SUBSTANCE EVALUATION REPORT

Public Name: **Butanone oxime (MEKO)**

EC Number(s): **202-496-6**

CAS Number(s): **96-29-7**

Submitting Member State Competent Authority:

Federal Institute for Occupational Safety and Health (BAuA)
Division 5 "Federal Office for Chemicals, Authorisation of Biocides"
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Year of evaluation (as given in the CoRAP): 2013

VERSION NUMBER: 1.1 **DATE: June 2014**

Conclusions of the most recent evaluation step	Tick relevant box(es)
Concern not clarified; Need to request further information from the Registrant(s) with the draft decision	
Concern clarified; No need of further risk management measures	
Concern clarified; Need for risk management measures; RMO analysis to be performed	
Other: possible candidate for harmonised classification and labelling	X
Other: Concern not clarified; outcome of on-going field measurement campaign in Germany is awaited.	X

DISCLAIMER

Executive summary

Grounds for concern

Initial Concern

Butanone oxime has been proposed for substance evaluation (SEV) based on article 44(1) of the REACH Regulation.

Butanone oxime was chosen for SEV to clarify whether a harmonised classification as category 1B carcinogen is justified. Butanone oxime is currently legally classified for carcinogenicity as carcinogen category 2 according to the CLP Regulation. The German Senate Commission on the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) proposed a reclassification of butanone oxime based on the available studies according to their classification system. The substance evaluation shall discuss the adequacy of the classification of butanone oxime as category 1B carcinogen.

The SEV should also elucidate if risks especially for professional workers are adequately controlled and get information to assess the actual working and workplace conditions to decide on the necessity for further risk management measures (RMM).

Butanone oxime is a high production volume chemical. The substance is produced with high tonnage (> 1000 t/a) and is widely used with high exposure for workers. 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.

Additional concerns

During the SEV additional concerns regarding the assessment of the human health hazards were identified which indicate the need for an update of the existing harmonized classification and labelling of butanone oxime. Based on the available data butanone oxime also meets the criteria for classification and labelling for acute oral toxicity and for narcotic effects according to the CLP Regulation. Moreover, the results from skin sensitisation testing are sufficient for the allocation of butanone oxime into a sub-category.

In addition, the substance evaluation has identified concerns on human health risks for the general population resulting from consumer use of butanone oxime that need further clarification.

Procedure

In the context of a consultation of German Enforcing Authorities the substance was considered to be related to high concern at real workplaces. Therefore in July 2012 butanone oxime was proposed for substance evaluation in compliance with article 44(1) of the REACH regulation.

On 2013-03-20 ECHA published the CoRAP and initiated a substance evaluation of butanone oxime. A meeting with representatives of the lead registrant was held on 2013-09-10. During the process of substance evaluation all data available until October 2013 were taken into account.

The evaluation of the toxicity has mainly been based on data presented by the registrants (aggregated IUCLID, and Chemical Safety Report, CSR (2011)). In addition, reviews by a variety of international bodies/regulatory programs and original publications were analysed.

Butanone oxime has been evaluated by the U.S. Environmental Protection Agency (US EPA 1986, 1989), in the OECD HPV Chemicals Programme (SIDS Initial Assessment Report for SIAM 17, OECD SIDS 2003), by the Government of Canada (Environment Canada Health Canada, CEPA March 2010), and by the German Committee on Hazardous Substances (AGS 2013).

Where relevant, the original publications were reviewed and evaluated as indicated in the text.

This substance evaluation includes all human health endpoints. The evaluation as well as the documentation in the SEV report focuses on certain aspects with relation to the initial concerns. Moreover, the available information in the registration dossiers (IUCLID section 2-4, 7) and the CSRs were checked for plausibility and indications of additional concerns for butanone oxime.

Hazard assessment

The provided information on classification and labelling of butanone oxime in lead registration was reviewed with regard to the current classification and labelling of the substance as listed under Index number 616-014-00-0 in Annex VI, Table 3.1 of the CLP Regulation (2008).

Butanone oxime was originally selected for SEV in order to clarify the concern about the adequacy of the classification as category 1B carcinogen according to the CLP Regulation.

Worker exposure assessment

The exposure assessment for workers included both, modelled data from the CSR (as provided by the registrants) and actual workplace measurement data as provided by the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA).

Consumer exposure assessment

The evaluation of consumer exposure to butanone oxime has been based on the recorded exposure scenarios, operational conditions, RMM and exposure estimates in the CSRs.

In order to identify possible consumer uses of butanone oxime that are not described in the CSRs additional literature, websites and databases have been searched (see chapter 9 for details). In addition, the product registers from Germany, Slovenia and Switzerland were consulted for information on butanone oxime in registered products.

The exposure scenarios and estimations in the CSRs were evaluated by the eMSCA and, in order to clarify the effects of inadequacies found in the data base of the CSRs, additional exposure calculations were performed by the eMSCA.

The eMSCA decided to limit the consumer exposure evaluation to exposure to butanone oxime from its registered consumer uses. Health risks for the general population from release of butanone oxime upon curing of silicone sealants or polyurethanes, from accidental exposure and from combined exposures are not covered by this substance evaluation.

Risk characterisation

Occupational uses

The risk assessment for workers includes the derivation of DNELs and DMELs by the eMSCA. For risk characterisation these DNELs and DMELs were compared with both modelled and measured exposure values.

Consumer uses

The risk assessment for consumers includes the derivation of DNEL/Cs and DMEL/Cs by the eMSCA. The risks regarding the carcinogenic properties of butanone oxime for the general population were not evaluated by the registrants. Therefore, the eMSCA has derived DMEL/Cs for the general population according to REACH Guidance Chapter R.8 (ECHA 2012a).

In order to assess whether risks from consumer uses are adequately controlled, the risk characterisation ratios (RCRs) were calculated using the exposure estimates by the registrants and the exposure estimates by the eMSCA as well as the DNEL/C derived by the registrants and the DNEL/C derived by the eMSCA.

Conclusions

Hazard assessment

The eMSCA concludes that the initial concern on the reclassification of butanone oxime as category 1B carcinogen was clarified. The available data suggest that butanone oxime meets the criteria for classification and labelling as carcinogen category 1B, H350 according to the CLP Regulation. The SEV leads to the need of an update of the existing harmonised classification and labelling of butanone oxime.

During the SEV other concerns were identified. The eMSCA concludes that the existing information on the toxicity of butanone oxime indicates that the substance also fulfils the criteria for classification and labelling for acute oral toxicity and narcotic effects. Further it was found that the data for skin sensitization of butanone oxime allow sub-categorisation.

In addition, based on the review of the available experimental data for acute dermal toxicity for butanone oxime, it is concluded that butanone oxime meets the criteria for classification and labelling as Acute Tox. 4, H312 according to the CLP Regulation and it seems that the reference indicating minimum classification (*) is no longer necessary. The legal classification of butanone oxime can be confirmed for Acute Tox. 4, H312. The available data on eye irritation do fulfil the criteria laid down in the CLP Regulation, and the legal classification as ‘Irreversible effects on the eye’ Category 1, H318 is warranted.

