Comparing with criteria for hazard category and sub-categories for skin sensitizers according to CLP a substance shall be classified for:

Skin sensitisation: Animal test results for Sub-category 1A:

GPMT of ≥ 30 % responding at ≤ 0.1 % intradermal induction dose or

≥ 60 % responding at > 0.1 % to ≤ 1 % intradermal induction dose or

Buehler assay of ≥ 15 % responding at ≤ 0.2 % topical induction dose or

≥ 60 % responding at > 0.2 % to ≤ 20 % topical induction dose.

Based on the available data, Sub-category 1A is not appropriate, because the criteria are not fulfilled.

Skin sensitisation: Animal test results for Sub-category 1B:

GPMT of ≥ 30 % to < 60 % responding at > 0.1 % to ≤ 1 % intradermal induction dose or

≥ 30 % responding at > 1.0 % intradermal induction dose or

Buehler assay of ≥ 15 % to < 60 % responding at > 0.2 % to ≤ 20 % topical induction dose or

≥ 15 % responding at > 20 % topical induction dose.

In comparison to the given criteria for the hazard category and sub-categories for skin sensitisation according to CLP butanone oxime fulfils the criteria for classification in the hazard class as skin sensitizer Sub-category 1B, H317, because a skin sensitisation response of ≥ 30 % at > 1.0 % intradermal induction dose was observed in the adjuvant type test method (GPMT); and of ≥ 15 % at > 20 % topical induction dose in the non-adjuvant type test method (Buehler assay).

4.6.1.5 Conclusions on classification and labelling

According to CLP butanone oxime has to be classified as:

Skin Sens. 1B and labelled with hazard statement H317: May cause an allergic skin reaction; with the pictogram “GHS07: Exclamation mark”, and with the signal word “Warning”.

4.6.2 Respiratory sensitisation

No data on respiratory sensitisation are available for butanone oxime.

4.7 Repeated dose toxicity

Table 19: Summary table of relevant repeated dose toxicity studies (oral < inhalation)

Method	Results	Remarks	Reference
Oral Sub-chronic 90-day drinking water study equivalent to OECD TG 408/ EU B.26, GLP compliant **Rat**; F344; male/female (10/sex/dose) Doses tested: 0, 312, 625, 1250, 2500, 5000 pm (nominal in water) Exposure duration: daily, ad libitum for 13 weeks	• **Effects indicative of anaemia:** ≥ 100/65 mg/kg bw/d (m/f): ↓ erythrocyte count (-10/-6 %); Hb (-5/-2 %) ≥ 100/30 mg/kg bw/d (m/f): ↑ reticulocyte count (78/25 %) ≥ 175/215 mg/kg bw/d (m/f): ↑ methaemoglobin ≥ 50/65 mg/kg bw/d (m/f): ↑ incidence and severity: haematopoietic cell proliferation in the spleen, haematopoietic proliferation in the bone marrow ≥ 175/215 mg/kg bw/d (m/f): liver: Kupffer cell erythrophagocytosis, haemosiderin pigmentation ≥ 175/120 mg/kg bw/d (m/f): kidney: renal tubular haemosiderin pigmentation **$NOAEL_{m/f}$ = 25/30 mg/kg bw/d** (erythrotoxicity) • **Effects on the respiratory tract:** ≥ 175/215 mg/kg bw/d (m/f): nose: degeneration of the nasal epithelium (olfactory epithelium, posterior nasal section) **$NOAEL_{m/f}$ = 100/120 mg/kg bw/d** (degeneration of the nasal olfac. epithel.) According to CLP: **no classification for STOT-RE** (based on guidance value STOT-RE 2, oral (rat): ≤ 100 mg/kg bw/d)	**Key study** Test substance: butanone oxime, purity: > 99 %	U.S. National Toxicology Program (NTP) (1999)
Oral Sub-chronic 90-day drinking water study equivalent to OECD TG 408/ EU B.26, GLP compliant **Mouse**; B6C3F1; male/female (10/sex/dose) Doses tested: 0, 625, 1250, 2500, 5000, 10000 ppm pm (nominal in water) Exposure duration: daily, ad libitum for 13 weeks	• **Effects indicative of anaemia:** ≥ 755/1010 mg/kg bw/d (m/f): ↑ hematopoietic cell proliferation in spleen, spleen: ↑ weight 1330/3170 mg/kg bw/d (m/f): liver: Kupffer cell erythrophagocytosis indicating intravascular haemolysis and haemosiderin pigmentation; kidney: renal tubule haemosiderin pigmentation **$NOAEL_{m/f}$ = 515/630 mg/kg bw** (extramedullary haematopoiesis, spleen) • **Effects on the urinary bladder epithelium:** m/f: ≥ 515/630 mg/kg bw/d: hyperplasia of the transitional epithelial lining **$NOAEL_{m/f}$ = 200/340 mg/kg bw** (urinary bladder epithelium effects) • **Effects on the nasal olfactory epithelium:** ≥ 755/630 mg/kg bw/d (m/f): degeneration of the olfactory epithelium (minimal to moderate) **$NOAEL_{m/f}$ = 515/340 mg/kg bw** (nasal olfactory epithelium effects) According to CLP: **no classification for STOT-RE** (based on guidance value STOT-RE 2, oral (rat): ≤ 100 mg/kg bw/d)	**Key study** Test substance: butanone oxime, purity: > 99 %	U.S. National Toxicology Program (NTP) (1999)

Oral (gavage) Developmental toxicity study according to OECD TG 414/ EU B.31, GLP compliant **Rat**; Sprague-Dawley; female (preliminary study: 6/dose; main study: 25/dose) Doses tested: 25, 100, 200, 400 mg/kg bw/day in preliminary study. 0, 60, 200, 600 mg/kg bw/day in main study; dose volume: 10 mL Exposure duration: GDs 6-15 (daily)	**Maternal toxicity** <u>*Preliminary study (dose range-finding study)*</u> • **Effects indicative of anaemia:** 400 mg/kg bw/d: clinical signs, transient: wobbly gait, weak body tone, general decreased responsiveness; ↓ bw; blood: reticulocyte (GD16/20: 81/36 %), ↑ methaemoglobin (GD16: 39 %, GD20: 9 %) ≥ 25 mg/kg bw/d: blood: ↑ methaemoglobin (GD16/20: 6/4 %), ↑ reticulocyte count (GD16/20: 18/14 %) ≥ 100 mg/kg bw/d: necropsy: enlarged spleen <u>*Main study*</u> ≥ 200 mg/kg bw/d: clinical signs, transient: wobbly gait, general decreased responsiveness, urine stains ≥ 60 mg/kg bw/d: necropsy: enlarged spleen **$LOAEL_f$ = 25 mg/kg bw/d** (enlarged spleen) According to CLP: **no classification for STOT-RE** (based on equivalent guidance value for studies with exposure shorter than 9 days (i.e. 10 % of the 90 days, STOT-RE 2, oral (rat): ≤ 1000 mg/kg bw/d)	**Key study** Test substance: butanone oxime, purity: > 99 %	TL19 (1990a), unpublished study report, confidential Derelanko et al. (2003)
Oral (gavage) Developmental toxicity study according to OECD TG 414/ EU B.31, GLP compliant **Rabbit**; New Zealand White; female (preliminary study: 5/dose; main study: 18/dose) Doses tested: 0, 10, 20, 40, 80 mg/kg bw/day in preliminary study. 0, 8, 14, 24, 40 mg/kg bw/day in main study; dose volume: 2 mL Exposure duration: GDs	**Maternal toxicity** <u>*Preliminary study (dose range-finding study)*</u> • **Effects indicative of anaemia:** 80 mg/kg bw/d for 2 days (cumulative 160 mg/kg bw) induced mortality: ≤ 48h in 2/5 females; between GD8-10 all 5/5 females died (data considered for classification to acute oral toxicity) clinical signs: dark red or reddish-green coloured urine; necropsy: enlarged spleen, brown discoloured lungs 40 mg/kg bw/d: mortality: 2/5 between GD10-11 ≥ 40 mg/kg bw/d: clinical signs: laboured breathing, decreased activity, few or no faeces, pale ears and/or eyes, eyes dark in colour, brown or reddish coloured fluid in the cage/tray; blood: ↑ reticulocyte (GD13/29: 78/5 %), ↑ methaemoglobin (GD13/29: 42/9 %) 10 mg/kg bw/d: blood: ↑ reticulocyte (GD13/29: 9/5 %), ↑ methaemoglobin (GD13/29: 6/4 %) <u>*Main study*</u> 40 mg/kg bw/d: mortality: 8/18 between GD11-24 clinical signs: decreased activity, wobbly gait, no faeces, greenish or reddish coloured fluid in the cage/tray, urine stains, emaciation, pale eyes and ears, and yellowish coloured crusty material in the nostrils; ↓: bw, food consumption; necropsy: fluid contents in the thoracic cavity, brown discoloration of the lungs, mucoid material attached to the mucosa of the stomach, pale liver, accentuated lobular markings on the liver, urinary bladder with dark red fluid contents and thickened mucosa **$LOAEL_f$ = 10 mg/kg bw/d** (effects indicative of anaemia)	**Key study** Test substance: butanone oxime, purity: > 99 %	TL19 (1990a), unpublished study report, confidential Derelanko et al. (2003)

6-18 (daily)	According to CLP: **no classification for STOT-RE** (based on equivalent guidance value for studies with exposure shorter than 90 days (STOT-RE 2, oral (rat): 28 day: guidance value ↑ by a factor of 3 → ≤ 300 mg/kg bw/d, 14 days: additionally guidance value ↑ by a factor of 2 → ≤ 600 mg/kg bw/d)		
Inhalation Combined chronic toxicity and carcinogenicity study similar to OECD TG 453/ EU B.33, GLP compliant Interim sacrifice after 3, 12, 18 or 26 months **Rat**; F344; male/female (80/sex/dose) Doses tested: 0, 15, 75 or 374 ppm (nominal) Exposure regimen: vapour (particle size distribution: MMAD: 2.3-2.6 µm, GSD: 2.1-2.8), 6h/d, 5d/wk for 3, 12, 18 and 26 months; whole body	• **Effects indicative of anaemia:** ***3 months:*** 374 ppm (1346 mg/m^3), m/f: blood: ↑: methaemoglobin (1.2 %), MCH (2 %), MCV (6 %), platelets (25 %), leukocytes (6 %), ↓: Hb (4 %), RBC (7 %), MCHC (4 %); ↑ weight, m/f, spleen: (33/33 %); necropsy: spleen: ↑: congestion (m); histopathology: pigment in reticuloendothelial cells (assumed to be haemosiderin), extramedullary haematopoiesis in spleen ***12 months:*** 374 ppm (1346 mg/m^3): blood: males: ↓ Hb, Ht, RBC and platelets, females: ↓ Hb, Ht, RBC and platelets, MCV, MCH; liver: ↑ weight (m), spleen: ↑ weight (m/f, 33 %); necropsy: spleen: congestion (m/f); histopathology: spleen: ↑ extramedullary haematopoiesis (f), ≥ 15 ppm (54 mg/m^3), m/f: spleen: ↑ congestion ≥ 75 ppm (270 mg/m^3): necropsy: spleen: enlarged; histopathology: spleen: pigment in reticuloendothelial cells (hemosiderin) (m) ***18 months:*** ≥ 15 ppm (54 mg/m^3): females: necropsy: spleen: ↑ congestion 374 ppm (1346 mg/m^3): females: histopathology: spleen: ↑ pigment in reticuloendothelial cells, extramedullary haematopoiesis **Reversibility:** haematology parameters, m/f: after 18/26 months • **Liver effects** ***3 months:*** 374 ppm (1346 mg/m^3): ↑ weight, m/f (23/15 %) ***12 months:*** ≥ 75 ppm (270 mg/m^3): basophilic foci and vacuoles in hepatocytes (m), ↓: hyperplasia/proliferation of the biliary duct and peribiliary fibrosis (m/f) ***18 months:*** 374 ppm (1346 mg/m^3), males: basophilic foci and vacuoles in hepatocytes, ↓: hyperplasia/proliferation of the biliary duct and peribiliary fibrosis ***26 months:*** ≥ 15 ppm (54 mg/m^3): ↑ spongiosis hepatis (m) ≥ 75 ppm (270 mg/m^3): ↑ intracytoplasmic vacuoles (m) 374 ppm (1346 mg/m^3): ↑ weight (m: 40 %); histopathology: m/f: ↑ basophilic foci in hepatocytes, spongiosis hepatis; vacuoles • **Effects on the olfac. epithelium in the nasal turbinates** ***12 months:*** ≥ 75 ppm (270 mg/m^3): degeneration on the olfactory epithium in the nasal turbinates characterized by thinning of the layers in the dorsal meatus in turbinate sections 2-4 (m/f) ***18 months:*** 374 ppm (1346 mg/m^3): degeneration of the olfactory epithelium in the dorsal meatus in turbinate sections 2-3 (m/f), 4 (m) ***26 months:*** ≥ 15 ppm (54 mg/m^3): dose-related ↑ degeneration of the olfactory epithelium in the dorsal meatus in turbinate sections 2-4 (m/f) • **Effects on testes:** ***3 months:*** 374 ppm (1346 mg/m^3): ↑ weight (82 %) ***26 months:***374 ppm (1346 mg/m^3): ↑ weight (82 %) without corroborate findings during histopathology **LOAEC$_{sys, m/f}$ = 15 ppm (54 mg/m^3)** based on spleen effects (congestion, increased pigmentation (hemosiderin) in the reticuloendothelial cells, and extramedullary haematopoiesis **LOAEC$_{local, m/f}$ = 15 ppm (54 mg/m^3)** based on effects of the olfactory epithelium in the nasal turbinates	**Key study** Test substance: butanone oxime, purity: > 99.9 %	Newton et al. (2001); TL18 (1994), unpublished study report, confidential

	According to CLP: **no classification for STOT-RE** (based on guidance value STOT-RE 2, inhalation, vapour: 3 months: ≤ 1 mg/L/6h/d; equivalent guidance value for longer studies: 12 months → ≤ 0.25 mg/L/6h/d; 18 months → ≤ 0.17 mg/L/6h/d; 26 months → ≤ 0.11 mg/L/6h/d)		
Inhalation Combined chronic toxicity and carcinogenicity study similar to OECD TG 453/ EU B.33, GLP compliant **Mouse** CD-1; male/female (60/sex/dose) Doses tested: 0, 15, 75 or 374 ppm (nominal) Exposure regimen: vapour (particle size distribution: MMAD: 2.1-2.7 µm, GSD: 2.7-3.4), 6h/d, 5d/wk for 3, 12, 18 and 26 months; whole body	• **Effects indicative of anaemia:** ***12 months:*** ≥ 15 ppm (54 mg/m^3): liver: ↑ pigment (hemosiderin) in reticuloendothelial cells ≥ 75 ppm (≥ 274 mg/m^3): blood: ↓ MCHC (2.7 %) (f) 374 ppm (1346 mg/m^3): blood: ↑: methaemoglobin (m: 0.5 %), ↑: platelets (f: 35 %), ↓: MCHC (f: 3.3 %) ***18 months:*** ≥ 15 ppm (54 mg/m^3): liver: ↑ pigment (hemosiderin) in reticuloendothelial cells • **Liver effects:** ***12 months:*** ≥ 15 ppm (54 mg/m^3): centrilobular hypertrophy, granulomatous inflammation, and necrosis (m/f) ≥ 75 ppm (≥ 274 mg/m^3): centrilobular hepatocellular hypertrophy and necrosis (m) 374 ppm (1346 mg/m^3): ↑ relative liver weight (m/f: 12/17 %) ***18 months:*** ≥ 15 ppm (54 mg/m^3): centrilobular hypertrophy, granulomatous inflammation, and necrosis (m/f) • **Effects on the olfac. epithelium in the nasal turbinates** ***12 or 18 months:*** ≥ 15 ppm (54 mg/m^3): degenerative changes and formation of replacement tissue on the olfactory epithelium in the nasal turbinates (m/f) **LOAEC$_{sys,\ m/f}$ = 15 ppm (54 mg/m^3)** based on effects indicative of anaemia **LOAEC$_{local,\ m/f}$ = 15 ppm (54 mg/m^3)** based on effects of the olfactory epithelium in the nasal turbinates According to CLP: **no classification for STOT-RE** (based on guidance value STOT-RE 2, inhalation, vapour: 3 months: ≤ 1 mg/L/6h/d; equivalent guidance value for longer studies: 12 months → ≤ 0.25 mg/L/6h/d; 18 months → ≤ 0.17 mg/L/6h/d)	**Key study** Test substance: butanone oxime, purity: > 99.9 %	Newton et al. (2001); TL18 (1993), unpublished study report, confidential

4.7.1 Non-human information

4.7.1.1 Repeated dose toxicity: oral

There are several oral repeated dose toxicity studies of butanone oxime with different time durations available. Butanone oxime was administered by gavage or with the drinking water to rats, mice or rabbits. Data from developmental toxicity studies in rats and rabbits (oral, gavage, according to OECD TG 414/EU B.31; TL19, 1990a,b, unpublished study report, confidential; Derelanko et al. 2003) and from a two-generation study with CD rats (oral, gavage, similar to OECD TG 416/EU B.35; TL17, 1992, unpublished study report, confidential; Tyl et al. 1996) were also evaluated with regards to repeated dose toxicity of butanone oxime. In all studies butanone oxime was used as test material. The results from the NTP studies in rats and mice and from the developmental toxicity studies in rats and rabbits are presented in the summary Table 19 (see there).