The following hazard classes appear to be appropriate for butanone oxime.

Table 1: Classification according to CLP Regulation as proposed by the eMSCA

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

Risks from occupational uses

The eMSCA will await the outcome of the discussions regarding the process of harmonised classification and labelling of butanone oxime as category 1B carcinogen and the outcome of a new field campaign before drawing final conclusions on the risk assessment of butanone oxime for workers.

Risks from consumer uses

The SEV showed that there are concerns indicating human health risks from consumer uses. The most likely routes of exposure to butanone oxime for the general population are inhalation and the dermal contact, exposure to the eyes is possible as well. Exposure via the oral route is considered not to be relevant for consumers due to the nature of the products.

Statement of reasons

Hazard assessment

Carcinogenicity: The available data for carcinogenicity of butanone oxime 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 the CLP Regulation.

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 (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 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 (Newton et al. 2001; TL9 1994, 1993 unpublished report).

Acute oral toxicity: The data from a preliminary dose range-finding study to a developmental toxicity study in rabbits (TL1 1990b, unpublished report; Derelanko et al. 2003) have shown that

butanone oxime induces lethality caused by haemolytic anaemia in this species. In females treated with 80 mg/kg bw butanone oxime starting on gestation day (GD) 6 mortalities were observed on GD8 until GD10. First deaths occurred on GD8 (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 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 ATE value of 160 mg/kg bw 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 the CLP Regulation (Annex I, Part 3, Table 3.1 Acute toxicity category 3: $50 < ATE \leq 300$ mg/kg bw).

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 that butanone oxime should be classified additionally due to its narcotic effects according to the CLP Regulation.

In rats single oral doses of ≥ 300 mg/kg bw butanone oxime administered by gavage produced narcotic effects (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). 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 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. 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 the CLP Regulation (Annex I, Part 3.8.2.2.2).

Skin sensitisation: Data on skin sensitisation of butanone oxime was obtained from animal testing accordance to the existing guidelines. 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 the 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 the CLP Regulation 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).

In addition butanone oxime meets the criteria for classification and labelling for acute dermal toxicity as Acute Tox. 4, H312 according to the CLP Regulation and it seems that the reference indicating minimum classification (*) is not longer necessary. The legal classification of butanone oxime can be confirmed for Acute Tox. 4, H312.

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

Risks from occupational uses

DNELs calculated by the eMSCA are lower than the values given by the registrants. A DMEL for carcinogenicity was not provided by the registrants and thus newly derived by the eMSCA. For the calculation of RCRs, the eMSCA used air monitoring data for butanone oxime collected in Germany between 1998 and 2011 and modelled dermal exposure data. Based on these data, risks were identified. However, the eMSCA considers that the air monitoring data do most likely not reflect the current situation at the work places, due to significant changes in the currently used formulations of paints and varnishes containing butanone oxime. A new field campaign is presently conducted in Germany. It is expected that more robust data of butanone oxime exposure will be provided. The eMSCA will await the outcome of the discussions regarding the harmonised classification and labelling of butanone oxime and the outcome of this new field campaign before drawing final conclusions on the risk assessment of butanone oxime for workers.

Risks from consumer uses

Based on the evaluation of all relevant information submitted on butanone oxime it is concluded that there is concern on consumer health risks from use of butanone oxime.

When analysing the exposure estimations in the CSRs, the eMSCA found that several factors produced a potential underestimation of consumer exposure. For instance, worker models have been used for the calculation which are not suitable for consumer uses, personal protection for consumers has been supposed in the quantitative risk assessment for consumers, the ConsExpo spray model for non-volatile substances has been used in spite of the volatility of butanone oxime and non-standard conditions and/or communicated risk management measures have been used without a proper justification.

In consequence, the eMSCA has performed own exposure estimations based on the standard procedures and parameters in the respective scenarios of the RIVM fact sheets[1]. When comparing these exposure estimates with the long-term inhalation DNECs derived by the registrants, RCRs above 1 were found in a series of product groups.

Moreover, the DNEL/Cs for butanone oxime for the general population provided by the registrants were assessed as not valid regarding the assessment factor (AF) for intraspecies differences, and the eMSCA has derived own DNEC/Ls for short-term/acute systemic effects by inhalation, for long-term systemic and local effects by inhalation and for systemic effects after short-term/acute and long-term exposure by dermal administration.

Comparing the inhalation DNEC for short-term/acute systemic effects with the external mean event concentrations, RCRs >1 were calculated for all contributing consumer exposure scenarios that comprise brushing and rolling or spraying. RCRs >1 were also found for the scenarios that cover

[1] H.J. Bremmer et al. (2007): Paint Products Fact Sheet. To assess the risks for the consumer. Updated version for ConsExpo 4. RIVM Report 320104008/2007,
ter Burg, W., et al. (2007): Do-It-Yourself Products Fact Sheet. To assess the risks for the consumer. RIVM Report 320104007/2007

mixing and loading of high solid paint, waterborne wall paint, general coating (floor), paint paste tube and yacht paint and also for the application of general coating (floor). These RCRs indicate that the corresponding risks are not adequately controlled.

Comparing the corrected long-term dermal DNEL with the dermal external dose on the day of exposure as calculated by the eMSCA, the RCRs exceeded 1 in all scenarios that comprise brushing and rolling or spraying. The comparison of the long-term inhalation DNEC for local and systemic effects with the mean concentration on day of exposure resulted in RCRs >1 in all scenarios that comprise brushing and rolling or spraying. RCRs >1 were also found for the scenarios that cover mixing and loading of high solid paint, general coating (floor), paint paste tube and yacht paint and for the application of general coating (floor). All these RCRs indicate that the corresponding risks are not adequately controlled.

Based on these data it is assumed that a combined risk characterisation via inhalation and the dermal route by summation of the respective RCRs also will result in RCRs that all exceed 1.

Due to the generic entry 28 in Annex XVII of the REACH Regulation the proposed harmonized classification of butanone oxime as Carc. 1B would result in a restriction to place the substance (or the substance in mixtures) on the market for the general public at concentrations ≥0.1 %. The eMSCA considers that as a consequence of a restriction according to entry 28 in Annex XVII most, if not all, assumed risks resulting from consumer uses of butanone oxime would be addressed. Therefore the result of a harmonised classification of butanone oxime should be awaited and the need of further community–wide regulatory risk management measures for the consumer uses should be re-assessed.