The results from further experimental studies on repeated dose toxicity after oral administration of butanone oxime are summarised in Table 20.

Table 20: Results from further repeated dose toxicity studies, oral administration of butanone oxime

Reference Species; strain; sex; method	Results
TL9 (1991), unpublished study report, confidential; Schulze and Derelanko (1993) Sub-chronic, 90-day study, oral (gavage), equivalent to OECD TG 408/EU B.26, GLP compliant **Rat**; Sprague-Dawley; male/female (10/sex/dose) Test substance: butanone oxime purity: > 99.8 % Doses tested: 0, 40, 125, 400 mg/kg bw/day (actual ingested) Exposure duration: daily, 5 days/week, 13 weeks	• **Effects indicative of anaemia:** m/f: ≥ 40 mg/k g bw/d: blood: ↓: RBC count, Hct; ↑: methaemoglobin level, leucocytosis, regenerative anaemia, compensatory reticulocytosis, Heinz body formation, further erythrocytic morphologic changes (not further specified); spleen: ↑ weight **$LOAEL_{m/f}$ = 40 mg/k g bw/d** (effects indicative of anaemia) **$NOAEL_{m/f}$ = 125 mg/kg bw/d** (neurobehavioral effects)
TL1 (1977), unpublished study report, confidential; TL23 (1988), unpublished study report, confidential; TL7 (1990), unpublished study report, confidential Sub-chronic, oral (gavage=, equivalent to OECD TG 408/EU B.26, no GLP compliance **Rat**; Sprague-Dawley; male/female (10/sex/dose) Test substance: butanone oxime purity: confidential (> 98 %) Doses tested: 0, 25, 75, 225 mg/kg bw/day (actual ingested) Exposure duration: daily, 5 days/week, 13 weeks	• **Effects indicative of anaemia:** m/f: ≥ 25 mg/kg bw/d: changes in blood parameters indicative of haemolytic anaemia (data not specified), and compensatory haematopoiesis, extramedullary haematopoiesis in spleen and liver (no more data) **$LOAEL_{m/f}$ = 25 mg/kg bw/d** (haemolytic anaemia and compensatory haematopoiesis)
TL14 (1995a), unpublished study report, confidential Sub-acute, oral (gavage), Method: assessment of peroxisome proliferation, hepatic glutathione and serum testosterone levels,	Up to 500 mg/kg bw/d: no peroxisome proliferation, no effect on testosterone level ≥ 250 mg/kg bw/d: ↑ hepatic glutathione levels after 14 days, hepatocellular hypertrophy after 14 and 28 days

Reference Species; strain; sex; method	Results
GLP compliant **Rat**, F344; male (15/dose) Test substance: butanone oxime purity: 99.2 % Doses tested: 0, 250,500 mg/kg bw/day (actual ingested) Exposure duration. Daily for 7, 14 or 28 days	
TL12 (1996), unpublished study report, confidential Sub-acute, oral (gavage), Japanese guideline, similar to OECD TG 407/EU B.7, GLP compliant **Rat**; Crj: CD(SD); male/female (7/sex/dose) Test substance: butanone oxime purity: confidential (> 98 %) Doses tested: 0, 4, 20, 100 mg/kg bw/day (actual ingested) Exposure duration: daily for 28 days, recovery period of 14 days	• **Effects indicative of anaemia:** ≥ 20 mg/kg bw/d: blood: ↑ reticulocyte ratio (m/f), ↑ platelet count (f); ↓ RBC count, Hct, Hb (f) 100 mg/kg bw (m/f): spleen: ↑ abs/rel organ weight, hypertrophy, congestion, hemosiderin granules; liver: Kupffer cells: ↑ hemosiderin granules; liver and spleen: extramedullary haematopoiesis; kidney: lipofuscin-like substance in tubular epithelium; reversibility of the most changes at the end of recovery (not further specified) **$LOAEL_{m/f}$ = 20 mg/kg bw/d** (effects on blood parameters indicative of anaemia) **$NOAEL_{m/f}$ = 4 mg/kg bw/d** (effects on blood parameters indicative of anaemia)

Reference Species; strain; sex; method	Results
TL17 (1992), unpublished study report, confidential; Tyl et al. (1996) Two-generation study, oral (gavage); EPA guideline with modifications, similar to OECD TG 416/EU B.35; GLP compliant **Rat**; CD Sprague-Dawley (Crl:CD[SD]BR) VAF/Plus); male/female (30/sex/dose; at least 20 pregnant females/group) Test substance: butanone oxime purity: > 99 % Doses tested: 0, 10, 100, 200 mg/kg bw/day; dosing volume: 2.0 ml/kg bw/day Exposure regimen: F0 generation: starting from 8 wk of age during 10 wk pre-mating, 3 wk mating period (continued dosing). F1 generation: starting from 11 wk of age in the same regime. (5 days/week);	• **Effects indicative of anaemia:** **200 mg/kg bw/d: mortality: 4/30 (13.3 %) F0m, 11/30 (36.7 %) F0f, 15/30 (50 %) in F1m, 8/30 (26.7%) in Flf** **disturbance of general behaviour: tremors, salivation, slow respiration, mouth breathing, lethargy, staggering, and rooting in bedding post dosing in F0m, tremors, ataxia, and convulsions (only in moribund animals), stupor, abnormal respiration (audible, irregular, raspy, laboured), dyspnoea, dehydration, excessive urination, bright yellow urine, and rooting in bedding in F0f, tremors, audible breathing, and rooting in bedding in Flm, and lethargy, abnormal respiration (laboured, gasping, and raspy), cyanosis, and rooting in bedding in Flf** **blood: consistent picture of anaemia in both sexes in both generations: ↓: RBC count, Hb, Hct, ↑: MCV, MCH, WBC count (no change in differential counts) F0m/f + Flm/f, methaemoglobin in F0m + Flm** **necropsy: ↑: abs. and rel. weights of spleen in F0m/f/Flm/f, rel. weights of liver in Flm + F0f/Flf** **histopathology: spleen: congestion, and in spleen and liver: extramedullary haematopoiesis and haemosiderosis in F0m/f + Flm/f** **100 mg/kg bw/d:** **clinical signs of toxicity: F0m: lethargy, staggering, and rooting in bedding; F0f: weaving, tremors, and rooting in bedding; Flm: slight dehydration, audible breathing, and rooting in bedding; and Flf: laboured breathing** **blood: consistent picture of anaemia in both sexes in both generations: F0m + F1m: ↓ RBC count (26/31 %), ↓ Hb (9/14 %), F0f + F1f: ↓ RBC count (16/25 %), ↓ Hb (8/11 %), ↑:WBC (no change in differential counts) in F0m, Flm + F0m: ↑ methaemoglobin (82%)** **necropsy: ↑ abs. and rel. weights of spleen** **histopathology: in spleen and liver extramedullary haematopoiesis and haemosiderosis in F0m/f + Flm/f** **10 mg/kg bw/d:** **clinical signs of toxicity: F0m +F1m: rooting in bedding** **blood: F0m: ↓ RBC count (10 %), Hb (6 %)** **necropsy: F0m: dark spleens (5/30)** **histopathology: spleen and liver extramedullary haematopoiesis and haemosiderosis in F0m/f + Flm/f** **LOAELm/f = 10 mg/kg bw/d (effects indicative of anaemia and neurobehavioral effects)**

4.7.1.2 Repeated dose toxicity: inhalation

For the inhalation route of exposure five repeated dose toxicity studies with butanone oxime are available. The study results from the combined chronic toxicity/carcinogenicity studies in rats and mice (according to OECD TG 453/EU B.33) were also evaluated regarding non-neoplastic effects. The results from these studies in rats and mice are presented in the summary Table 19 (see there). In all studies butanone oxime was used as test material. The results from further experimental studies on repeated dose toxicity following inhalation route of exposure are summarised in Table 21.

Table 21: Repeated dose toxicity studies, inhalation exposure to butanone oxime

Reference Species; strain; sex; method	Results
TL4 (1990), unpublished study report, confidential Sub-acute, inhalation (vapour), whole body; similar to OECD TG 412/ EU B.8; GLP compliant **Rat;** F344; male/female; Test substance: butanone oxime purity: 99.9 % Doses tested: 0, 30, 101, 340 ppm (nominal) Exposure duration: 6h/d, 5d/wk, 4 weeks	• **Effects indicative of anaemia:** 404 ppm (1440 mg/m^3/6h/d) (m/f): blood: ↓ (10 %): Hb, Hct, RBC, MCHC; ↑: methaemoglobin (0.5 %), reticulocytes (threefold), platelets (30 %), leukocytes (13 %); liver and spleen: ↑ weights (30 %), no related histological effects in these organs **LOAEC$_{sys, m/f}$ = 102 ppm (360 mg/m^3/6h/d)** (effects on blood parameters) **NOAEC$_{sys, m/f}$ = 25 ppm (90 mg/m^3)** (effects on blood parameters) **NOAEC$_{local, m/f}$ = 404 ppm (1440 mg/m^3/6h/d)**
TL4 (1990), unpublished study report, confidential Sub-acute, inhalation (vapour), whole body; equivalent to OECD TG 412/EU B.8, GLP compliant **Mouse;** CD-1; male/female; Test substance: butanone oxime purity: 99.9 % Doses tested: 30, 101, 341 ppm (nominal) Exposure duration: 6h/d, 5d/wk, 4 weeks	• **Effects indicative of anaemia:** 400 ppm (1440 mg/m^3/6h/d) (m/f): blood: ↑: methaemoglobin (1-2 %), spleen: ↑ weight (30 %), no histology data **NOAEC$_{sys}$ = 102 ppm (360 mg/m^3/6h/d)** (effects on blood parameters) **NOAEC$_{local}$** = no data available
TL14 (1995b), unpublished study report, confidential; Newton et al. (2002) Effects on the olfactory epithelium and recovery were assessed, inhalation (vapour), whole body, equivalent to OECD TG 413/EU B.29, GLP compliant **Mouse;** CD-1; male (Main study: 10/dose/interval; satellite groups: 5/dose/interval) Test substance: butanone oxime purity: 99.2 %	• **Effects on the nasal olfactory epithelium:** ≥ 10 ppm (36 mg/m³/6h/d) (m): After 1, 2, 4, 13 wk: nasal cavity: 10 % of the total olfactory tissue affected, degeneration of the olfactory epithelium in dorsal meatus of the anterior region dose-related ↑ in incidence and severity: ≥ 30 ppm after 1 wk, replacement by squamous/squamoid and/or respiratory epithelium within prolonged recovery of 13 wk; ≥ 10 ppm after exposure for 13 wk, full recovers within 4 wk **LOAEC$_{local}$ = 30 ppm (108 mg/m^3) after 1 wk (30 total hours of exposure)** (based on degeneration of the olfactory epithelium in the nasal cavity) **NOAEC$_{local}$ = 3 ppm (10.8 mg/m³/6h/d)** (based on degeneration of the olfactory epithelium in the nasal cavity)

Doses tested: 0.3, 10, 30, 100 ppm (10.8, 36, 108, 360 mg/m3) (analytical conc.) Exposure duration: 6h/d, 5d/wk, for 1, 2, 4, 13 wks, recovery period of 4 or 13 wk, microscopy limited to nasal turbinates;	

4.7.1.3 Repeated dose toxicity: dermal

No information is available in experimental animals.

4.7.1.4 Repeated dose toxicity: other routes

No information is available.

4.7.1.5 Human information

No information is available.

4.7.1.6 Other relevant information

No information is available.

4.7.1.7 Summary and discussion of repeated dose toxicity

The assessment of target organ toxicity through repeated exposure to butanone oxime is based on animal testing. No information with respect to repeated dose toxicity of butanone oxime in humans is available.

Repeated dose toxicity studies on butanone oxime have been conducted in rats and mice using oral application and inhalation. The information on health effects after long-term repeated exposure of butanone oxime by inhalation was complemented by the non-neoplastic results from the combined chronic toxicity and carcinogenicity studies in rats and mice. In addition the results of the oral developmental toxicity studies in rats and rabbits and of a two-generation toxicity study in rats were considered for the evaluation of the specific target organ toxicity (repeated exposure) of butanone oxime.

Oral route: Gavage and drinking water studies with durations of 4 and 13 weeks have been conducted with rats, and one 13-week drinking water study with mice. The maternal toxicity data from developmental toxicity studies using rats and rabbits and the toxicity data of adult rats from repeated oral exposure by gavage observed from a two-generation toxicity study are also included in the assessment of butanone oxime toxicity.

The major target of butanone oxime toxicity was the haematopoietic system (blood) of rats, mice and rabbits. Further lesions observed compromise neurobehavioral effects in rats and rabbits,

degeneration of the nasal olfactory epithelium in rats and mice and hyperplasia of the urinary bladder transitional epithelium in mice.

Butanone oxime caused dose-related increased **effects on blood** parameters indicative of haemolytic anaemia and compensatory medullary haematopoiesis, as well as extramedullary haematopoiesis in the spleen and liver. In studies with rats and mice, the effects on the blood increased regarding incidence and severity were observed at doses ≥ 10 mg/kg bw/d, serious effects were seen in male and female rats at ≥ 175/215 mg/kg bw/d and in male and female mice at ≥ 755/1010 mg/kg bw/d. The effects were methaemoglobinaemia, formation of Heinz bodies, increased reticulocyte count, increased incidences of haematopoietic proliferation in the bone marrow, regenerative haematopoietic cell proliferation in the spleen and liver, liver Kupffer cell erythrophagocytosis and haemosiderin pigmentation, as well as renal tubule haemosiderin pigmentation.