CONTENTS

TABLES

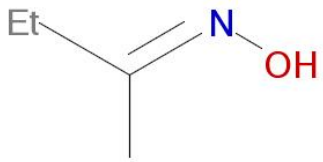
1 IDENTITY OF THE SUBSTANCE AND PHYSICAL AND CHEMICAL PROPERTIES

1.1 Name and other identifiers of the substance

Table **2**: Substance identity

Public Name:	butanone oxime
EC number:	202-496-6
EC name:	butanone oxime
CAS number (in the EC inventory):	96-29-7
CAS number:	96-29-7
CAS name:	Butanone, oxime
IUPAC name:	butan-2-one oxime
Index number in Annex VI of the CLP Regulation	616-014-00-0
Molecular formula:	C_4H_9NO
Molecular weight range:	87.12 g/mol
Synonyms:	MEKO Antioxidant B antiskinning agent KL-841 SKINO

Structural formula:



1.2 Composition of the substance

Name: butanone oxime

Description: mono constituent substance

Degree of purity: There is only one major isomer for butanone oxime (MEKO), which is trans/anti. During the oximation process, the size of the ethyl group and its rotation favours formation of primarily (>99 %) trans/anti isomer which is stable.

For further information, please refer to the IUCLID File.

1.3 Physico-chemical properties

Table 3: Overview of physicochemical properties

Property	Value	Remarks	Reference
Physical state 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*
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 (log value)	*0.63 at 25°C*	*equivalent or similar to OECD Guideline 117 (Partition Coefficient (n-octanol / water), HPLC Method)*	*EPIWIN Systpro Database, 1992*
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	*Butanonoxim 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 Enviroment. Therefore ist could be assumed that this value should also be valid.

2 MANUFACTURE AND USES

2.1 Quantities

Table 4: Aggregated tonnage (per year)

1 – 10 t	10 – 100 t	100 – 1000 t	**1000- 10,000 t**	10,000-50,000 t
50,000 – 100,000 t	100,000 – 500,000 t	500,000 – 1000,000 t	> 1000,000 t	Confidential

2.1.1 Manufacturing processes

Butanone oxime is produced from hydroxylamine and butanone by oximation in closed systems.

2.2 Identified uses

2.2.1 Uses by workers in industrial settings

- Intermediate use of butanone oxime
- Formulation of liquid paints containing butanone oxime
- Industrial application of paints containing butanone oxime

2.2.2 Use by professional workers

- Professional application of paints containing butanone oxime

2.2.3 Uses by consumers

- Consumer application of coatings

2.3 Uses advised against

2.3.1 Uses by workers in industrial settings advised against

The registrants do not advice against any uses.

2.3.2 Use by professional workers advised against

The registrants do not advice against any uses.

2.3.3 Uses by consumers advised against

The registrants do not advice against any uses.

3 CLASSIFICATION AND LABELLING

3.1 Harmonised Classification in Annex VI of the CLP Regulation

Butanone oxime is listed by Index number 616-014-00-0 in Annex VI of the CLP Regulation. The following table shows the CLP classification in Annex VI, Table 3.1 of butanone oxime.

Table 5: Classification and labelling of butanone oxime according to Annex VI, Part 3, and Table 3.1 (list of harmonised classification and labelling of hazardous substances) of CLP Regulation

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 GHS05 GHS08 Dgr		
Skin Sens. 1	H317	H317				
Eye Dam. 1	H318	H318				
Carc. 2	H351	H351				

Signal Words	Pictograms
Danger	 Exclamation mark Corrosion Health hazard

Based on the review of the available experimental data for acute dermal toxicity for butanone oxime, it is concluded that butanone oxime meets the criteria for classification and labelling as Acute Tox. 4, H312 (CLP Regulation) and the reference indicating minimum classification "(*)" is not longer necessary. The legal classification of butanone oxime is confirmed for Acute Tox. 4, H312. The available data on eye irritation do fulfil the criteria laid down in the CLP Regulation, and the legal classification as 'Irreversible effects on the eye' Category 1, H318 is warranted.

The SEV of butanone oxime has verified the concern that a more severe classification regarding carcinogenicity is needed, and also the classification of butanone oxime for its acute oral toxicity and narcotic effects, and a refined evaluation on sub-categorisation of butanone oxime as skin sensitizer. The SEV leads to the need for an update of the existing harmonised classification and labelling of butanone oxime.

3.2 Self classification

Self-classification notifications for butanone oxime by industry are available in the C&L Inventory (http://echa.europa.eu/information-on-chemicals/cl-inventory). In the following table an overview of classification of notifications for butanone oxime is given (14 March 2014).

Table 6: Classification and labelling according to CLP Regulation as provided by the registrants

Classification		Labelling			Specific Concentration limits, M-Factors	Number of Notifiers
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		1559
Skin Sens. 1	H317	H317		GHS05		
Eye Dam. 1	H318	H318		GHS08		
Carc. 2	H351	H351		Dgr		
		H315		GHS07		92
Acute Tox. 4	H312	H312		GHS05		
Skin Sens. 1	H317	H317		GHS08		
Eye Dam. 1	H318	H318		Dgr		
Carc. 2	H351					
Acute Tox. 4	H312	H312		GHS07		36
Skin Sens. 1	H317	H317		GHS05		
Eye Dam. 1	H318	H318		GHS08		
Carc. 2	H351			Dgr		
Acute Tox. 4	H312	H312		GHS07		33
Skin Sens. 1	H317	H317		GHS05		
Eye Dam. 1	H318	H318		GHS08		
Carc. 2	H351	H351		Dgr		
Aquatic Chronic 3	H412	H412				
Acute Tox. 3	H311	H311		GHS06		28
Skin Sens. 1	H317	H317		GHS05		
Eye Dam. 1	H318	H318		GHS08		
Carc. 2	H351	H351		Dgr		
Aquatic Chronic 3	H412	H412				
Flam. Liq. 3	H226	H226		GHS07		24
Acute Tox. 4	H312	H312		GHS02		
Skin Sens. 1	H317	H317		GHS05		
Eye Dam. 1	H318	H318		GHS08		
Carc. 2	H351	H351		Dgr		
		H373		GHS07		16
Acute Tox. 4	H312	H312		GHS05		
Skin Sens. 1	H317			GHS08		
Eye Dam. 1	H318	H318		Dgr		
Carc. 2	H351	H351				
Acute Tox. 4	H312	H312(H312)		GHS07		4
Skin Sens. 1	H317	H317(H317)		GHS05		
Eye Dam. 1	H318	H318(H318)		GHS08		
Carc. 2	H351	H351(H351)		Dgr		
Not Classified						2

Acute Tox. 4	H312	H312		GHS07		2
Skin Sens. 1	H317	H317		GHS05		
Eye Dam. 1	H318	H318		GHS08		
Carc. 2	H351	H351		Dgr		
Acute Tox. 4	H312	H312		GHS07		2
Skin Sens. 1	H317	H317		GHS05		
Eye Dam. 1	H318	H318		GHS08		
Carc. 2	H351(Dermal)	H351		Dgr		
Acute Tox. 4	H312	H312		GHS05		1
Skin Sens. 1	H317	H317		GHS08		
Eye Dam. 1	H318	H318		Dgr		
Carc. 2	H351	H351				
Acute Tox. 4	H312	H312		GHS02		1
Skin Sens. 1	H317	H317		GHS05		
Eye Dam. 1	H318	H318		GHS08		
Carc. 2	H351	H351		Dgr		
		H226		GHS07		1
Acute Tox. 4	H312	H312		GHS02		
Skin Sens. 1	H317	H317		GHS05		
Eye Dam. 1	H318	H318		GHS08		
Carc. 2	H351	H351		Dgr		
Acute Tox. 4	H312	H312		GHS07		1
Skin Sens. 1	H317	H317		GHS05		
Eye Dam. 1	H318	H318		GHS08		
Carc. 2	H351	H351		Dgr		
Acute Tox. 4	H312	H312		GHS07		1
Skin Sens. 1	H317	H317		GHS05		
Eye Irrit. 2	H318	H318		GHS08		
Carc. 2	H351	H351		Dgr		
Flam. Liq. 3	H226	H226		GHS02		1
Acute Tox. 3	H311	H311		GHS06		
Skin Sens. 1	H317	H317		GHS05		
Eye Dam. 1	H318	H318		GHS08		
Carc. 2	H351	H351		Dgr		
Acute Tox. 4	H302	H302		GHS07		1
Acute Tox. 4	H312	H312		GHS09		
Skin Corr. 1B	H314			GHS05		
Skin Sens. 1	H317	H317		GHS08		
Eye Dam. 1	H318	H318		Dgr		
Carc. 2	H351	H351				
Aquatic Chronic 2	H411					

4 ENVIRONMENTAL FATE PROPERTIES

Not evaluated.

5 HUMAN HEALTH HAZARD ASSESSMENT

The evaluation of the toxicity of butanone oxime is based on data presented by the registrants (aggregated IUCLID, CSR) and on reviews performed by a variety of international bodies/regulatory programs. A literature research including publications on butanone oxime was performed until October 2013.

Butanone oxime was evaluated by the U.S. Environmental Protection Agency (US EPA 1986, 1989), in the OECD HPV Chemicals Programme (SIDS Initial Assessment Report for SIAM 17, OECD SIDS 2003), by the Government of Canada (Environment Canada Health Canada, CEPA March 2010), and by the German Committee on Hazardous Substances (AGS 2013). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in April 2013, literature was searched in the online databases DIMDI (medline, xtoxline), Chem ID plus Advanced (pubmed, Tox Net), Web of Knowledge and Chemical Abstracts starting from 2006, and using the following key words for butanone oxime: butanone oxime; ethyl methyl ketoxime; ethyl methyl ketone oxime; MEKO; 96-29-7; repeated dose toxicity, oral, inhalation, dermal; carcinogenicity/cancer; toxicity for reproduction. Data available up to October 2013 have been assessed and considered for the assessment of butanone oxime.

5.1 Toxicokinetics (absorption, metabolism, distribution and elimination)

5.1.1 Non-human information

For basic toxicokinetics results from 4 experimental studies are available. Of these, 3 studies are considered by the registrants as key studies and one further study as supporting study. For dermal absorption one study considered as key study by the registrant is available.

In all studies butanone oxime (purity 96 % or 99.5 %) 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 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 24h 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 % to 7 % after 72 hours of dosing, with no tissue demonstrating any marked accumulation of radioactivity.

Metabolite profile in urine, 0-8h 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), glucorunides, 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 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; TL3, unpublished report 2000). The biotransformation of butanone oxime was studied in liver microsomes and cytosol from male and female rats, mice and humans. 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, was evaluated by autoradiography at selected time points: 20 minutes, 1, 3, 9 and 24 hours (TL5, unpublished report 1981). 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 secretion 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 the male F344 rat 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.

5.1.2 Human information

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

5.1.3 Summary and discussion on toxicokinetics

No information is available on the toxicokinetics, metabolism and distribution of butanone oxime in humans. The data submitted for this endpoint are suitable for evaluation. No data on the toxicokinetics of butanone oxime after exposure by inhalation are found.

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 doses of 2.7 mg/kg bw butanone oxime to rats were strikingly different, with less conversion to CO_2 in the intravenous doses than the oral doses, 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 5-6 % 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. 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, undergo widespread uptake, was distributed over the entire body, was extensively metabolized to CO_2 and MEK, which are excreted via the lungs, and glucuronide conjugates of butanone oxime and its metabolites or other polar metabolites, which are excreted in urine and bile, and was not accumulate in tissues. Distribution of butanone oxime was clearly different following intravenous administration 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 administration 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 more 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.

Conclusion from SEV:

There is sufficient information available for evaluation of toxicokinetics of butanone oxime. No further action is recommended.

5.2 Acute toxicity

5.2.1 Non-human information

5.2.1.1 Acute toxicity: oral

For the acute oral toxicity results from 4 experimental studies in rats are submitted by the registrants. Of these, two studies were considered as key studies by the registrants, and one further study as supporting study. Since original data were not available from the TL6 (1982) the data from this study was disregarded from the assessment by the registrants.

Additionally, mortalities observed in repeated dose toxicity studies during days 0-3 may be 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) (TL1 1990b, unpublished report; Derelanko et al. 2003) are discussed as deaths of animals were observed in these studies.

In all studies butanone oxime (purity 99.98 %) was used as test material.

The results of experimental studies on acute toxicity after oral administration are summarised in the following table.

Table 7: Studies on acute oral toxicity

Reference **Species; strain; sex; method**	**LD_{50} / Results**
TL7 (1991), unpublished report; Schulze and Derelanko (1993) **Rat**; Sprague-Dawley; male, female acute neurotoxicity study	**$LD_{50, rat\ m/f}$ > 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 (gait, aerial righting reflex, reversible within 24h); suggested a transient narcoleptic response
TL2, unpublished report (1978a) **Rat**; Sprague-Dawley; male; protocol similar to OECD TG 401	**$LD_{50, male\ rat}$ ca. 2326 mg/kg bw** 1500 mg/kg bw: no mortality; 1,908 mg/kg bw: 22.2 % deaths; 2,427 mg/kg bw: 50 % deaths; ≥ 3,089 mg/kg bw: 100 % deaths. Mortality occurred within 48 hours.
TL8 (1971a), unpublished report **Rat**; strain and sex not specified; in-house protocol	**$LD_{50, rat}$ ca. 2528 mg/kg bw**
TL6 (1982), unpublished report **Rat**; Sherman-Wistar; male, female; method not specified	**$LD_{50, male\ rat}$ ca. 930 mg/kg bw** **$LD_{50, female\ rat}$ ca. 1620 mg/kg bw**
TL1 (1990b), unpublished report; Derelanko et al. (2003) **Rabbit;** New Zealand White; female; Other: gavage, exposure: gestation day (GD) GDs6-18 (daily) According to OECD TG 414/EUB.31	*Preliminary study (dose range-finding study):* 80 mg/kg bw/d for 2 days **(cumulative 160 mg/kg bw)** induced **mortality** in 5/5 females (GDs8-10) ≤ 48h; 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 (GDs10-11) **$LD_{50, female\ rabbit}$ = 160 mg/kg bw** *Main study:* 40 mg/kg bw/d for 5 days **(cumulative 200 mg/kg bw)**: induced **mortality** in 8/18 females **(**GDs11-24); 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**

5.2.1.2 Acute toxicity: inhalation

For the acute inhalation toxicity results from two experimental studies in rats are submitted. One study was declared as key study by the registrants, and one further study as supporting study.