In developmental toxicity studies in rats and rabbits, oral administration of butanone oxime to dams by gavage produced clear evidence of maternal toxicity in both species which showed effects indicative of anaemia. The effects on the blood occurred at ≥ 25 mg/kg bw/d in rats and at ≥ 10 mg/kg bw/d in rabbits. Pregnant animals may show particular sensitivity as mortalities were not seen in non-pregnant rats at 25 mg/kg bw/d. In the two-generation toxicity study in rats oral (gavage) administration of 10 mg/kg bw/d and higher induced reduced red blood cell counts and haemoglobin concentration in F0 males associated with extramedullary haematopoiesis and haemosiderosis in liver and spleen. Findings of extramedullary haematopoiesis and haemosiderosis in liver and spleen, unaccompanied by any other indications of blood toxicity were also seen in Fl male and female rats receiving 10 mg/kg bw/d. Based on the haematology and microscopic findings in spleen and liver an increased anaemia response with a clear dose relation is suggested. Increased spleen weights and splenic and hepatic extramedullary haematopoiesis (haematopoietic cell proliferation) and haemosiderosis (pigment deposition from haemoglobin breakdown products) observed at ≥ 100 mg/kg bw/d (cut off value for classification as STOT-RE2) were consistent with haemolytic anaemia and compensatory erythropoiesis. The effects at this dose levels (≥ 100 mg/kg bw/d) were accompanied by reduced body weight and weight gain, reduced feed consumption, and clinical signs of toxicity (cyanosis).

Overall, the lowest oral $LOAEL_{sys}$ for adverse effects on the blood of butanone oxime was 10 mg/kg bw/d, based on reduced red blood cell counts and haemoglobin concentration associated with extramedullary haematopoiesis and haemosiderosis in liver and spleen of adult male and female rats observed in a two-generation reproduction study (similar to OECD TG 416/EU B.35; TL17, 1992, unpublished study report, confidential; Tyl et al. 1996). For short-term exposures the lowest oral $LOAEL_{sys}$ of butanone oxime was also 10 mg/kg bw/d, based on signs indicative of anaemia in adult female rabbits observed in a range-finding developmental study (according to OECD TG 414/EU B.31; TL19, 1990b, unpublished study report, confidential; Derelanko et al. 2003).

In a sub-chronic study in rats, **transient neurobehavioral changes** (cage removal, posture, impaired gait, arousal, salivation, approach response, rearing responses, and disturbed aerial righting reflex) were noted immediately after dosing with 400 mg/kg bw/d. These changes in neurobehavioral function were consistent with CNS depression, but no evidence of cumulative neurotoxicity was detected. A dose of 125 mg/kg bw/d butanone oxime did not induce changes in neurobehavioral function or nervous system structure in rats. Female rabbits (dams) treated with 40 mg/kg bw/d and higher during the GD6-18 exhibited neurological effects, e.g. decreased activity and wobbly gait. For neurobehavioral effects of butanone oxime a $NOAEL_{sys}$ of 125 mg/kg bw/d was derived in male and female Sprague-Dawley rats from a sub-chronic toxicity study (equivalent

to OECD TG 408/ EU B.26; TL9, 1991, unpublished study report, confidential; Schulze and Derelanko 1993).

Degenerative effects on the olfactory epithelium in the nasal turbinates were noted in the sub-chronic drinking water studies in male and female rats at ≥ 2500 ppm (≥ 175/215 mg/kg bw/d) and in male mice at ≥ 5000 ppm (≥ 755 mg/kg bw/d) and in female mice at ≥ 2500 ppm (≥ 630 mg/kg bw/d). For butanone oxime a NOAEL of 100 mg/kg bw/d for effects on the nasal olfactory epithelium was determined in a sub-chronic drinking water study (equivalent to OECD TG 408/EU B.26) with male and female F344 rats (NTP 1999).

Hyperplasia of the urinary bladder transitional epithelium occurred in exposed male and female mice via drinking water for 13 weeks at ≥ 2500 ppm (≥ 515/630 mg/kg bw/d). A $NOAEL_{sys}$ for changes in the urinary bladder (hyperplasia of the transitional epithelium associated with inflammatory reactions) of butanone oxime was established in a sub-chronic drinking water study (equivalent to OECD TG 408/EU B.26) at 110 mg/kg bw/d in male mice and at 340 mg/kg bw/d in female mice (NTP 1999).

Inhalation: Repeated exposure of rats and mice to butanone oxime by inhalation produced methaemoglobin formation, haemolytic anaemia including compensatory regenerative cell proliferation of haematopoietic cells and spleen haemosiderosis, non-neoplastic liver effects (rats: basophilic foci and hepatocyte vacuoles; mice: hypertrophy and necrosis) increased weight of the testes (rats only), and degenerative changes on the olfactory epithelium in the nasal turbinates primarily in the dorsal meatus followed by formation of replacement tissue.

Effects on the blood were observed in sub-acute, sub-chronic and chronic studies in rats and mice. In a sub-acute study in rats butanone oxime caused effects on blood parameters including increased levels of methaemoglobin at concentrations of ≥ 102 ppm (≥ 360 mg/m^3/6h/d) (TL4, 1990, unpublished study report, confidential). A NOAEC of 25 ppm (90 mg/m^3) was derived for effects on the blood. In the combined chronic toxicity and carcinogenicity study in rats (with interim analysis, sacrifices at 3, 12, and 18 months), similar effects on blood parameters were seen at 374 ppm (1346 mg/m^3) after exposures of 3 or 12 months in males and females. Spleen effects (increased organ weight, extramedullary haematopoiesis, and haemosiderosis) occurred at the same concentration and duration of exposure. No effects on blood parameters and no findings in the spleen were noted after 18 months in males or after 26 months in both sexes. In mice, a 4-week inhalation toxicity study showed a slight increase in methaemoglobin levels as well as increased spleen weights at 400 ppm (1440 mg/m^3) and a NOAEC was derived at 100 ppm (360 mg/m^3). At the 12 months sacrifice of an 18 months combined chronic toxicity and carcinogenicity study in mice the effects of butanone oxime on the blood occurred less clear than in rats. A slight methaemoglobin formation was noted in males at 374 ppm (1346 mg/m^3). Methaemoglobin did not appear to be formed in females, but there was a significant increase in platelets (35 %) in the 374 ppm (1346 mg/m^3) group and a significant decrease in mean corpuscular haemoglobin concentration (MCHC) at 76 ppm (2.7 %) and 374 ppm (3.3 %). At termination of the study, no indications of any treatment-related effects on the differential leukocyte count or erythrocyte morphology in either male or female mice were observed. The lowest LOAEC value for haematotoxic effects of butanone oxime was established in rats and mice at 15 ppm (54 mg/m^3) derived from combined chronic toxicity and carcinogenicity studies (similar to OECD TG 453/ EU B.33; 26/18 months study, whole body inhalation, 6h/d, 5d/wk) in both species (Newton et al. 2001; TL18, 1994, 1993, unpublished study reports, confidential).

Liver effects were observed in rats and mice on a dose-related manner in the life-time studies (combined chronic toxicity and carcinogenicity studies, inhalation). The liver changes, indicating hepatotoxicity, included increased incidences of basophilic foci and vacuoles in the hepatocytes of male rats exposed at 75 ppm (270 mg/m^3) and in both sexes exposed at 374 ppm (1346 mg/m^3). Liver effects were seen in mice as increases in centrilobular hypertrophy and necrosis and were noted at 15 ppm (54 mg/m^3) and higher. Accordingly, the LOAEC for systemic effects was derived at 15 ppm (54 mg/m^3) for mice based on the observed liver effects.

As further finding in the combined chronic toxicity and carcinogenicity study **enlarged testes** were seen in male rats exposed at 75 and 374 ppm (270 and 1346 mg/m^3), which did not correlate with any microscopic findings.

Effects on the respiratory system were reported from the inhalation combined chronic toxicity and carcinogenicity studies in rats and mice (similar to OECD TG 453/EU B.33, whole body exposure, 6h/d, 5d/wk). Mice appear to be more susceptible to the nasal effects of butanone oxime than rats. In the nasal turbinates degenerative effect on the olfactory epithelium of the nasal turbinates was noted at all tested exposure concentrations (≥ 15 ppm; equivalent to ≥ 54 mg/m^3). 15 ppm was derived as the lowest LOAEC for effects on the respiratory tract in the mouse observed both after 12 and 18 months of exposure (Newton et al. 2001; TL18 1993, unpublished study report, confidential).

4.8 Specific target organ toxicity (CLP Regulation) – repeated exposure (STOT-RE)

4.8.1 Summary and discussion of repeated dose toxicity findings relevant for classification as STOT-RE according to CLP Regulation

The evaluation of target organ toxicity through repeated exposure to butanone oxime is based on animal tests conforming to internationally agreed test guidelines. There were studies in rats, mice and rabbits. No information is available on toxicity after repeated exposure to butanone oxime in humans.

Dose-related toxic effects were observed in rats and mice in studies with different testing time periods for both examined routes (oral, inhalation), and were also noted in the developmental toxicity studies in rats and rabbits, and in a two-generation toxicity study in rats given butanone oxime by oral application.

Target organs of toxicity after repeated oral administration of butanone oxime are the haematopoietic system, the nervous system, the liver and the urinary bladder in experimental animals. Effects on the nasal olfactory epithelium were seen after exposure by the oral route and inhalation, thus considered to be a systemic effect.

Haemolytic anaemia was the main toxic effect corresponding with decreases in red blood cell parameters (RBC count, Hb, Hct), damaged erythrocytes (Heinz bodies), methaemoglobinaemia, breakdown product of haemoglobin, and increased degrees of deposited haemosiderin in spleen, liver and kidney, and extramedullary haematopoiesis in spleen and liver, and clinical signs (paleness, cyanosis). The effects on the erythrocytes were generally less severe with the inhalation exposure. The rabbit and the rat appeared to be more sensitive than the mouse to the haemolytic effects of butanone oxime.

In rats anaemic blood effects were observed in sub-chronic oral toxicity studies at doses of ≥ 25 mg/kg bw/d and in a two-generation toxicity study at ≥ 10 mg/kg bw/d. Haematotoxicity was more pronounce in male and female rats at ≥ 175/215 mg/kg bw/d and in mice at doses of ≥ 755/1010 mg/kg bw/d after a sub-chronic exposure. In a two-generation toxicity study in rats, effects on the blood indicative of haemolytic anaemia with concomitant extramedullary haematopoiesis and haemosiderosis in liver and spleen (and increased spleen weights) was observed at 100 mg/kg bw/d and higher.

In developmental studies in rats and rabbits, oral administration by gavage of butanone oxime to dams produced clear evidence of maternal toxicity in both species. Effects on the blood occurred at ≥ 25 mg/kg bw/d in rats and at ≥ 10 mg/kg bw/d in rabbits. Mortalities that occurred in pregnant rabbits after treatment with two oral doses of 80 mg/kg bw/d butanone oxime during the gestation phase, i.e. methaemoglobin formation within the first 48 hours, were covered by classification for acute oral toxicity.

The lowest LOAEC value for effects of butanone oxime indicative of anaemia was established in rats and mice exposed by inhalation at 15 ppm (54 mg/m^3) derived from combined chronic toxicity and carcinogenicity studies (similar to OECD TG 453/EU B.33) in both species (Newton et al. 2001; TL18, 1994, 1993, unpublished study reports, confidential). The red blood cell reduction was at least partly compensated by increased erythrocyte production resulting in release of increased reticulocytes to the blood stream. With increasing demand on the regenerative activity by the bone marrow, extramedullary erythropoiesis was seen mainly in the spleen and the liver. The degree of anaemia was not progressive with long-life repeated inhalation exposure. This development was primary driven by this compensatory erythropoiesis. In the combined chronic toxicity and carcinogenicity study in rats, adaptation by continuous excitation of erythrocyte production was evident with values for most of the erythrocyte parameters being similar between butanone oxime-exposed and control male rats after 18 months of exposure and for females by study termination after 26 months. It is to note that as a consequence of an elevated decompensation of damaged erythrocytes that persistent distress in the liver and the spleen may occur.

Effects on the nasal olfactory epithelium were seen after exposure by the oral route and inhalation, thus considered to be a systemic effect. In sub-chronic drinking water studies (equivalent to OECD TG 408/EU B.26) in male and female rats effects on the nasal olfactory epithelium were seen at ≥ 2500 ppm (≥ 175/215 mg/kg bw/d), and in male mice at ≥ 5000 ppm (≥ 755 mg/kg bw/d) and in female mice at ≥ 2500 ppm (≥ 630 mg/kg bw/d).

In combined chronic toxicity and carcinogenicity studies (similar to OECD TG 453/EU B.33, whole body exposure, 6h/d, 5d/wk) repeated exposure by inhalation to butanone oxime of rats and mice caused effects on the olfactory epithelium of the nasal turbinates at all tested exposure concentrations (≥ 15 ppm; equivalent to ≥ 54 mg/m^3).

In the sub-chronic studies transient neurobehavioral changes were noted immediately after oral application of rats with 400 mg/kg bw/d and in rabbits with ≥ 40 mg/kg bw/d. No changes in neurobehavioral function or nervous system structure was noted in rats at dose level of 125 mg/kg bw/d butanone oxime (see 4.3 Specific target organ toxicity – single exposure (STOT SE)).

4.8.2 Comparison with criteria of repeated dose toxicity findings relevant for classification as STOT-RE

Target organ toxicity, repeated exposure (STOT-RE) means specific, target organ toxicity arising from a repeated exposure to a substance or mixture. All significant health effects that can impair function, reversible and irreversible, immediate and/or delayed are included.

Classification of substances as specific target organ toxicants following repeated exposure is based on the weight of all evidence available, including the use of recommended guidance values which take into account the duration of exposure and the dose/concentration which produced the effect(s), and are placed in one of two categories, depending upon the nature and severity of the effect(s) observed. STOT-RE is assigned on the basis of findings of 'significant' or 'severe' toxicity. In this context 'significant' means changes which clearly indicate functional disturbance or morphological changes which are toxicologically relevant. 'Severe' effects are generally more pronounced or serious than 'significant' effects and are of a considerably adverse nature which significantly impact on health.

Categories for specific target organ toxicity-repeated exposure:

'*Category 1:* Substances that have pronounced significant toxicity in humans or that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to produce significant toxicity in humans following repeated exposure. Substances are classified in Category 1 for target organ toxicity (repeated exposure) on the basis of:

- Reliable and good quality evidence from human cases or epidemiological studies, or
- Observations from appropriate studies in experimental animals in which significant and/or severe toxic effects, of relevance to human health, were produced at generally low exposure concentrations. '

Thus classification in Category 1 is applicable, when significant toxic effects observed in a 90-day repeated dose study conducted in experimental animals are seen to occur within the guidance value ranges according to CLP (Annex I, Part 3, Table 3.9.2, Guidance values to assist in Category 1 classification):

Oral (rat):	C ≤ 10 mg/kg bw/d
Inhalation (vapour, rat):	C ≤ 0.2 mg/L/6h/d.'

No information is available on toxicity after repeated exposure to butanone oxime in humans. Studies in rats, mice and rabbits indicate that the haematological and neurological systems are relevant targets of the toxicity of butanone oxime. However, no significant/severe toxic effects from both the oral and inhalation toxicity studies were observed at dose levels approximately equal to the STOT-RE 1 cut-offs according to CLP (guidance values in Annex I, Part 3, Table 3.9.2).

'*Category 2:* Substances that, on the basis of evidence from studies in experimental animals, can be presumed to have the potential to be harmful to human health following repeated exposure. Substances are classified in Category 2 for target organ toxicity (repeated exposure) on the basis of observations from appropriate studies in experimental animals in which significant toxic effects, of relevance to human health, were produced at generally moderate exposure concentration. Classification in Category 2 is applicable, when significant toxic effects observed in a 90-day repeated dose study conducted in experimental animals are seen to occur within the guidance value

ranges according to CLP (Annex I, Part 3, Table 3.9.3, Guidance values to assist in Category 2 classification):

Oral (rat): $10 < C \leq 100$ mg/kg bw/d

Inhalation (vapour, rat): $0.2 < C \leq 1.0$ mg/L/6h/d.‘

The haematological and neurological systems and the respiratory tract are relevant targets of the toxicity of butanone oxime.