In both studies butanone oxime (purity 99.98 %) was used as test material.

The results of experimental studies on acute inhalation toxicity are summarised in the following table.

Table 8: Studies on acute inhalation toxicity

Reference Species; strain; sex; method	LC_{50} / Results
TL2 (1984a), unpublished report **Rat**; F344; male, female; protocol similar to OECD TG 403	**$LC_{50, rat}$ > 4.83 mg/L/4h** (analytical) (male/female); vapour, whole body, 4h; no mortality 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
TL8 (1971a), unpublished report **Rat**; strain not specified; male, female; in-house protocol	**$LC_{50, rat}$ > 13.2 mg/L/4h** (calculated, modified Haber's law); vapour, whole body, 8h exposure; no mortality at 10.5 mg/L (highest tested concentration; analytical; male/female)

5.2.1.3 Acute toxicity: dermal

For the acute dermal toxicity results from two experimental studies in rabbits were submitted. One study was considered as key study by the registrants, and one further study as supporting study.

In both studies butanone oxime (purity 99.98 %) was used as test material.

The results of experimental studies on acute toxicity after dermal exposure are summarised in the following table.

Table 9: Studies on acute dermal toxicity

Reference Species; strain; sex; method	LD_{50} / Results
TL1 (1991b), unpublished report **Rabbit;** New Zealand White; male, female; protocol similar to OECD TG 402	**$LD_{50, rabbit, m/f}$ > 1000 mg/kg bw** (Limit Test); occlusive, 24h; no mortality
TL2 (1984b), unpublished report **Rabbit**; New Zealand White; male, female; protocol similar to EPA OTS 798.1100 Guideline	**$LD_{50, rabbit, m/f}$ = 1848 mg/kg bw** 2.0 mL/kg (equivalent to 1848 mg/kg bw, calculated based on density of 0.924 g/mL); occlusive, 24h, 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

5.2.1.4 Acute toxicity: other routes

No data were submitted.

5.2.2 Human information

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

5.2.3 Summary and discussion of acute toxicity

The data for acute toxicity of butanone oxime was obtained from animal testing. The data submitted for registration on the endpoint acute toxicity were suitable for evaluation. To evaluate the endpoint acute oral toxicity of butanone oxime, e.g. derivation of the LD_{50} value, data from a developmental study in rabbits were added. Sufficient information is available for the evaluation of acute toxicity. No further information required.

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

Taken together, from experiments with single and repeated exposure, the rabbit appears to be more sensitive than the rat to the toxic effects of butanone oxime. Therefore, the data from a developmental toxicity study in rabbits were included in the evaluation of the acute oral toxicity of butanone oxime. In this study mortality was observed in female rabbits treated with butanone oxime during the gestation phase. In the preliminary dose range-finding study all 5 rabbits receiving doses of 80 mg/kg bw starting on GD6 were found dead between the GDs8-10 due to haemolytic anaemia. First deaths occurred after two dosages (cumulative 160 mg/kg bw) on GD8. 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 (GDs10-11). 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. It is concluded that butanone oxime is acutely toxic after oral administration.

Acute inhalation toxicity: In the available studies the LC_{50} value for butanone oxime could not be established as no death occurred at the highest concentration tested in these studies. After a 4 hour whole body exposure of 4.83 mg/L butanone oxime as vapour no deaths occurred in male and female rats. In an 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. The calculation for a 4 hour exposure by using the modified Haber's law was accepted: $C^n * t = const$, 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. Based on the available data 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. 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.

Justification for classification or non-classification

Acute oral toxicity: In contrast to the registrants the eMSCA is of the opinion that there is concern about classification of butanone oxime for acute oral toxicity.

Based on the available oral LD_{50} values from studies with rats, butanone oxime does not fulfil the criteria for classification for acute oral toxicity according to the CLP Regulation. However, the data from a preliminary dose range-finding study to a developmental toxicity study in rabbits (TL1 1990b, unpublished report; Derelanko et al. 2003) have shown that butanone oxime induces acute lethality in this species. In female rabbits treated with 80 mg/kg bw butanone oxime starting on GD6 mortalities were observed on GD 8 until GD10 due to haemolytic anaemia. First deaths occurred on the GD8 (after two dosages on GD6 and 7, cumulative 160 mg/kg bw),, all 5 females died until GD10.

In the synopsis of the available data from single dose studies in rats and from repeated dose studies in rabbits, the rabbit appears 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 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 ATE value of 160 mg/kg bw observed in a developmental toxicity study in rabbits butanone oxime should be classified for acute oral toxicity. According to the CLP Regulation (Annex I, Part 3, Table 3.1 Acute toxicity category 3: $50 < ATE \leq 300$ mg/kg bw) butanone oxime fulfils the criteria for classification as Acute Tox. 3, H301: Toxic if swallowed.

Conclusion: Acute Tox. 3, H301

Acute inhalation toxicity: Based on the available data, butanone oxime does not fulfil the criteria for classification for acute inhalation toxicity according to the CLP Regulation.

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 butanone oxime as a vapour (TL8 1971a, unpublished report). By using the modified Haber's law 13.2 mg/L for a 4 hour exposure was calculated. 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. It is assumed that the real LC_{50} value for butanone oxime exceeds the cut-off value of 20 mg/L/4h (vapours) for classification in the acute inhalation toxicity hazard category 4 according to the CLP Regulation.

Conclusion: no classification

Acute dermal toxicity: The current Annex VI entry for butanone oxime includes 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 concluded that butanone oxime meets the criteria for classification and labelling as Acute Tox. 4, H312 according to the CLP Regulation 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 (TL1 1991, unpublished report), performed to a comparable protocol as OECD TG 402, no lethality was observed at the highest dose tested of 1000 mg/kg bw. In the second study (TL2 1984b, unpublished report), the dermal LD_{50} was found to be 2.0 mL/kg bw (equivalent to 1848 mg/kg bw). Based on this LD_{50} value of 1848 mg/kg bw, butanone oxime meets the criteria for classification as Acute Tox. 4, H312: Harmful in contact with

skin according to the CLP Regulation (Annex I, Part 3, Table 3.1 Acute toxicity category 4: 1000 < ATE ≤ 2000 mg/kg bw).

Conclusion: Acute Tox. 4, H312

Narcotic effects: Based on the available data from acute oral, inhalation and dermal toxicity, there is reasonable suspicion that butanone oxime meets the criteria for classification additionally as a specific target organ toxicant after a single exposure due to its narcotic effects according to the CLP Regulation. 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 (Schulze and Derelanko 1993). In the acute inhalation toxicity study a strong but transient narcotic effect occurred in both sexes at 4.83 mg/L/4h during the exposure (TL2 1984a, unpublished report). In a dermal acute toxicity study in rabbits butanone oxime produced significant effects on the nervous system. Narcosis was observed at single doses of 0.2 mL/kg bw (equivalent to 185 mg/kg bw) and higher. Narcosis was transient at the low dose level of 0.02 mL/kg bw (equivalent to 18 mg/kg bw) occurring during the first 48 hours following exposure. Furthermore, the potential of butanone oxime to produce neurotoxicity was studied in specific investigations. An acute neurotoxicity study and a sub-chronic study both in rats and with oral exposure by gavage were performed (Schulze and Derelanko 1993; TL7 1991, unpublished report; TL21 1991, unpublished report). In both studies the observations were characterised as 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 changes (narcoleptic response) in gait, and aerial righting reflex. No progressive long-term, irreversible neurotoxic changes were associated with repeated butanone oxime administration for 13 weeks. Based on this data, butanone oxime meets the criteria for the 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 the CLP Regulation (Annex I, Part 3.8.2.2.2).

Conclusion: STOT SE 3, H336

The following information is taken into account for hazard / risk assessment:

$LD_{50,\ oral,\ rat,\ m/f}$ > 900 mg/kg bw (TL7 1991, unpublished report; Schulze and Derelanko 1993)

$LD_{50,\ oral,\ rabbit,\ f}$ = 160-200 mg/kg bw (TL1 1990b, unpublished report; Derelanko et al. 2003)

$LC_{50,\ inhalation,\ rat,\ m/f}$ > 13.2 mg/L/4h (TL8 1971a, unpublished report)

$LD_{50,\ dermal,\ rabbit,\ m/f}$ = 1848 mg/kg bw (TL2 1984b, unpublished report)

$LOAEL_{dermal,\ rabbit,\ m/f}$ = 185 mg/kg bw, based on methaemoglobin formation, and splenic erythrophagocytosis (TL2 1984b, unpublished report)

$LOEL_{dermal,\ rabbit,\ m/f}$ = 18 mg/kg bw based on reversible narcotic effects (TL2 1984b, unpublished report)

Conclusion from SEV:

There is sufficient information available for evaluation of acute toxicity of butanone oxime.

The SEV has verified the concern that butanone oxime caused acute oral toxicity and narcotic effects that meets the criteria for classification and labelling according to CLP criteria. It leads to the need for an update of the existing harmonised classification and labelling. A proposal for harmonised classification of butanone oxime should be prepared.

5.3 Irritation

5.3.1 Skin

To evaluate skin irritation of butanone oxime results from two experimental studies in rabbits are available. One study was considered as key study by the registrants, and one further study as supporting study.

In both studies butanone oxime (purity 99.98 %) was used as test material.

The results of experimental studies on skin irritation are summarised in the following table.

Table 10: Studies on skin irritation

Reference Species; strain; method	Results
TL2 (1978b), unpublished report **Rabbit**; New Zealand White; no specific test method: occluded exposure over 24h	slightly irritating to non-abraded and abraded skin of rabbits; PDII (Primary dermal irritation index): ca. 1.5 (mean (erythema and oedema)), not fully reversible within 72 h; scores reversible at the end of the observation period
TL8 (1971b), unpublished report **Rabbit**; New Zealand White; equivalent to OECD TG 404	not irritating

5.3.2 Eye

One study in rabbits was submitted. Butanone oxime (purity 99.98 %) was used as test material. The results of the experimental study on eye irritation are summarised in the following table.

Table 11: Study on eye irritation

Reference Species; strain; method	Results
TL2 (1978c), unpublished report **Rabbit**; New Zealand White; equivalent to OECD TG 405	**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

5.3.3 Respiratory tract

No information is available on the respiratory tract irritation in animals.

Butanone oxime causes degeneration on the nasal olfactory epithelium in rats and mice after repeated exposure by inhalation and after oral administration in mice, which was concentration

related increased in incidence and severity (TL9 1993, 1994, unpublished reports; TL10 1995ab, unpublished report; Newton et al. 2001; NTP 1999). In the inhalation studies degeneration of the olfactory epithelium lining the dorsal meatus was seen in the anterior region of the nasal cavity. In a few instances, the olfactory epithelium covering the tips of the nasoturbinal scrolls projecting into the dorsal region of the nasal cavity was also degenerated. Large areas of olfactory epithelium lying laterally and posterior were unaffected. In general, approximately 10 % or less of the total olfactory tissue was affected. In several instances, the degenerated olfactory epithelium was reepithelialised by squamous/squamoid and/or respiratory types of epithelium. The incidence and severity of the degeneration present after one week of exposure did not increase with the longer exposures. The olfactory degeneration was found to be reversible. Recovery was complete within four weeks following exposures at 10 ppm (36 mg/m^3) and nearly complete within 13 weeks after exposures at 30 ppm (108 mg/m^3) and 100 ppm (360 mg/m^3). A NOAEL for the olfactory degeneration was considered to be 3 ppm (10.8 mg/m^3) (Newton et al. 2002).

5.3.4 Summary and discussion of irritation

The evidence for skin and eye irritation of butanone oxime was obtained from animal testing. Sufficient information is available for the evaluation of skin and eye irritation. No further information required.

Butanone oxime has been shown to be slightly irritating to the skin of rabbits, and it induces serious eye damage in rabbits.

Butanone oxime causes concentration-depending degeneration on the nasal olfactory epithelium in rats and mice after repeated exposure by inhalation, which were reversible within four weeks following exposures at 10 ppm (36 mg/m^3) and nearly complete within 13 weeks after exposures at 30 ppm (108 mg/m^3) and 100 ppm (360 mg/m^3).

No information was available on the respiratory irritation in humans.

Justification for classification or non-classification

Skin irritation: Based on the available data, butanone oxime does not fulfil the criteria for classification for skin irritation according to the CLP Regulation.

Conclusion: no classification

Serious eye damage/eye irritation: butanone oxime has the potential to seriously damage the eyes and is classified as Eye Dam. 1, H318 according to the CLP Regulation. Evaluation of the observed butanone oxime effects on the eye of rabbits was based on the nature, intensity and reversibility of responses. The available eye irritation study showed that butanone oxime caused irreversible effects on the eye/serious damage to the eyes. 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. In addition, irreversible effects on the eye were observed in 2/6 rabbits. Conjunctivae necrosis was observed in these rabbits which was not reversible at the end of observation period. Based on these results, butanone oxime meets the criteria for classification and labelling as 'Irreversible effects on the eye' Category 1, H318: Causes serious eye damage according to the CLP Regulation. The legal classification was confirmed.