Repeated dose toxicity studies with butanone oxime in rats, mice and rabbits showed haematotoxicity such as anaemia after exposure by oral application or inhalation. The observations of haemotoxic effects caused by butanone oxime are considered represent a borderline case regarding classification for target organ toxicity arising from a repeated exposure. There is no doubt that butanone oxime produced significant health effects after repeated exposure. The effects of butanone oxime on the blood observed after repeated exposure by both the oral and the inhalation routes are considered as ‘adverse’ and at the high dose levels they can equally be considered as ‘severe’. Anaemic findings and secondary effects observed in rats after repeated oral administration of 100 mg/kg bw/d and higher in a two-generation toxicity study and at the highest concentration tested of 374 ppm (1346 mg/m^3) in a 2-year inhalation combined chronic toxicity and carcinogenicity study were not severe enough to justify classification. There was a tendency of reversibility of most of the disturbed erythrocyte parameters in male and female rats at termination of the combined chronic toxicity and carcinogenicity study. The observed increase in haemosiderosis in the spleen, liver or kidney was not combined with severe morphological changes like necrosis, fibrosis or cirrhosis. In conclusion, the effects observed from both the oral and inhalation toxicity studies at dose levels approximately equal to the STOT-RE 2 cut-offs according to CLP (Annex I, Part 3, guidance values: oral (rat): $10 < C \leq 100$ mg/kg bw/d; inhalation (vapour, rat): $0.2 < C \leq 1.0$ mg/L/6h/d) are not considered as significant toxic effects according to the CLP criteria (CLP Guidance, 3.9.2.5.2. Haemotoxicity).

Effects on the nasal olfactory epithelium were seen in rats and mice after exposure to butanone oxime by the oral route and inhalation. Signs of degenerative effects on the nasal olfactory epithelium were noted in male and female rats at doses of ≥ 2500 ppm (≥ 175/215 mg/kg bw/d), and in male mice of ≥ 5000 ppm (≥ 755 mg/kg bw/d) and in female mice of ≥ 2500 ppm (≥ 630 mg/kg bw/d) in sub-chronic drinking water studies which were all above the STOT-RE 2 cut-offs according to CLP (Annex I, Part 3, guidance values: oral (rat): $10 < C \leq 100$ mg/kg bw/d). After long-life repeated exposure to butanone oxime by inhalation effects on the olfactory epithelium of the nasal turbinates were noted in rats and mice at all concentration tested (≥ 15 ppm, equivalent to 0.054 mg/L/6h/d). Findings on the nasal olfactory epithelium observed in rats and mice up to the highest concentration tested of 374 ppm (1.346 mg/L/6h/d) were not severe enough to justify classification. It is concluded that butanone oxime does not fulfil the criteria for classification as STOT-RE according to CLP (STOT-RE 2 cut-offs according to Annex I, Part 3, guidance values: inhalation, vapour, rat: $0.2 < C \leq 1.0$ mg/L/6h/d (3 months); equivalent guidance value for longer studies: ≤ 0.17 mg/L/6h/d (18 months); ≤ 0.11 mg/L/6h/d (26 months).

In the sub-chronic studies (90-day studies) transient neurobehavioral changes were noted immediately after oral application of rats with 400 mg/kg bw/d and in rabbits with ≥ 40 mg/kg bw/d. No changes in neurobehavioral function or nervous system structure was noted in rats at dose level of 125 mg/kg bw/d butanone oxime. Based on these available data, butanone oxime does not fulfil the criteria for classification for target organ toxicity arising from a repeated oral exposure according to CLP (STOT-RE 2: oral (rat): $10 < C \leq 100$ mg/kg bw/d). However these

data are considered for the classification of butanone oxime on specific, non-lethal target organ toxicity arising from single exposure (STOT SE 3). For more details see Section ‘4.3 Specific target organ toxicity – single exposure (STOT SE)’.

4.8.3 Conclusions on classification and labelling of repeated dose toxicity findings relevant for classification as STOT-RE

There is no concern for specific target organ toxicity arising from a repeated oral or inhalation exposure to butanone oxime based on the available data.

According to CLP butanone oxime has not to be classified as STOT-RE.

4.9 Germ cell mutagenicity (Mutagenicity)

Table 22: Summary table of relevant *in vitro* mutagenicity studies

Method	Results	Remarks	Reference
In vitro study **Bacterial gene mutation test (Ames test,** gene mutation), equivalent or similar to OECD TG 471/EU B.14; GLP compliant S. typhimurium TA 1535, TA 1537, TA 98 and TA 100 (met. act.: with and without) Doses tested: 0, 0.1, 0.5, 1.0, 2.5, 5.0 mg/plate; solvent: ethanol (50 µL/plate) Control: neg/ pos.: yes	**Negative** No mutagenic effects For S. typhimurium TA1535, TA1537, TA1538, TA98, TA 100; in concentrations up to 5.0 mg/plate); met. act.: with and without Cytotoxicity: 2.5 and 5.0 mg/plate in all strains except TA98 in absence of S9 mix, rat; TA1537 in presence of S9 According to CLP: **no classification for germ cell mutagenicity**	**Key study** Test according to the plate incorporation and pre-incubation method Test material: butanone oxime, purity: 99.5 %	TL2 (1983), unpublished study report, confidential
In vitro study **Mammalian cell gene mutation assay** (mouse lymphoma study; gene mutation), equivalent or similar to OECD TG 476/ EU B.17, GLP compliance not specified Mouse lymphoma L5178Y cells met. act.: with and without S9 activation Dose: up to 6.5 µL/mL L5178Y/TK$^{+/-}$ Mouse lymphoma assay Control: neg./pos.: yes	**Negative** negative with and without metabolic activation (with metabolic activation weak positive effects at both highest doses 5.5 and 6.5 µL/mL without relevance due to high induced cytotoxicity) Cytotoxicity: yes, at all doses tested (↑ depending on the dose) According to CLP: **no classification for germ cell mutagenicity**	**Key study** Test material: butanone oxime, purity: 99.5 %	Rogers-Back et al. (1988)
In vitro study **DNA damage and repair, unscheduled DNA synthesis in mammalian cells in vitro** (DNA damage and/or repair), comparable to OECD TG 482/EU B.18 (Genetic toxicology: DNA damage and repair, unscheduled DNA synthesis in mammalian cells in vitro), GLP compliance not specified Hepatocytes: male F344 rats Dose: up to 5000 pg/mL Control: neg./pos.: yes	**Negative** negative for hepatocytes: male F344 rats (all strains/cell types tested); met. act.: not applicable; Cytotoxicity: yes (5000 and 1500 pg/mL) According to CLP: **no classification for germ cell mutagenicity**	**Key study** Test material: butanone oxime, purity: confidential (> 98 %)	TL11 (1995), unpublished study report, confidential
In vitro study **In vitro sister chromatid exchange assay in mammalian cells,** Comparable to OECD TG 479/EU B.19 (Genetic toxicology: In vitro sister chromatid exchange assay in mammalian cells); GLP compliance assumed CHO cells Dose: up to 500 µg/mL (-S9); 5000 µg/mL (+S9); Control: neg./pos.: yes	**Negative** No induction of sister chromatid exchanges (SCE) in cultured Chinese hamster ovary (CHO) cells with and without S9 activation According to CLP: **no classification for germ cell mutagenicity**	**Key study** Test material: butanone oxime, purity: 99.5 %	NTP (1999)
In vitro study **In vitro mammalian chromosome aberration test, c**omparable to OECD TG	**Negative** No induction of chromosome aberration in cultured CHO cells with and without S9	**Key study** Test material:	NTP (1999)

Method	Results	Remarks	Reference
473/EU B.10, GLP compliance assumed CHO cells Dose: up to 5000 µg/mL (-/+S9) Control: neg./pos.: yes	activation Up to 200 first-division metaphase cells were scored/dose According to CLP: **no classification for germ cell mutagenicity**	butanone oxime, purity: 99.5 %	

Table 23: Summary table of relevant *in vivo* mutagenicity studies

Method	Results	Remarks	Reference
In vivo study Sex-linked recessive lethal (SLRL) test in Drosophila melanogaster (gene mutation), comparable to OECD TG 477/EU B.20 (Genetic Toxicology: Sex-linked recessive lethal test in Drosophila melanogaster), GLP compliant Drosophila melanogaster, male (15/dose) **oral**: feed; neg./pos. control: yes Doses tested:7500 ppm in 5 % sucrose in aqueous solution (nominal in diet), Exposure duration: 3 consecutive days;	**Negative** No evidence of mutations in the post-meiotic germ cells of male Drosophila melanogaster toxicity: yes According to CLP: **no classification for germ cell mutagenicity**	**Key study** Test material: butanone oxime, purity: 98.5 %	TL21 (1991), unpublished study report, confidential
In vivo study Chromosome aberration assay in Sprague-Dawley rats (chromosome aberration), comparable to OECD TG 475/EU B.11 (Mammalian bone marrow chromosome aberration test) **Rats**, Sprague-Dawley, male and female (5/dose); **oral** (gavage); control: neg./pos.: yes Doses tested: 300, 600, 1200 mg/kg bw (nominal in water); Exposure duration: single dose; observation period: 6, 24, 48h	**Negative** No significant increase in chromosome aberrations in the bone marrow of male/female rats toxicity: yes, clinical signs within 4 hours of dosing at each dose level tested According to CLP: **no classification for germ cell mutagenicity**	**Key study** Test material: butanone oxime, purity: 99.98 %	TL11 (1990), unpublished study report, confidential
In vivo study Mouse peripheral blood micronucleus test in B6C3F1 mice (clastogenic/genotoxic potential), comparable to OECD TG 474/EU B.12 (Mammalian erythrocyte micronucleus test), GLP compliant **Mice**, B6C3F1, male/female (5/sex/group); **oral** (drinking water), control: neg: yes Doses tested: 0, 625, 1250, 2500, 5000 or 10,000 ppm (nominal in water) (m: up to	**Negative** No increase in the frequency of micronucleated normochromatic erythrocytes in the peripheral blood (males/females) 10000 ppm, m/f: ↓ (76/79.8 %) in proportion of normochromatic erythrocytes among the total erythrocyte population toxicity: yes According to CLP: **no classification for germ cell mutagenicity**	**Key study** Test material: butanone oxime, purity: 99.5 %	NTP (1999)

Method	Results	Remarks	Reference
1330 mg/kg bw; f: up to 3170 mg/kg bw) Exposure duration: daily, 13 weeks			
In vivo study The potential to produce DNA and RNA adducts in the liver by butanone oxime, No guideline followed, GLP compliant **Rat**, Wistar, male/female **inhalation**, Positive control: 2-nitropropane Doses tested: 375 - 1000 ppm (1350 - 3600 mg/m^3) Exposure duration: 6h	**Negative** Rat liver: no DNA adduct formation Additional information: Induction of adducts in rat liver RNA Positive control: ↑ 8-oxodeoxyguanosine, N^2-aminodeoxyguanosine and 8-aminodeoxyguanosine in rat liver	**Key study** Test material: butanone oxime, purity: 99.5 %	TL10 (2000), unpublished study report, confidential; Friedewald et al. (2001); Völkel et al. (1999)

4.9.1 Non-human information

4.9.1.1 In vitro data

Butanone oxime was tested for germ cell mutagenicity in the following in vitro studies: bacterial reverse mutation assays (Ames test) conducted by several methods in standard bacterial strains in the presence or absence of rat liver activating enzymes (comparable to OECD TG 471/EU B.14), a further single bacterial reverse mutation assay conducted by the pre-incubation method with and without metabolic activation, a mouse lymphoma study (comparable to OECD TG 476/EU B.17), and an UDS test (comparable to OECD TG 482/EU B.18). In addition, in cytogenetic tests with cultured Chinese hamster ovary cells (CHO) the induction of sister chromatid exchanges (comparable to OECD TG 479/EU B.19) and the chromosome aberration (comparable to OECD TG 473/EU B.10) was evaluated both in the presence or absence of S9 activation. In all studies butanone oxime was used as test material. The results of in vitro studies on germ cell mutagenicity are summarised in Table 22 (s. there).

Butanone oxime did not induce reverse mutations in Salmonella typhimurium strains (TA 1535, TA 1537, TA 1538, TA 98, TA 100; in concentrations up to 10000 µg/plate) or Escherichia coli (WP2 uvr A) in the presence or absence of rat or hamster liver activating enzymes (TL2, 1983, unpublished study report, confidential; TL12, 1996, unpublished study report, confidential; Rogers-Back et al. 1988; NTP 1999). A single bacterial reverse mutation assay conducted by the pre-incubation method reported a mutagenic response in only tester strain TA 1535 and only in the presence of high (not standard) levels of hamster liver activating enzymes (NTP 1999). A mouse lymphoma study found evidence of mutagenic activity in mouse lymphoma L5178Y cells in the absence of S9 activation but in the presence of cytotoxicity (growth inhibition of 50-92.5 % at doses of 2.8-6.5 µL/mL). Following S9 activation, a negative response was observed (Rogers-Back et al. 1988). A DNA damage and repair assay, unscheduled DNA Synthesis (UDS) test in rat primary hepatocytes (male F344 rats; tested concentrations 5000 and 1500 pg/mL) was negative (TL11, 1995, unpublished study report, confidential). In cytogenetic tests with cultured CHO cells, no induction of SCE was observed at concentrations up to toxicity (500 µg/mL) in the absence of S9 or up to the assay limit (5000 µg/mL) in the presence of S9, in addition, no increase in chromosomal

aberrations was observed in cultured CHO cells treated with up to 5000 µg/mL butanone oxime, with or without S9 (NTP 1999).

4.9.1.2 In vivo data

Butanone oxime was investigated in a Drosophila melanogaster sex-linked recessive lethal (SLRL) test (comparable to OECD TG 477/EU B.20), a chromosome aberration assay in Sprague-Dawley rats (comparable to OECD TG 475/EU B.11), for its clastogenic/genotoxic potential in vivo in a mouse micronucleus test in the peripheral blood (comparable to OECD TG 474/EU B.12), and for its potential to produce DNA and RNA adducts in the liver in a study with rats exposed by inhalation to 375-1000 ppm (1350-3600 mg/m^3) butanone oxime for 6 hours. In all studies oxime was used as test material. The results of in vivo studies on germ cell mutagenicity are summarised in

Table 23 (s. there).

A Drosophila melanogaster SLRL test (for sex-linked recessive mutations) showed no evidence of mutations in the post-meiotic germ cells of male Drosophila melanogaster when administered 7500 ppm butanone oxime in their feed for three consecutive days (TL21, 1991, unpublished study report, confidential). In a chromosome aberration assay in male and female Sprague-Dawley rats no significant increase in chromosomal aberrations in the bone marrow was found after single oral doses by gavage of up to 1200 mg/kg bw butanone oxime (TL11, 1990, unpublished study report, confidential). In a mouse peripheral blood micronucleus test no increase in the frequency of micronucleated normochromatic erythrocytes was observed in the peripheral blood of male or female B6C3F1 mice administered up to 1330/3170 mg/kg bw/d butanone oxime via drinking water for 13 weeks. The percentage of normochromatic erythrocytes among the population of circulating erythrocytes was markedly decreased at the highest dose tested (1330/3170 mg/kg bw/d) in male and female mice (NTP 1999). The potential for the formation of DNA and RNA-adducts by butanone oxime was investigated in liver DNA and RNA from male and female rats exposed to butanone oxime by inhalation for 6 hours. DNA adducts could not be observed, additionally information is given by induction of DNA adducts in rat liver RNA (TL10, 2000, unpublished study report, confidential; Friedewald et al. 2001; Völkel et al. 1999).