Conclusion: Irreversible effects on the eye' Category 1, H318

Respiratory tract irritation: There is no data on respiratory tract irritation.

The following information is taken into account for hazard / risk assessment:

Skin: not irritating (rabbit)

Eye: Irreversible effects on the eye category 1, H318 (rabbit)

Respiratory tract: no data available

Conclusion from SEV:

There is sufficient information available for evaluation of butanone oxime for its potential to induce dermal and eye irritation. No further action is recommended.

The present data have shown that butanone oxime is not irritating to rabbit skin, but has the potential to seriously damage the eyes of rabbits. However, calculation of a DNEL for short-term/acute local effects is not possible because no dose-response data are available for the eye effects. From repeated dose toxicity studies by oral administration in male mice and after inhalation in rats and mice degeneration on the nasal olfactory epithelium was noted, which was reversible within 13 weeks after exposures. There is no data on respiratory irritation.

5.4 Corrosivity

No information is available on skin corrosion in rabbits from animal experiments.

5.5 Sensitisation

5.5.1 Skin

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 under GLP conditions are available, in addition a local lymph node assay (LLNA) in mice according to OECD TG 429, and further a mouse ear swelling test (MEST). No human data on the sensitising potential of butanone oxime are available. One GPMT and the Buehler assay are considered by the registrants as key studies. A further GPMT and the LLNA were disregarded by the registrants.

In the available studies butanone oxime (purity 99.98 %) was used as test material.

The results of experimental studies on skin sensitisation are summarised in the following table.

Table 12: Studies on skin sensitisation

Reference Species; sex; strain; method	Results
TL11 (1983), unpublished report **Guinea pig**; female; Hartley; GPMT, according to OECD TG 406 Key study	**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 %; 48 h: 8/10, 80 % Negative Control: 24h/48h: 0/10 Reliability check: 0.1 % DNCB: 24h/48h: 10/10
TL12 (1989), unpublished report **Guinea pig**; female; Hartley; Buehler assay, according to OECD TG 406 Key study	**Skin sensitising** Induction: 25 % in propylene e.d.; Challenge: 5 % in propylene glycol e.d. TG (1. chall.): 24h: 6/10, 60 %; 48 h: 5/10, 50 % (2. chall.): 24h: 9/10, 90 %; 48 h: 8/10, 80 % Negative Control: 24h/48h: 0/10 Reliability check: 0.1 % DNCB: 24h/48h: 10/10
TL13 (1989), unpublished report **Guinea pig**; female; Hartley; GPMT, OECD TG 406	**Skin sensitising** Specifics not reported, summary results Induction: 4 % i.d., 100 % e.d.; Challenge: 50 % e.d. TG: 7/10, 70 %
Gad et al. (1986, 1988) **Mouse**; female; CF-1; MEST	**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
TL14 (2009), unpublished report **Mouse**; female; CBA; mLLNA, according to OECD TG 429	**Not sensitising** Vehicle: acetone/olive oil (4:1v/v); 50 %, 100 % Stimulation index: 50 %: 1.3; 100 %: 1.0 Reliability check: hexyl cinnamic aldehyde (CAS 101-86-0)

5.5.2 Respiratory system

No information is available. Currently no validated in vivo methods are available.

5.5.3 Summary and discussion on sensitisation

Skin sensitisation: The data for skin sensitisation of butanone oxime was obtained from animal testing. The data submitted for registration to the endpoint skin sensitisation are suitable for evaluation. Sufficient information is available for the evaluation of skin sensitisation. No further information required. In two GPMT, and a Buehler assay animals exhibited positive results. In a MEST a moderate potency for skin sensitisation was determined 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.

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).

No information was available that butanone oxime has lead to sensitisation by skin contact in human.

Respiratory sensitisation: No data for respiratory sensitisation of butanone oxime were available.

Justification for classification or non-classification

Skin sensitisation: Data for skin sensitisation of butanone oxime was obtained from animal testing according to existing testing guidelines. Butanone oxime has shown a clear evidence of skin sensitisation in guinea pigs (GPMT and Buehler assay). The results of a 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 the available data, butanone oxime is classified as skin sensitizer category 1 (legal classification). The available results from animal testing are sufficient for a refined evaluation allowing the sub-categorisation of butanone oxime.

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

Sub-category 1A for skin sensitisation based on animal test results:

GPMT of ≥ 30 % responding at ≤ 0.1 % i.d induction dose or ≥ 60 % responding at > 1.0 % to ≤ 1 % i.d 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.

Sub-category 1B for skin sensitisation based on animal test results:

GPMT of ≥ 30 % to < 60 % responding at > 0.1 % to ≤ 1 % i.d induction dose or ≥ 30 % responding at > 1.0 % i.d 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 the CLP Regulation 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). Based on the available data, butanone oxime meets the criteria for classification in the hazard class as skin sensitizer sub-category 1B, H317.

Conclusion: Skin sensitizer sub-category 1B, H317

The following information is taken into account for hazard / risk assessment:

Skin: skin sensitizer, 1B

Conclusion from SEV:

There is sufficient information available for evaluation of skin sensitisation of butanone oxime.

Butanone oxime is a skin sensitizer in guinea pigs and meets the criteria for classification in the hazard class as skin sensitizer sub-category 1B: H317. Butanone oxime was evaluated by two GPMT, a Buehler assay and a MEST, which have shown a moderate sensitising potential.

The SEV has verified the concern that a sub-categorisation regarding skin sensitisation is needed. The results from skin sensitisation testing of butanone oxime are sufficient for a refined evaluation allowing the sub-categorisation according to the CLP criteria. It leads to the need for an update of the existing harmonised classification and labelling according to the CLP Regulation. A proposal for harmonised classification of butanone oxime should be prepared.

The available data trigger a qualitative risk characterisation for the moderate skin sensitisation potential of butanone oxime. Moderate skin sensitizers are allocated to the moderate hazard category band on the basis that exposure to these substances should be well-controlled.

5.6 Repeated dose toxicity

5.6.1 Non-human information

5.6.1.1 Repeated dose toxicity: oral

Two sub-chronic oral (drinking water, gavage) toxicity studies (equivalent to OECD TG 408) considered by the registrants as key studies were available. Four further studies (one sub-chronic study in rats, two sub-acute studies in rats, and a sub-chronic study in mice) as supporting studies were submitted by the registrants. The data from developmental toxicity studies in rats and rabbits (oral, gavage, according to OECD TG 414) (TL1 1990a,b, unpublished report; Derelanko et al. 2003) and from a two-generation study with CD rats (oral, gavage, similar to OECD TG 416/B.35) (TL15 1992, unpublished report; Tyl et al. 1996) regarding repeated dose toxicity of butanone oxime were not evaluated by the registrants. The eMSCA has discussed these data for this endpoint.