4.9.2 Human information

No information is available.

4.9.3 Other relevant information

No information is available.

4.9.4 Summary and discussion of mutagenicity

The possibility that butanone oxime may induce heritable mutations in the germ cells of humans were examined in tests by in vitro and in vivo methods. No information is available in humans.

In vitro: Butanone oxime did not induce reverse mutations in Salmonella typhimurium strains or Escherichia coli. The tests were conducted up to the limit dose recommended by guideline and cytotoxicity was noted at the highest tested dose level. A single reverse mutation bacterial assay conducted by the pre-incubation method reported a mutagenic response in only tester strain TA 1535 and only in the presence of high (not standard) levels of hamster liver activating enzymes.

In mammalian in vitro systems, butanone oxime did not induce chromosomal aberrations in rat hepatocytes, gene mutation in mouse lymphoma cells, sister chromatid exchange or chromosome aberrations in cultured CHO cells.

In vivo: Butanone oxime did not induce mutations in the post-meiotic germ cells of male Drosophila melanogaster and micronuclei in peripheral blood erythrocytes in male and female B6C3F1 mice treated via drinking water, and showed no significant increase in chromosomal aberrations in the bone marrow of rats. In liver DNA from butanone oxime exposed rats by inhalation for 6 hours, DNA adducts could not be observed.

4.9.5 Comparison with criteria

Hazard classification for germ cell mutagenicity primarily aims to identify substances causing heritable mutations or being suspected of causing heritable mutations. A secondary aim is that the mutagenicity in germ cell as well as in soma cells offers supporting information with respect to the mode of action of carcinogenic substances. This hazard class is primarily concerned with substances that may cause mutations in the germ cells of humans that can be transmitted to the progeny. However, the results from mutagenicity or genotoxicity tests in vitro and in mammalian somatic and germ cells in vivo are also considered in classifying substances and mixtures within this hazard class.

Hazard categories for germ cell mutagens:

'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 form human epidemiology studies. Substances to be regarded as if they induce heritable mutations in the germ cells of humans.

Category 1B: The classification in Category 1B is based on positive result(s) from

- in vivo heritable germ cell mutagenicity tests in mammals; or
- in vivo somatic cell mutagenicity tests in mammals, in combination with some evidence that the substance has potential to cause mutations to germ cells. It is possible to drive this supporting evidence from mutagenicity/genotoxicity tests in germ cells in vivo, or by demonstrating the ability of the substance or its metabolite(s) to interact with the genetic material of germ cells; or
- tests showing mutagenic effects in the germ cells of humans, without demonstration of transmission to progeny; for example, an increase in the frequency of aneuploidy in sperm cells of exposed people.'

No data are available which justify a classification of butanone oxime as mutagen Category 1 in accordance with CLP.

'Category 2: 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.'

The evaluation of the genotoxic potential of butanone oxime based on a battery of in vitro and in vivo tests conforming to internationally agreed test guidelines. It is concluded that for butanone oxime no genotoxic potential in vivo could be established.

4.9.6 Conclusions on classification and labelling

There is no concern for direct genotoxic properties of butanone oxime based on the available data from in vitro and in vivo tests.

According to CLP classification of butanone oxime for germ cell mutagenicity is not warranted.

4.10 Carcinogenicity

Table 24 Summary table of relevant carcinogenicity studies

Method	Results	Remarks	Reference
Chronic toxicity and carcinogenicity study, similar to OECD TG 453/EU B.33, GLP compliant **Rat**; F344; male/female (80/sex/dose; 10/sex/dose/ interval) **Inhalation:** vapour (particle size distribution: MMAD: 2.3-2.6 µm, GSD: 2.1-2.8), whole body Doses tested: Exposure duration: 6h/d, 5d/wk for 26 months, interim sacrifice at 3, 12 and 18 months	**Positive: Malignant and benign liver tumours** **Carcinomas in male rats exposed by inhalation to 374 ppm (1346 mg/m^3), and adenomas, dose-related increase in males at 15 ppm (54 mg/m^3) and higher** 0, 15, 75, 374 ppm, equivalent to 54, 270, 1346 mg/m^3, **males: liver carcinomas** 0/50, 0/51, 1/51, 12/51; statistically significant at 374 ppm 0, 15, 75, 374 ppm, equivalent to 54, 270, 1346 mg/m^3, **males: liver adenomas** 0/50, 2/51, 5/51, 18/51; statistically significant at 75 and 374 ppm 0, 15, 75, 374 ppm, equivalent to 54, 270, 1346 mg/m^3, **males: fibroadenomas in mammary gland** (2/50, 2/50, 4/50, 9/50; statistically significant at 374 ppm 0, 15, 75, 374 ppm, equivalent to 54, 270, 1346 mg/m^3, females: liver adenomas 0/50, 0/50, 2/50, 4/51; not statistically significant 0, 15, 75, 374 ppm, equivalent to 54, 270, 1346 mg/m^3, females: fibroadenomas in mammary gland 10/50, 7/50, 9/50, 17/50; not statistically significant **LOAEC$_{sys, m}$ = 15 ppm (54 mg/m^3) for liver tumour development** **NOAEC$_{sys}$ not available** According to CLP butanone oxime fulfils the criteria for classification as **Carc. 1B, H350: May cause cancer**	**Key study** Test material: butanone oxime, purity: > 99.9 %	Newton et al. (2001); TL18 (1994), unpublished study report, confidential
Chronic toxicity and carcinogenicity study, similar to OECD TG 453/EU B.33, GLP compliant **Mouse**; CD-1; male/female (60/sex/dose; 10/sex/dose/ interval) **Inhalation:** vapour (particle size distribution: MMAD: 2.1-2.7 µm, GSD: 2.7-3.4), whole body	**Positive: Malignant and benign liver tumours** **Carcinomas in male mice exposed by inhalation to 374 ppm (1346 mg/m^3); and adenomas in all test groups, ≥ 15 ppm (≥ 54 mg/m^3); decrease in latency for liver carcinomas at 374 ppm (1346 mg/m^3)** 0, 15, 76, 374 ppm, equivalent to 54, 274, 1346 mg/m^3, **males: liver carcinomas** 2/50, 2/50, 1/50, 10/50; statistically significant at 374 ppm (1346 mg/m^3) 0, 15, 76, 374 ppm, equivalent to 54, 274, 1346 mg/m^3, males: liver adenomas 4/50, 11/50, 10/50, 11/50, not statistically significant, within historical control range 0, 15, 76, 374 ppm, equivalent to 54, 274, 1346 mg/m^3, females: liver adenomas 0/50, 0/50, 1/50, 3/50; not statistically significant **LOAEC$_{sys, m}$ = 15 ppm (54 mg/m^3) for liver tumour development** **NOAEC not available** According to CLP butanone oxime fulfils the criteria for classification as	**Key study** Test material: butanone oxime, purity: > 99.9 %	Newton et al. (2001); TL18 (1993), unpublished study report, confidential

Doses tested: 0, 15, 75, 374 ppm (nominal) Exposure duration: 6h/d, 5d/wk for 18 months, interim sacrifice at 12 months	**Carc. 1B, H350: May cause cancer**		

4.10.1 Non-human information

4.10.1.1 Carcinogenicity: oral

No information is available.

4.10.1.2 Carcinogenicity: inhalation

There are combined chronic toxicity and carcinogenicity studies (similar to OECD TG 453/ EU B.33) in rats and mice available. In the carcinogenicity part of the studies F344 rats (50/sex/group) and CD-1 mice (50/sex/group) were exposed 6h/day, 5 days/week for 26 months (rats) or 18 months (mice) via whole-body inhalation exposures to target butanone oxime vapour concentrations of 0, 15, 75, and 374 ppm (corresponding to 0, 54, 270, and 1346 mg/m^3). Satellite groups of rats and mice (10/sex/group/interval) were exposed for 3, 12, or 18 months (rats) or 12 months (mice) to evaluate chronic toxicity (Newton et al. 2001; TL18, 1993, 1994, unpublished study report, confidential). The age of the test animals was not reported but due to the long study duration and because the study was conducted similar to OECD TG 453, it is assumed that at exposure start mice and rats were – as preferred in such studies – around the age of weaning (4 – 10 weeks) (OECD TG 543, 2009). In both studies butanone oxime was used as test material. The results of the combined chronic toxicity and carcinogenicity studies in rats and mice are summarised in Table 24 (see there).

Results regarding clinical laboratory studies (haematology, clinical biochemistry, urinalysis) and non-neoplastic microscopic findings observed in rats and mice are presented in ‘Chapter 4.7 Repeated dose toxicity’ (for more details see there).

Results from chamber monitoring showed that particle size distributions and mass concentrations of background particulate were similar among all the chambers including the air control, indicating that there was no measurable butanone oxime present as an aerosol. The chamber levels of methyl ethyl ketone, a possible hydrolysis product of butanone oxime, were less than 1 %.

The analyses of the survival rate in the rat and mice studies with butanone oxime found no statistically significant difference in survival among the exposure groups when compared to control. At termination of the rat study after treatment over a period of 26 months, in the control group the survival rate was 34 % in the males and 60 % in the females. At termination of the study in mice after 18 months, survival over all groups averaged 50 % in the male mice and 60 % in the females (see Table 25).

Table 25: Percent survival after exposure for 18 months in mice and 26 months in rats

Butanone oxime	Mice (%)		Rats (%)	
Exposure (ppm)	Males	Females	Males	Females
0	43	61	34	60
15	57	51	37	58
75	52	62	27	60
374	48	65	43	76

Results from the study in rats:

At termination of the rat study, mean body weights and body weight gains from study initiation were significantly elevated by exposure to butanone oxime in both the males and females. After 13 weeks of exposure, the 374 ppm males were 13 % heavier than the control males and the females were 4 % heavier.

Butanone oxime-related increases in absolute and relative organ weights were seen in the liver, spleen and testes. After treatment for 3 months in the 374 ppm group, the absolute liver weights in the males and females were elevated relative to the control group weights by about 23 and 13 %, respectively. The weight difference was still statistically significant in the males after 12 months. After 18 months no significant difference was noted. At study termination (26 months) the liver weights were again significantly elevated in males from the 374 ppm group (40 %) relative to control weights.

After treatment for 3 and 12 months, the absolute spleen weights in the 374 ppm group were elevated by about 33 % greater than the control group spleen weights in both males and females. By study termination (26 months) there was no significant difference in the spleen weights relative to control weights.

The absolute and relative testes weights were statistically significantly elevated in the 374 ppm group after 3, 18, and 26 months of treatment but not at 12 months. After treatment for 3 and 18 months the increase was small, but by study termination (26 months), the testes weights in the 374 ppm group were 82 % greater than that of the control males. There was no microscopic correlation associated with this increase in testes weights.

Treatment-related macroscopic findings were not observed after 3 or 12 months of treatment. At interim sacrifice after 18 months of treatment an increased incidence of red/tan discoloration of the liver was observed in 2/9 male and 2/10 female rats in the 75 ppm group and 6/9 male rats in the 374 ppm group. After 26 months of treatment tan to red discoloration of the liver occurred with greater incidence in males and females from the 374 ppm group. In the males at 374 ppm, an increased incidence of nodules/masses of the liver was observed.

Microscopic findings were noted in the spleen of rats after treatment with 374 ppm for 3 months. These were correlated to the increased organ weight an increased incidence of congestion. Pigment deposition in reticuloendothelial cells and extramedullary haematopoiesis also occurred with greater severity in the 374 ppm group males and females. After 12 months of treatment, there was an increase in the severity of congestion in the spleen of male and female rats of all test groups; this roughly correlated with increased spleen weights. In addition, there was an increase in the severity of pigment deposition in reticuloendothelial cells in males of the 75 and 374 ppm groups and an increase in the severity of extramedullary haematopoiesis in females in the 374 ppm group. After treatment of 18 months increased severity of congestion was observed in females at all tested concentrations, and greater severity of pigment deposition in reticuloendothelial cells and of

extramedullary haematopoiesis in the 374 ppm exposure group. At terminal sacrifice (after 26 months) in females there was a statistically significant greater incidence of lymphoreticular mononuclear-cell leukaemia in the control group than in all test groups. In males this observation was limited to the 374 ppm test group. The previous findings in the spleen, e.g. congestion, extramedullary haematopoiesis, and pigment in reticuloendothelial cells could not be evaluated in those animals with leukaemia because the tumour cells effaced the architecture of the organ.

At 12 and 18 months sacrifice, the incidence and severity of basophilic foci and hepatocyte vacuoles in the liver were increased in males in the 374 ppm group. Also observed in the liver was a decrease in the incidence of hyperplasia/proliferation of the biliary duct in male and female rats in the 374 ppm group after 12 months of treatment and of males at the 18 months sacrifice, and further a decrease of peribiliary fibrosis in male rats in the 374 ppm group after 12 and 18 months of treatment. After 26 months of inhalation exposure to butanone oxime an increased number of animals with malignant and benign neoplasms in the liver were noted. In male rats statistically significant increased incidence of hepatocellular carcinoma occurred at 374 ppm and a concentration-related statistically significant increase in hepatocellular adenoma in male rats at 75 and 374 ppm compared to the concurrent controls. The comparison of the liver adenoma incidence of male F344 rats at 15 ppm (2/51, 4 %) with data from the historical control data base of the same strain and test laboratory has shown that the incidence at 15 ppm was within the historical control range of liver adenoma in F344 rats in this test laboratory (range of 3 - 4 %). However, specific details on historical control data of this species and laboratory, such as incidences of specific tumour types in control animals, were not available. Data of the NTP Historical Controls Report (2010) on F344 rats determined a mean percentage of occurring liver carcinomas of 1.01 % and 0.33 % for male and female control rats, respectively, after chronic inhalation exposure (clean air control).
In the study by Newton et al. (2001), an increase in hepatocellular adenoma (not statistically significant; in historical range lab controls) was also found in female rats. An overview of neoplastic changes in the liver of male and female test and control rats after 26 months of treatment, as well as historical control data reported in the NTP Historical Controls Report (2010) are given in Table 26. The overview compromises animals killed at terminal sacrifice and all unscheduled deaths.

Table 26: Neoplastic changes in the liver of rats (male/female), 26 months treatment, and historical control data (HCD) from the NTP Historical Controls Report (2010) on F 344 rats after chronic inhalation exposure to clean air

Concentration	HCD	0	15 ppm	75 ppm	374 ppm
Adenoma, male	1/299 (0.33 %)	0/50 (0 %)	2/51 (3.9 %)	**5*/51 (9.8 %)**	**18**/51 (35.3 %)**
Adenoma, female	1/300 (0.33 %)	0/50 (0 %)	0/50 (0 %)	2/50 (4.0 %)	4/50 (7.8 %)
Carcinoma, male	3/299 (1.0 %)	0/50 (0 %)	0/51 (0 %)	1/51 (2.0 %)	**12**/51 (23.5 %)**
Carcinoma, female	1/300 (0.33 %)	0/50 (0 %)	0/50 (0 %)	0/50 (0 %)	0/50 (0 %)
Combined adenoma and carcinoma (m/f)	0.33/0.17 (normalised to 50 animals)	0/0	2/0	**6**/2**	**27**/4**

*Mean value significantly different from concurrent control at $p \leq 0.05$; ** Mean value significantly different from control at $p \leq 0.01$

Further findings in the liver were an increase in the incidence of basophilic foci in males and females at 374 ppm (with increased severity in males at 15, 75 and 374 ppm; and in females at

374 ppm), a slight increased incidence of spongiosis hepatis in males at ≥ 15 ppm (with an increased severity at 75 and 374 ppm), and slight increases in the incidence of intracytoplasmic vacuoles in males at 75 and 374 ppm and in females at 374 ppm. There was a decrease in the incidence of two findings in the liver of males and females at 374 ppm, these were peribiliary fibrosis and hyperplasia/proliferation of the biliary duct.

At the terminal sacrifice (26 months exposure by inhalation) an increased incidence of mammary gland fibroadenomas was noted in male and female rats compared to the concurrent controls. Tests of statistically significance for mammary gland fibroadenomas showed a statistically significant dose response ($p < 0.05$) and differences between control and high dose groups in male rats at 374 ppm. An increase of mammary gland fibroadenomas was also observed in females, but achieved no statistically significance. Historical control data was not available for this tumour type, species and laboratory, but values obtained from the NTP Historical Controls Report (2010) for this tumour type and species are reported in Table 27, together with the incidences of mammary gland fibroadenomas of male and female test and control rats determined in the current study.

Table 27: Number of mammary gland fibroadenomas in rats, 26 months treatment, and historical control data (HCD) of the NTP Historical Controls Report (2010) on F 344 rats after chronic inhalation exposure to clean air (normalised to 50 test animals)

Concentration	HCD	0	15 ppm	75 ppm	374 ppm
Fibroadenoma, male	1.17/50	2/50	2/51	4/51	9/51*
Fibroadenoma, female	23/50	10/50	7/50	9/50	17/50

*Mean value significantly different from the concurrent control at $p \leq 0.05$

It is concluded that long-term exposure by inhalation to butanone oxime caused tumour development in the liver of male and female rats. There was a significantly increased incidence of liver carcinomas and adenomas in male rats at 75 and 374 ppm compared to the concurrent controls and historical control data (NTP Historical Controls Report, 2010). In female rats an increase in hepatocellular adenoma was also noted, but the difference to controls did not achieve statistical significance. The incidence of fibroadenomas in the mammary gland was significantly increased in male rats at 374 ppm (actual concentration of 1346 mg/m^3) compared to the concurrent controls and historical control data reported in the NTP Historical Controls Report (2010). Therefore it was concluded that under the exposure conditions of this study, butanone oxime is a carcinogen in F344 rats.

Results from the study in CD-1 mice:

Mean body weights and body weight gains were not significantly affected by exposure to butanone oxime.

At the 12 months interim sacrifice, significant effects in mouse organ weights were noted in the liver. In the females there was a dose-related increase with statistical significance in the 374 ppm group with a 17 % increase in the liver/brain weight ratios. In the males, there was a 12 % increase in the liver/brain weight ratio that was not statistically significantly different. At termination of the study after exposure duration of 18 months, there was no butanone oxime-related effect on absolute or relative organ weights.

There were no butanone oxime-related macroscopic findings at the 12 month interim sacrifice. Microscopically, changes were seen in the liver indicating hepatotoxicity, and occurred with greater incidence primarily in animals exposed to 75 and 374 ppm. These changes consisted of

centrilobular hepatocellular hypertrophy and necrosis. No butanone oxime-related tumour development was noted after one year exposure. Although occurring in all groups including controls, liver changes appeared with greater incidence in the animals from the 374 ppm group after 18 months of treatment. These changes consisted of centrilobular hepatocellular hypertrophy, pigment deposition in the reticuloendothelial cells, necrosis, and granulomatous inflammation. An increased incidence of liver adenomas and carcinomas primarily in male mice was seen in the 374 ppm group compared to the concurrent controls and to data of a study on spontaneous tumour formation in the same species (Maita et al., 1988). An overview of neoplastic changes in the liver of male and female mice exposed to butanone oxime and of concurrent control mice is given in Table 28.

Table 28: Neoplastic changes in the liver of mice, 18 months exposure, and results of a study by Maita et al. (1988), examining the spontaneous tumour formation (STF) in CD-1 mice (normalised to 50 test animals)

Butanone oxime concentration	**STF**	**0**	**15 ppm**	**75 ppm**	**374 ppm**
Number examined (male/female)	50/50	50/50	50/50	50/50	50/50
Adenoma (m/f)	13.2/2.6	4/0	11/0	10/1	11/3
Carcinoma (m/f)	4.5/0.5	2/0	2/0	1/0	**10*/0**
Combined adenoma and carcinoma (m/f)	8.9/0.03	6/0	13/0	11/1	**18**/3**

*Mean value significantly different from control at $p \leq 0.05$; ** Mean value significantly different from control at $p \leq 0.01$

In male mice, there was an increase in tumour induction in the liver and a decrease in latency for liver carcinomas in the 374 ppm group, relative to the control, 15 and 75 ppm groups. There was a slight increase in the incidence of liver adenoma in females from the 374 ppm group. However, the increase was not statistically significant. Historical control data for this species and laboratory was not available, but results of a study (Maita et al. 1988) examining the spontaneous tumour formation (STF) in CD-1 mice also support these findings (Table 28).

It was concluded that under the exposure conditions of this study, butanone oxime is a carcinogen in CD-1 mice.

Overall in combined chronic toxicity and carcinogenicity studies in rats and mice exposed by inhalation to vapours of butanone oxime sufficient evidence of animal carcinogenicity was demonstrated. Two animal experiments using two species (rat and mouse) resulted in clear evidence for carcinogenicity. A causal relationship has been established between butanone oxime and a statistically significant increased incidence of a combination of benign and malignant tumours in well-conducted studies. Being similar to OECD TG 453/EU B.33 both studies are well conducted and do not cast doubts about the relevance of the results. Tumour development was noted by inhalation of relative low concentrations in rats and mice. Butanone oxime caused an increased incidence of liver tumours in both species. There was an increased incidence of malignant and benign liver tumours in both sexes of rats and mice at all tested exposure concentrations. In both species, the liver tumours appeared relatively late in the life of the animals, with no significant increase in tumours after 12 months of exposure in mice and after 18 months of exposure in rats. Lifespan shortening was not observed. The incidence of liver carcinomas was significantly increased in male rats and mice. The female rats and mice showed no increased incidence of liver carcinomas. A LOAEC of 15 ppm (54 mg/m^3) for carcinogenicity (liver tumour development) was derived for rats and mice. A statistically significantly increased incidence of mammary gland

fibroadenomas was also observed in male rats at the high concentration of 374 ppm. A NOAEC for carcinogenicity was not derived for the rat and also not for the mouse.

4.10.1.3 Carcinogenicity: dermal

No information is available.

4.10.2 Human information

No information is available.

4.10.3 Other relevant information

No information is available.

4.10.4 Summary and discussion of carcinogenicity

Data on carcinogenicity of butanone oxime was obtained from animal testing conforming to internationally agreed test guidelines. Carcinogenicity studies on butanone oxime have been conducted in rats and mice using the inhalation route of exposure. There are no epidemiological studies available which demonstrate that butanone oxime induced cancer in humans.

Evidence from animal experiments

The carcinogenic potential of butanone oxime has been studied in two combined chronic toxicity and carcinogenicity studies and in two species. Butanone oxime was administered by whole-body inhalation as a vapour for 6h/day, 5 days/week for 26 months to F344 rats and 18 months to CD-1 mice, and both sexes each. Satellite groups of rats and mice (10/sex/group/interval) were exposed for 12 months (mice) and 3, 12, or 18 months (rats) to evaluate chronic toxicity. Studies using the oral or the dermal route of exposure are not available.

There is sufficient evidence of carcinogenicity in experimental animals. Carcinogenic potential of butanone oxime was demonstrated for the inhalation route of exposure. The evidence of carcinogenicity is based on well documented animal experiments in rats and mice. The combined chronic toxicity and carcinogenicity studies in rats and mice (similar to OECD TG 453/EU B.33) have demonstrated that butanone oxime causes liver tumours (adenomas and carcinomas) in both species at all tested exposure concentrations. However, statistically significant increases in incidence were observed at 75 ppm (270 mg/m^3) and 374 ppm (1346 mg/m^3) for liver adenomas in male rats and at 374 ppm (1346 mg/m^3) for liver carcinomas in male rats and mice. An increased incidence of liver adenomas occurred also in female rats and mice at 270 and 1346 mg/m^3, but was not statistically significant. A dose-response relationship for tumour induction in the liver of rats and mice was observed in both sexes. The incidence of fibroadenomas in the mammary gland was also significantly increased in male rats at 1346 mg/m^3.

These available data from long-term inhalation studies with butanone oxime in rats and mice have provided clear evidence that butanone oxime induced cancer in both species. Butanone oxime induced malignant and benign tumours in the liver of rats and mice in well performed experimental studies.

Since 2000, butanone oxime is classified as carcinogen Category 2 and is listed in Annex VI of CLP as Carc. 2; H351. It is assumed that the reported study results for carcinogenicity do not comply with the legal classification of butanone oxime as carcinogen Category 2. Based on the available data on carcinogenicity butanone oxime fulfils the criteria for classification and labelling as Category 1B carcinogen, H350 according to CLP.

Human data

There are no human data on butanone oxime-induced carcinogenicity available.

Germ cell mutagenicity data

Butanone oxime has been tested regarding genotoxicity in a variety of systems including rat hepatocytes and an in vivo peripheral blood micronucleus test with an administration period of 90 days. The results from mutagenicity or genotoxicity tests in vitro and in vivo were mostly negative, including bacterial mutagenicity, unscheduled DNA-synthesis in primary rat hepatocytes, micronucleus tests in rats and mice, and an in vivo study that utilized inhalation exposure and was found to be negative for DNA adducts in rat liver cells.

Mode of action (MoA)

The modes of action for butanone oxime induced **liver tumours in rats and mice** following long-term exposure by inhalation have not yet been identified.

For butanone oxime the results from mutagenicity or genotoxicity tests in vitro and in vivo were mostly negative (see above ‘Germ cell mutagenicity data’).

Findings obtained from related compounds for carcinogenicity may give indications of a likely mechanism of the observed liver carcinogenicity of butanone oxime. As a possible mechanism for the butanone oxime-induced hepatocarcinogenicity in rats and mice the noted bioactivation of ketoximes is discussed. Ketoximes are known to undergo NADPH-dependent liver microsomal metabolism to nitric oxide/nitrogen monoxide (· NO) and ketones. In addition, nitric oxide synthase can catalyse the oxidative denitration of the >C=N-OH group of amidoximes. Mechanistically, the reaction is believed to proceed via a transient, cytochrome P450-catalyzed conversion of their >C=N- function to a peroxide (Caro et al. 2001). For the related compound acetoxime (acetone oxime; $(CH_3)_2C=N-OH$; CAS 127-06-0) as a possible mechanism for activation the oxidation to the hepatocarcinogen 2-nitropropane (CAS 79-46-9; classified as Carc. 1B, H350; Index No 609-002-00-1) is postulated: $(CH_3)_2C=NOH + O \rightarrow (CH_3)_2CHNO_2$ (Mirvish et al. 1982). Correspondingly, it is assumed that butanone oxime will already be metabolically activated to reactive intermediates in the carcinogenesis. Toxicokinetic studies have shown that butanone oxime is extensively metabolized, yielding CO_2, methyl ethyl ketone, glucuronides, and other polar metabolites (Burka et al. 1998). Three metabolic pathways for butanone oxime could be distinguished: Hydrolysis to 2-butanone, oxidation to butane 2-nitronate, and a possibly third reductive pathway (Janku et al. 2000). Oxidation of butanone oxime to a carcinogenic agent (e.g., nitronates of secondary-nitroalkanes which are mutagenic and tumourigenic in rodents) mediated by sulfotransferase (cytosolic enzyme) has been also postulated to play a role in the MoA for the liver tumourigenicity of butanone oxime. A similar MoA has been assumed which is mechanistically described for another secondary nitroalkane 2-nitropropane. For the genotoxic hepatocarcinogen 2-nitropropane,

an activation pathway involving sulfontransferases to give acetoxime *O*-sulfonate is assumed. The genotoxicity of 2-nitropropane in rats has been attributed to aryl sulfontransferase-mediated formation of DNA-reactive nitrenium ions from the anionic form of 2-nitropropane, propane 2-nitronate (Sodum et al. 1993; Sodum et al. 1994; Sodum and Fiala 1997, 1998; Kreis et al. 2000). 2-Nitropropane produces characteristic base modifications in rat liver RNA and DNA, including the amination and the oxidation of C8 of guanine (Fiala et al. 1995). The ultimate reactive metabolite postulated in the pathway is hydroxylamine *O*-sulfonate which aminates/oxidizes nucleosides through a nitrenium ion intermediate. Hydroxylamine *O*-sulfonate is a presumed product of the hydrolysis of acetoxime *O*-sulfonate formed postulated to be formed from 2-nitropropane/propane 2-nitronate by sulfate conjugation.

In experiments comparing the oxidation of butanone oxime and acetoxime it was shown that the incubation of liver microsomes from mice, rats and several human liver samples with butanone oxime resulted in the formation of nitronates, but at very low rates. No sex and species differences in the rates of microsomal oxidation of butanone oxime to butane 2- nitronate were observed (Völkel et al. 1999).

From the available data, it appears that the biotransformation of butanone oxime in the tumourigenicity is complex with many interacting steps of several enzymes potentially involved. Further it is considered that one of several possible mechanisms for the increased incidences of liver tumours in rats and mice may be the metabolism of butanone oxime to reactive intermediates (e.g., nitronates), mediated by sulfontransferase. A number of other factors and mechanisms for the tumour response of butanone oxime may be also involved.

No effects of butanone oxime on hepatic peroxisome proliferation and on serum testosterone levels were observed in male F344 rats after oral treatment for 4 weeks (TL14, 1995a, unpublished study report, confidential).

No species-specific mode of action for butanone oxime carcinogenesis was identified; as a default the tumour responses in rats and mice are considered as relevant for the man.

In summary, the negative genotoxicity studies with butanone oxime support the adoption that the hepatocarcinogenicity of butanone oxime in rats and mice is, inter alia, is attributed to other/further mechanisms. At present it is expected that tumour initiation in the liver of rats and mice is induced by an interaction of activated butanone oxime-metabolite(s) with nucleic acids, and enhanced tumour development following cytotoxic effects of butanone oxime in the liver. Due to uncertainties in the available information it is not possible to reach a final conclusion regarding likely modes of action of hepatocarcinogenicity in experimental animals. Accordingly, it is assumed that the potential mechanisms behind butanone oxime carcinogenesis in the liver of rats and mice after long-term exposure by inhalation are highly complex involving a number of events and factors which are still unknown.

The modes of action for butanone oxime induced **mammary gland tumours in male and female rats** following long-term exposure by inhalation have not been identified until now.

Significantly increased incidences of fibroadenomas in the mammary gland were only seen in male rats exposed to 374 ppm butanone oxime. At termination of the long-term study an increase of mammary gland fibroadenomas was also observed in female rats, but achieved no statistically significance. From the scientific literature it is known that several factors greatly influence the susceptibility, magnitude and type of neoplastic response, and growth rate of mammary neoplasms in the rat. These include genetic factors, degree of differentiation of mammary gland at time of chemical exposure, physiological and hormonal status, and diet.

There is no indication in the available investigations that the determined carcinogenicity in rats and mice has no relevance to humans.

Conclusion in respect to carcinogenicity

There is clear evidence that butanone oxime induced carcinogenicity in rats and mice after long-term exposure by inhalation. Carcinogenicity in animals is derived from two independent studies, carried out at different times. In two well performed experiments it was shown that butanone oxime induced malignant and benign tumours in the liver of the two species: rats and mice.

Butanone oxime-induced tumour development in the liver is observed in rats and mice at all tested exposure concentrations (≥ 15 ppm; actual concentration of 54 mg/m^3). However, statistically significant increases in incidence were observed only at the mid and high concentration of 270 and 1346 mg/m^3 for liver adenomas in male rats and at 1346 mg/m^3 for liver carcinomas in male rats and mice. An increased incidence of liver adenomas compared to the concurrent controls occurred also in female rats and mice at 270 and 1346 mg/m^3, but was not statistically significant. A dose-response relationship for tumour induction in the liver of rats and mice was observed in both sexes. A LOAEC of 15 ppm (54 mg/m^3, lowest concentration tested in the study) for carcinogenicity (liver tumour development) was derived for rats and mice.

A statistically significantly increased incidence of mammary gland fibroadenomas was also observed in male rats at the high concentration of 1346 mg/m^3.

Under the conditions described in the combined chronic toxicity and cancerogenicity studies a NOAEC for carcinogenicity was not derived for the rat and also not for the mouse.

4.10.5 Comparison with criteria

Carcinogen means a substance or a mixture of substances which induce cancer or increase its incidence. Substances which have induced benign and malignant tumours in well performed experimental studies in animals are considered also to be presumed or suspected human carcinogens unless there is strong evidence that the mechanism of tumour formation is not relevant for humans.

For the purpose of classification for carcinogenicity, substances are allocated to one of two categories. Classification of a substance as a carcinogen in Category 1A and 1B is based on consideration of the strength of the evidence of available data for classification with considerations of all other relevant information (weight of evidence) being taken into account as appropriate. In certain instances, route-specific classification may be warranted, if it can be conclusively proven that no other route of exposure exhibits a hazard.

Hazard categories for carcinogens:

'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 or 1B.'

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

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

The classification in Category 1A or 1B is based on strength of evidence together with additional considerations (s. section 3.6.2.2 of CLP). 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).'

Butanone oxime is possibly carcinogenic to humans. But there are no data available of cancer in humans related to butanone oxime exposition. Therefore classification as Category 1A carcinogen is not appropriate.

The decision of classification of a substance in Category 1B based on animal experiments means a causal relationship has been established between the agent and an increased incidence of malignant neoplasm's or of an appropriate combination of benign and malignant neoplasms in

a) two or more species of animals or in two or more independent studies in one species carried out at different times or in different laboratories or under different protocols;

b) in both sexes of a single species;

c) occurrence of malignant neoplasm to an unusual degree with regard to the incidence, site, type of tumour or age at onset, or when there are strong findings of tumours at multiple sites.

In comparison to the given criteria for CLP butanone oxime fulfils the criteria for Category 1B carcinogen.

There is sufficient evidence of carcinogenicity from well performed experimental studies on animals. Butanone oxime caused tumours in two rodent species carried out independently.

Butanone oxime induced cancer in both sexes when administered by whole-body inhalation as a vapour 6h/day, 5 days/week for a period of 26 months to F344 rats and 18 months to CD-1 mice.

Tumours induced by butanone oxime were found in the liver (malignant and benign) in rats and mice and in the mammary gland (benign) in rats.

Tumours in the liver (adenomas and carcinomas) occurred in both species at all tested exposure concentrations (15, 75, 374 ppm, equivalent to 54, 270 and 1346 mg/m^3). Statistically significant increases in incidence were observed at the mid and high concentration for liver adenomas in male rats and at the high concentration for liver carcinomas in male rats and mice compared to the respective control groups. An increased incidence of liver adenomas compared to the concurrent controls occurred also in female rats and mice at the mid and high concentration, but was not statistically significant. A statistically significantly increased incidence of mammary gland fibroadenomas was also observed in male rats at the high concentration (374 ppm, equivalent to 1346 mg/m^3).

A dose-response relationship for tumour induction in the liver was observed in both species, and in the mammary gland in rats only.

'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 the strength of evidence together with additional considerations (s. section 3.6.2.2 of CLP). Such evidence may be derived either from limited evidence of carcinogenicity in human studies or from limited evidence of carcinogenicity in animal studies.'

Following consideration would lead to classification as Category 2:

a) the evidence is limited to a single experiment;

b) there are unresolved questions regarding the adequacy of the design, conduct or interpretation of the studies;

c) the agent increases the incidence only of benign neoplasm or lesions of uncertain neoplastic potential; or

d) the evidence of carcinogenicity is restricted to studies that demonstrate only promoting activity in a narrow range of tissues or organs.

Category 2 is not appropriate because the results from the available data do not match the criteria for Category 2 classification. The evidence is neither limited to a single experiment, nor limited with regard to benign neoplasm, or promoting activity.

In conclusion, the available data for carcinogenicity of butanone oxime does not comply with the legal classification of butanone oxime as carcinogen Category 2. Butanone oxime rather fulfils the criteria for classification and labelling as Category 1B carcinogen, H350 according to CLP.

4.10.6 Conclusions on classification and labelling

According to CLP butanone oxime has to be classified as:

Carc. 1B and labelled with hazard statement H350: May cause cancer; with the pictogram "GHS08: Health hazard", and with the signal word "Danger".

4.11 Toxicity for reproduction

Table 29: Summary table of relevant reproductive toxicity studies (fertility)

Method	Results	Remarks	Reference
Two-generation toxicity study **Oral (gavage),** EPA guideline with modifications (similar to OECD TG 416/EU B.35), GLP compliant **Rat**; CD Sprague-Dawley (Crl:CD[SD]BR) VAF/Plus); male/female (30/sex/dose) Doses tested: 0, 10, 100, 200 mg/kg bw/day (actual ingested) Exposure regimen: F0 generation: starting from 8 wk of age during 10 wk pre-mating (5d/wk); 3 wk mating period to produce the F1 generation, gestation, and lactation for 7 d/wk (continued dosing)	**Parental parameters** **<u>200 mg/kg bw/d:</u>** <u>*Mortality:*</u> 4/30 (13.3 %) F0m, including 3 during pre-breed period; 11/30 (36.7 %) F0f; 15/30 (50.0 %) F1m including 8 during pre-breed period, 1 during the first bred, 3 during the second breed; 8/30 (26.7 %) F1f including 4 during the pre-breed period, 3 during the vaginal cytology (first breed) and 1 during the lactation of her F2b litter <u>*Clinical signs:*</u> ↓ bw and bw gain in both generations and m/f; ↓ feed consumption in F0m/f + F1f; F0m: tremors, salivation, slow respiration, mouth breathing, lethargy, staggers, and rooting in bedding (post-dosing, presumably from the "taste" of the dosing solution); F0f: tremors, ataxia, and convulsions (only in animals prior to demise), stupor, abnormal respiration (audible, irregular, raspy, laboured), dyspnoea, dehydration, excessive urination, bright yellow urine, and rooting in bedding; F1m: tremors, audible breathing, and rooting in bedding; F1f: lethargy, abnormal respiration (laboured, gasping, and raspy), cyanosis, and rooting in bedding <u>*Haematology:*</u> F0m/f + F1m/f: anaemia with ↓: RBC count, Hct, Hb, ↑: RBC size (MCV), nucleated RBC count, reticulocyte count, MCH, WBC count; F0m + F1m: methaemoglobin <u>*Necropsy:*</u> F0m/f + F1m/f: ↑ abs. and rel. (significant) spleen weight; F1m + F0f + F1f: ↑ rel. (significant) liver weight <u>*Histology:*</u> F0m/f + F1m/f: spleen: congestion, extramedullary haematopoiesis and haemosiderosis, liver: extramedullary haematopoiesis and haemosiderosis **<u>100 mg/kg bw/d:</u>** <u>*Clinical signs:*</u> F0m: lethargy, staggers, and rooting in bedding; F0f: weaving, tremors, and rooting in bedding; F1m: slight dehydration, audible breathing, rooting in bedding; F1f: laboured breathing <u>*Haematology:*</u> F0m/f + F1m/f: anaemia with ↓: RBC count, Hct, Hb, ↑: RBC size (MCV), nucleated RBC count, reticulocyte count, MCH; F0m + F1m: ↑: WBC count, methaemoglobin <u>*Necropsy:*</u> F0m/f and F1m/f: ↑ abs. and rel. (significant) spleen weight; <u>*Histology:*</u> F0m/f and F1m/f: spleen and liver: extramedullary haematopoiesis and haemosiderosis **<u>10 mg/kg bw/d:</u>** <u>*Clinical sign:*</u> F0m + F1m: rooting in bedding <u>*Haematology:*</u> F0m: ↓ RBC count, Hb <u>*Necropsy:*</u> F0m: dark spleens (5/30) <u>*Histology:*</u> F0 m/f + F1m/f: spleen and liver: extramedullary haematopoiesis and haemosiderosis **$LOAEL_{sys\ m/f}$ = 10 mg/kg bw/d (toxicity to the haematopoietic system)** based on effects in the spleen: hematopoietic cell proliferation, pigmentation and congestion and liver: haematopoiesis	**Key study** Test material: butanone oxime, purity: > 99 %	TL17 (1992), unpublished study report, confidential; Tyl et al. (1996)

Method	Results	Remarks	Reference
	and pigmentation in both sexes of F0 and F1 adults **Reproductive parameters** - no significant effects of treatment on number of F0 or Fl females, pre- or post-breed, which were cycling, or on cycle length, number of females not cycling, or number of females with abnormal cycles - no effects at any dose for F0 and Fl (a + b) generations for any reproductive indices - prenatal mortality and stillbirth indices exhibited no significant trends or pair wise comparisons, although there appeared to be slight dose-related increases for both parameters in F0 matings and for stillbirth index only in Fl (a + b) matings, but were well within the historical control data **Offspring parameter** - no effects of treatment at any dose on total or live litter size, sex ratio, or pup body weights per litter, with sexes pooled or separate (pnd 0—21) for Fl and F2 (a + b) litters **NOAEL = 200 mg/kg bw/d for reproductive toxicity (fertility)** According to CLP: **no classification for reproductive toxicity**		

Table 30: Summary table of relevant developmental toxicity studies

Method	Results	Remarks	Reference
Two-generation toxicity study Oral (gavage), EPA guideline with modifications (similar to OECD TG 416/EU B.35), GLP compliant Rat; CD Sprague-Dawley (Crl:CD[SD]BR) VAF/Plus); male/female (30/sex/dose) Doses tested: 0, 10, 100, 200 mg/kg bw/day (actual ingested) Exposure regimen: F0 generation: starting from 8 wk	Parental parameters 200 mg/kg bw/d: *Mortality:* 4/30 (13.3 %) F0m, including 3 during pre-breed period; 11/30 (36.7 %) F0f; 15/30 (50.0 %) F1m including 8 during pre-breed period, 1 during the first bred, 3 during the second breed; 8/30 (26.7 %) F1f including 4 during the pre-breed period, 3 during the vaginal cytology (first breed) and 1 during the lactation of her F2b litter *Clinical signs:* ↓ bw and bw gain in both generations and m/f; ↓ feed consumption in F0m/f + F1f; F0m: tremors, salivation, slow respiration, mouth breathing, lethargy, staggers, and rooting in bedding (post-dosing, presumably from the "taste" of the dosing solution); F0f: tremors, ataxia, and convulsions (only in animals prior to demise), stupor, abnormal respiration (audible, irregular, raspy, laboured), dyspnoea, dehydration, excessive urination, bright yellow urine, and rooting in bedding; F1m: tremors, audible breathing, and rooting in bedding; F1f: lethargy, abnormal respiration (laboured, gasping, and raspy), cyanosis, and rooting in bedding *Haematology:* F0m/f + F1m/f: anaemia with ↓: RBC count, Hct, Hb, ↑: RBC size (MCV), nucleated RBC count, reticulocyte count, MCH, WBC count; F0m + F1m: methaemoglobin *Necropsy:* F0m/f + F1m/f: ↑ abs. and rel. (significant) spleen weight; F1m + F0f + F1f: ↑ rel. (significant) liver weight *Histology:* F0m/f + F1m/f: spleen: congestion, extramedullary haematopoiesis and haemosiderosis, liver: extramedullary	Test material: butanone oxime, purity: > 99 %	TL17 (1992), unpublished study report, confidential; Tyl et al. (1996)

Method	Results	Remarks	Reference
of age during 10 wk pre-mating (5d/wk); 3 wk mating period to produce the F1 generation, gestation, and lactation for 7 d/wk (continued dosing); F0 and F1 weanlings were necropsied after 2 wk post wean F1 generation: starting from 11 wk of age in the same regime (5 d/wk);	haematopoiesis and haemosiderosis 100 mg/kg bw/d: *Clinical signs:* F0m: lethargy, staggers, and rooting in bedding; F0f: weaving, tremors, and rooting in bedding; F1m: slight dehydration, audible breathing, rooting in bedding; F1f: laboured breathing *Haematology:* F0m/f + F1m/f: anaemia with ↓: RBC count, Hct, Hb, ↑: RBC size (MCV), nucleated RBC count, reticulocyte count, MCH; F0m + F1m: ↑: WBC count, methaemoglobin *Necropsy:* F0m/f and F1m/f: ↑ abs. and rel. (significant) spleen weight; *Histology:* F0m/f and F1m/f: spleen and liver: extramedullary haematopoiesis and haemosiderosis 10 mg/kg bw/d: *Clinical sign:* F0m + F1m: rooting in bedding *Haematology:* F0m: ↓ RBC count, Hb *Necropsy:* F0m: dark spleens (5/30) *Histology:* F0 m/f + F1m/f: spleen and liver: extramedullary haematopoiesis and haemosiderosis $LOAEL_{sys\ m/f}$ = 10 mg/kg bw/d (toxicity to the haematopoietic system) based on effects in the spleen: hematopoietic cell proliferation, pigmentation and congestion and liver: haematopoiesis and pigmentation in both sexes of F0 and F1 adults Reproductive parameters - no significant effects of treatment on number of F0 or Fl females, pre- or post-breed, which were cycling, or on cycle length, number of females not cycling, or number of females with abnormal cycles - no effects at any dose for F0 and Fl (a + b) generations for any reproductive indices - prenatal mortality and stillbirth indices exhibited no significant trends or pair wise comparisons, although there appeared to be slight dose-related increases for both parameters in F0 matings and for stillbirth index only in Fl (a + b) matings, but were well within the historical control data Offspring parameter - no effects of treatment at any dose on total or live litter size, sex ratio, or pup body weights per litter, with sexes pooled or separate (pnd 0—21) for Fl and F2 (a + b) litters - no treatment-related clinical observations for Fl or F2 (a + b) pups during lactation - no treatment-related necropsy findings of pups during lactation or of Fl or F2a pups, 10/sex/dose, which were necropsied at weaning - no treatment-related changes in haematology or organ weights in Fl, F2a, or F2b weanlings, 10/sex/dose Overall, no evidence of postnatal toxicity was found at any dose tested.		
Developmental toxicity study, according to OECD TG 414/ EU B.31, GLP compliant Oral (gavage) Rat; Sprague-Dawley , female (25/dose) Doses tested: 0, 60, 200, 600 mg/kg bw/day; dose	Preliminary study (dose range-finding study) NOAEL = 400 mg/kg bw/d for developmental toxicity, based on all gestational parameters evaluated during caesarean section including viable foetuses, early and late resorptions, foetal sex ratios, gravid uterus weights and foetal body weights; no foetal external malformations or developmental variations $LOAEL_{sys\ f}$ = 25 mg/kg bw/d for maternal toxicity (toxicity to the haematopoietic system) based on signs of anaemia (↑ methaemoglobin (GD16/20: 6/4 %), ↑ reticulocyte (GD16/20: 18/14 %) Main study NOAEL = 600 mg/kg bw/d for developmental toxicity, based on any parameters evaluated during caesarean section including the number of corpora lutea, implantation sites, viable foetuses, resorptions, foetal sex ratios, and foetal body weights; no treatment-related foetal malformations; no visceral or skeletal malformations $LOAEL_{sys\ f}$ = 60 mg/kg bw/d for maternal toxicity	Key study Test material: butanone oxime, purity: > 99 %	TL19 (1990a), unpublished study report, confidential; Derelanko et al. (2003)

Method	Results	Remarks	Reference
volume: 10 mL Exposure regimen: GD6-15 (daily), observation period: until sacrifice on GD20	(toxicity to the haematopoietic system) based on spleen enlargement According to CLP: no classification for developmental toxicity		
Developmental toxicity study, according to OECD TG 414/ EU B.31, GLP compliant Oral (gavage) Rabbit; New Zealand White; female (18/dose) Doses tested: 0, 8, 14, 24, 40 mg/kg bw/day; dose volume: 2 mL Exposure regimen: GDs 6-18 (daily), observation period: until sacrifice on GD29	<u>Preliminary study (dose range-finding study)</u> 80 mg/kg bw/d: mortality in 5/5 dams between GD8-10; first mortality: ≤ 48h in 2/5 females (see Section '4.2 Acute toxicity') 40 mg/kg bw/d: mortality in 2/5 on GD10 or 11, 1 dam aborted on GD20, 2/5 survived to scheduled sacrifice on GD29 20 and 40 mg/kg bw/d: 100 % pregnancy rate 10 and 80 mg/kg bw/d: 60 % pregnancy rate Control: 80 % pregnancy rate <u>Main study</u> 40 mg/kg bw/d on GD6-18: mortality in 8/18 dams (44 %) between GD11-24; 3 abortions LOAEL = 40 mg/kg bw/d for developmental toxicity, based on abortions in 3/10 adult females in pregnant rabbits NOAEL = 24 mg/kg bw/d for developmental toxicity, based on any treatment-related gestational effects, malformations or developmental variations (↓ mean number of viable foetuses of 5.3, but fell in the historic control range of 4.6-9.1); not noted at 20 mg/kg bw/d in the preliminary study $LOAEL_{sys\ f}$ = 10 mg/kg bw/d for maternal toxicity (toxicity to the haematopoietic system) based on signs of anaemia in the dams (increase in methaemoglobin and reticulocytes appeared at GD13 and progressively increased with time until GD19 (3 days after the end of exposure)) According to CLP: no classification for developmental toxicity	Key study Test material: butanone oxime, purity: > 99 %	TL19 (1990b), unpublished study report, confidential; Derelanko et al. (2003)

4.11.1 Effects on fertility

4.11.1.1 Non-human information

Butanone oxime was tested for effects on sexual function and fertility in a two-generation toxicity study in rats (similar to OECD TG 416/EU B.35). The study was performed to evaluate the potential of butanone oxime administered by gavage to CD Sprague-Dawley rats to produce alterations in parental fertility, maternal pregnancy and lactation, and growth and development of the offspring for two generations, one litter per generation for the F0 to F1 generation, and at least one litter per generation in two breedings for the F1 to F2 generation. In the study butanone oxime was used as test material. The results of the experimental study on fertility are summarised in Table 29 (see there).

4.11.1.2 Human information

No information is available.

4.11.2 Developmental toxicity

4.11.2.1 Non-human information

Butanone oxime was tested for adverse effects on development in developmental toxicity studies (similar to OECD TG 414/EU B.31) in rats and rabbits. In both species a preliminary dose range-finding study and a main study were performed. Sprague-Dawley rats were administered butanone oxime oral by gavage during GD6–15 and New Zealand White rabbits were treated during GD 6-18. In both studies butanone oxime (purity: confidential) was used as test material. The results of these experiments on developmental toxicity are summarised in Table 30 (see there).

4.11.2.2 Human information

No information is available.

4.11.3 Other relevant information

No information is available.

4.11.4 Summary and discussion of reproductive toxicity

Effects on sexual function and fertility: Data on reproductive toxicity was obtained from animal testing. No information is available on effects of butanone oxime on sexual function and fertility in humans.

In a two-generation toxicity study, with one breed for the first generation and two breeds (the second for initially unsuccessful animals) for the second generation the effects of butanone oxime on sexual function and fertility was examined in rats. Toxicity in adult animals was noted in both generations and both sexes. Treatment-related parental deaths occurred at 200 mg/kg bw/d. At 100 and 200 mg/kg bw/d signs of haemolytic anaemia and compensatory erythropoiesis was present and contributed to the increased spleen weights and extramedullary haematopoiesis (hematopoietic cell proliferation) and haemosiderosis (pigment deposition from haemoglobin breakdown products) in spleens and livers. At 10 mg/kg bw/d the consistent parental findings were extramedullary haematopoiesis and haemosiderosis in spleens and livers unaccompanied with further lesions. A NOAEL for systemic effects of adult toxicity could not be established in this study. There were no treatment-related effects on parental reproductive parameters, on parental reproductive behaviour or on parental reproductive organ histology in rats dosed by gavage up to 200 mg/kg bw/d butanone oxime. There were no treatment-related effects on any offspring parameters, including pre- and postnatal survival and growth, for either generation. For butanone oxime a NOAEL of 200 mg/kg bw/d for reproductive toxicity in rats was established.

Effects on development: Data on developmental toxicity was obtained from animal testing. No information is available on effects of butanone oxime on development in humans.

Effects of butanone oxime on development were investigated in rats and rabbits. In Sprague-Dawley rats and New Zealand White rabbits results of a preliminary dose range-finding study and of the main study are available. Based on the results of these studies, butanone oxime is not considered to be developmentally toxic at maternally toxic dose levels of up to 600 mg/kg bw/d in the rat. NOAEL values of 400 and 600 mg/kg bw/d for developmental toxicity, based on absence of treatment-related gestational effects, malformations or developmental variations at the highest dose

tested, could be derived in these studies. For maternal toxicity LOAEL values of 25 mg/kg bw/d (preliminary dose range-finding study), based on signs of anaemia, and 60 mg/kg bw/d (main study), based on spleen enlargement could be established.

Rabbits proved to be more sensitive to butanone oxime toxicity. Butanone oxime was significantly more toxic to the rabbit than the rat. Three rabbits aborted and 8/18 females, which have received oral doses of 40 mg/kg bw/d by gavage during the gestation phase, were found dead between GD11-24. The preliminary study in rabbits showed maternal toxicity indicative of haemolytic anaemia (increases in methaemoglobin and reticulocytes) at 10 mg/kg bw/d and higher. No treatment-related gestational effects, malformations or developmental variations were observed in the rabbit at dose levels at or below 24 mg/kg bw/d.

The results available from examination the effects on sexual function and fertility in rats and on developmental toxicity in rats and rabbits do not provide information concerning butanone oxime as a reproductive or developmental toxicant.

4.11.5 Comparison with criteria

For the purpose of classification for reproductive toxicity, substances are allocated to one of two categories. Within each category, effects on sexual function and fertility, and on development, are considered separately. In addition, effects on lactation are allocated to a separate hazard category.

Reproductive toxicity includes adverse effects on sexual function and fertility in adult males and females, as well as developmental toxicity in the offspring. In this classification system, reproductive toxicity is subdivided under two main headings: (a) Adverse effects on sexual function and fertility; (b) Adverse effects on development of the offspring.

Classification is made on the basis of the appropriate criteria and assessment of the total weight of evidence. Classification as reproductive toxicant is intended to be used for substances which have an intrinsic, specific property to produce an adverse effect on reproduction, e.g. adverse effects on sexual function and fertility, or on development of the offspring, and in addition adverse effects on or via lactation, and substances shall not be so classified if such an effect is produced solely as a non-specific secondary consequence of other toxic effects.

According to CLP the following applies for the classification of a substance as reproductive toxicants:

- *Hazard categories for reproductive toxicants*

'Category 1: Known or presumed human reproductive toxicant

Substances are classified in Category 1 for reproductive toxicity when they are known to have produced an adverse effect on sexual function and fertility, or on development in humans or when there is evidence from animal studies, possibly supplemented with other information, to provide a strong presumption that the substance has the capacity to interfere with reproduction in humans. The classification of a substance is further distinguished on the basis of whether the evidence for classification is primary from human data (Category 1A) or from anima data (Category 1B).'

'Category 1A: Known human reproductive toxicant

The classification of a substance in Category 1A is largely based on evidence from human.

No data are available which justify a classification of butanone oxime as 'Category 1A, known human reproductive toxicant' in accordance with CLP.

'Category 1B: Presumed human reproductive toxicant

The classification of a substance in Category 1B is largely based on evidence from animal studies. Such data shall provide clear evidence of an adverse effect on sexual function and fertility or on development in the absence of other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of other toxic effects. However, when there is mechanistic information that raises doubt about the relevance of the effect for humans, classification in Category 2 may be more appropriate.'

The study results available from examination the effects on sexual function and fertility in rats and on developmental toxicity in rats and rabbits have not provide information concerning butanone oxime as a reproductive or developmental toxicant in humans.

'Category 2: Suspected human reproductive toxicant

Substances are classified in Category 2 for reproductive toxicity when there is some evidence from humans or experimental animals, possibly supplemented with other information, of an adverse effect on sexual function and fertility, or on development, and where the evidence is not sufficiently convincing to place the substance in Category 1. If deficiencies in the study make the quality of evidence less convincing, Category 2 could be more appropriate classification. Such effects shall have been observed in the absence of other toxic effects, or if occurring together with other toxic effects the adverse effect on reproduction is considered not to be a secondary non-specific consequence of the other toxic effects.'

Data on reproductive toxicity (effects on sexual function and fertility) and on developmental toxicity was obtained from animal testing.

Effects on sexual function and fertility:

In the available two-generation toxicity study in the rat no reproductive toxicity, e.g., effects on parental reproductive parameters, on parental reproductive behaviour or on parental reproductive organ histology, was observed at 200 mg/kg bw/d, the highest dose studied. Toxicity to the haematopoietic system was observed in adults at all doses studied (≥ 10 mg/kg bw/d).

In conclusion, available results of a study examining effects of butanone oxime on sexual function and fertility in rats give no indications that butanone oxime is a reproductive toxicant.

Effects on development:

In rats no developmental toxicity was noted at the highest dose tested of 600 mg/kg bw/d. Maternal toxicity indicative of haemolytic anaemia occurred at all dose tested (≥ 10 mg/kg bw/d).

In rabbits no developmental toxicity was observed in the absence of excessive maternal toxicity. At the highest dose tested of 40 mg/kg bw/d excessive mortality and abortions in 3/10 adult pregnant rabbits occurred in unreliable results. Maternal toxicity (toxicity on the haematopoietic system) occurred at all dose tested (≥ 10 mg/kg bw/d).

In conclusion, available results of studies examining effects of butanone oxime on developmental toxicity in rats and rabbits give no indications that butanone oxime is a developmental toxicant.

- *Hazard category for lactation effects*

'Effects on or via lactation:

Effects on or via lactation are allocated to a separate single category. It is recognised that for many substances there is no information on the potential to cause adverse effects on the offspring via lactation. However, substances which are absorbed by women and have been shown to interfere with lactation, or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified and labelled to indicate this property hazardous to breastfed babies. This classification can be assigned on the:

(a) human evidence indicating a hazard to babies during the lactation period; and/or

(b) results of one or two generation studies in animals which provide clear evidence of adverse effect in the offspring due to transfer in the milk or adverse effect on the quality of the milk; and/or

(c) absorption, metabolism, distribution and excretion studies that indicate the likelihood that the substance is present in potentially toxic levels in breast milk.'

The data on effects on or via lactation was obtained from animal testing.

A two-generation toxicity study in the rat, which involves direct exposure or exposure via the milk of the offspring postnatally, provided information on effects on or via lactation. Direct observations of the pups during lactation have not shown adverse effects, such as deaths, decreased viability, clinical signs such as reduced bodyweight gain etc. An impaired nursing behaviour was not reported.

Data available from the two-generation study with butanone oxime in rats do not provide evidence of adverse effects on the offspring due to transfer in the milk.

4.11.6 Conclusions on classification and labelling

Sexual function and fertility:

Well-documented test results from a study on sexual function and fertility in adult male and female rats provide no evidence of butanone oxime-induced adverse effects. According to CLP, classification of butanone oxime as reproductive toxicant (fertility) is not warranted.

Developmental toxicity:

Well-documented test results from studies on development of the offspring from rats and rabbits provide no evidence of butanone oxime-induced adverse effects.

According to CLP, classification of butanone oxime as developmental toxicant is not warranted.

Lactation:

Results from a two-generation study with butanone oxime in rats have not provided clear evidence of adverse effects on the offspring due to transfer in the milk.

According to CLP, classification of butanone oxime as reproductive toxicant via lactation is not warranted.

4.12 Other effects

Not evaluated in the scope of this dossier.

5 ENVIRONMENTAL HAZARD ASSESSMENT

Not evaluated in the scope of this dossier.

6 OTHER INFORMATION

None

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8 ANNEXES

Confidential Annex

ABBREVIATIONS and ACRONYMS

abs.	Absolute
ATE	Acute Toxicity Estimates value; Dose/concentration that cause mortality
bw	Body weight
C	Carbon
C&L	Classification and labelling
CAS	Chemical abstracts service
CLH	Harmonised classification and labelling
CLP	Regulation (EC) No 1272/2008 of the European Parliament and of the Council of December 2008 on classification, labelling and packaging of substances and mixtures
CNS	Central nervous system
Dgr	Danger
DNA	Deoxyribonucleic acid
EC	European Community
ECHA	European Chemicals Agency
e.d.	Epidermal
e.g.	for example
et al.	and others
f/F	Female
GD	Gestation day
GHS05	Hazard pictogram, Symbol: Corrosion
GHS06	Hazard pictogram, Symbol: Skull and crossbones

GHS07	Hazard pictogram, Symbol: Exclamation mark
GHS08	Hazard pictogram, Symbol: Health hazard
GPMT	Guinea Pig Maximisation Test
h	Hour
H	Hazard statement
Hb	Haemoglobin
Hct	Haematocrit
i.d.	Intradermal
i.e.	id est (that is to say)
IUCLID	International uniform chemical information database
IUPAC	International union of pure and applied chemistry
kg	Kilogram
LC_{50}	50 % letal concentration, death of 50 % (one half) of a group of test animals
LD_{50}	50 % letal dose, death of 50 % (one half) of a group of test animals
LOAEC	Lowest Observed Adverse Effect Concentration
LOAEL	Lowest Observed Adverse Effect Level
LOEL	Lowest Observed Effect Level
m/M	Male
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume erythrocytes
MEK	Methyl ethyl ketone
MEST	Mouse Ear Swelling Test
mg/kg bw	Milligrams per kilogram body weight
mg/kg bw/d	Milligrams per kilogram body weight per day
mg/m^3	Milligrams per cubic meter
N	Nitrogen
neg.	Negative
No.	Number
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
O	Oxygen
OECD	Organisation for Economic Co-operation and Development
OECD TG	OECD Test Guideline
OH	Hydroxyl group
pH	Hydrogen ion concentration
ppm	Parts per million
pos.	Positive
REACH	Regulation (EC) No. 1907/2006 of the European Parliament and of the Council concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals
RBC	Red blood cell count
rel.	Relative
RNA	Ribonucleic acid
SEV	Substance evaluation
sig.	Significant
STOT RE	Specific target organ toxicity – repeated exposure
STOT SE	Specific target organ toxicity – single exposure
TG	Test group
TL	Test lab
UDS	Unscheduled DANN Synthesis Assay

WBC	White blood cell
wk	week(s)
↑	Increase
↓	Decrease