In all studies butanone oxime (purity 99.98 %) was used as test material.

The results of experimental studies on repeated dose toxicity after oral administration are summarised in the following table.

Table 13: Studies on repeated dose toxicity after oral administration

Reference Species; strain; sex; method	Results
U.S. National Toxicology Program (NTP) (1999) **Rat**; F344; male/female; sub-chronic, 90 days, oral: drinking water, equivalent to OECD TG 408	• Effects indicative of anaemia: ≥ 65/100 mg/kg bw/d (m/f): anaemia ≥ 30/100 mg/kg bw/d (m/f): ↑ reticulocyte count ≥ 50/65 mg/kg bw/d (m/f): ↑ incidence and severity: hematopoietic cell proliferation in the spleen, hematopoietic 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 • 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 olfactory epithelium) **$NOAEL_{m/f}$ = 25/30 mg/kg bw/d** (erythrotoxicity)
Schulze and Derelanko (1993); TL21 (1991), unpublished report **Rat**; Sprague-Dawley; male/female; sub-chronic, 90 days, oral: gavage, equivalent to OECD TG 408	• Effects indicative of anaemia: ≥ 40 mg/k g bw/d (m/f): blood: elevated methemoglobin level, leukocytosis, regenerative anaemia, compensatory reticulocytosis, Heinz body formation, further erythrocytic morphologic changes, spleen: ↑ weight • Narcotic effects: 400 mg/kg bw/d (m/f): clinical signs: changes (transient and reversible) in

	neurobehavioral function consistent with CNS depression (hypoactivity, ataxia, impaired aerial righing); dark-coloured urine **$LOAEL_{m/f}$ = 40 mg/k g bw/d** (anaemia) **$NOAEL_{m/f}$ = 125 mg/kg bw/d** (neurobehavioral effects)
TL2 (1977), unpublished report; TL16 (1988); TL17 (1990) **Rat**; Sprague-Dawley; male/female; sub-chronic, oral: gavage, equivalent to OECD TG 408	• Effects indicative of anaemia: ≥ 25 mg/kg bw/d (m/f): changes in blood parameters indicative of haemolytic anaemia, and compensatory haematopoiesis and extramedullary haematopoiesis in spleen and liver **$LOAEL_{m/f}$ = 25 mg/kg bw/d** (haemolytic anaemia and compensatory haematopoiesis)
TL10 (1995a), unpublished report **Rat**; F344; male; sub-acute, oral: gavage, 7, 14 or 28 days (daily), other method: peroxisome proliferation, hepatic glutathione and serum testosterone levels were assessed	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
TL18 (1996), unpublished report **Rat**; Crj: CD(SD); male/female; sub-acute, oral: gavage, Japanese guideline for 28-day RDT testing with a recovery period of 14 days, similar to OECD TG 407/EU B.7	• Effects indicative of anaemia: ≥ 20 mg/kg bw/d: blood: ↑ reticulocyte ratio (m/f), ↑ platelet count (f); ↓ RBC count, hematocrit, haemoglobin (f) 100 mg/kg bw (m/f): liver: hypertrophy of Kupffer cells; liver and spleen: extramedullary haematopoiesis; reversibility of the most changes at the end of recovery **$LOAEL_{m/f}$ = 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)
U.S. National Toxicology Program (NTP) (1999) **Mouse**; B6C3F1; male/female; sub-chronic, oral: drinking water, equivalent to OECD TG 408	• Effects on the urinary bladder epithelium: ≥ 515/630 mg/kg bw/d (m/f): 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) • Effects indicative of anaemia: ≥ 755/1010 mg/kg bw/d (m/f): ↑ hematopoietic cell proliferation, spleen: ↑ weight 1330/3170 mg/kg bw/d (m/f): liver: Kupffer cell erythrophagocytosis indicating intravascular haemolysis and hemosiderin pigmentation; kidney: renal tubule hemosiderin pigmentation **$NOAEL_{m/f}$ = 515/630 mg/kg bw** (extramedullary haematopoiesis in the spleen)
TL1 (1990a), unpublished report; Derelanko et al. (2003) **Rat**; Sprague-Dawley; female; developmental toxicity study, oral: gavage, exposure: GDs6-15 (daily), according to OECD TG 414/EU B.31	**Maternal toxicity** *Preliminary study (dose range-finding study)* • 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 % in the lethal range, GD20: 9 %) ≥ 25 mg/kg bw/d: blood: ↑ methaemoglobin (GD16/20: 6/4 %), reticulocyte (GD16/20: 18/14 %) ≥ 100 mg/kg bw/d: necropsy: enlarged spleen *Main study* ≥ 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)
TL1 (1990b), unpublished report; Derelanko et al. (2003) **Rabbit;** New Zealand White; female; developmental toxicity study, oral: gavage, exposure: GDs6-18 (daily), according to OECD TG 414/EU B.31	**Maternal toxicity** *Preliminary study (dose range-finding study)* • Effects indicative of anaemia: 80 mg/kg bw/d: GDs8-10: mortality: 5/5; clinical signs: dark red or reddish-green coloured urine; necropsy: enlarged spleen, brown discoloured lungs 40 mg/kg bw/d: GDs10-11: mortality: 2/5 ≥ 40 mg/kg bw/d: clinical signs: laboured breathing, decreased activity, few or no

	faeces, pale ears and/or eyes, eyes dark in colour and 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 %) *Main study* 40 mg/kg bw/d: GD11-24: 8/18 mortality; 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** (haematotoxic effects)
TL15 (1992), unpublished report; Tyl et al. (1996) **Rat**; CD Sprague-Dawley (Crl:CD[SD]BR VAF/Plus); male/female; two-generation study, oral: gavage, Exposure: 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 d/wk); EPA guideline with modifications, similar to OECD TG 416/EU B.35	200 mg/kg bw/d: mortality: 4/30 (13.3 %) F0m, 11/30 (36.7 %) F0f, 15/30 (50 %) in Flm, 8/30 (26.7%) in Flf; clinical signs of toxicity: 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; necropsy: ↑: abs. and rel. weights of spleen in F0/Flm/f, rel. weights of liver in Flm + F0/Flf; blood: consistent picture of anaemia in both sexes in both generations: ↓: RBC count, Hb, Ht, ↑: MCV, MCH, WBC count (no change in differential counts) F0/Flm/f, methaemoglobin in F0/Flm; histopathology: spleen: congestion, and in spleen and liver: extramedullary haematopoiesis and haemosiderosis in F0/Flm/f 100 mg/kg bw/d: clinical signs of toxicity: lethargy, staggering, and rooting in bedding in F0m; weaving, tremors, and rooting in bedding in F0f; slight dehydration, audible breathing, and rooting in bedding in Flm; and laboured breathing in Flf; necropsy: ↑ abs. and rel. weights of spleen; blood: consistent picture of anaemia in both sexes in both generations: F0/F1m: ↓ RBC count (26/31 %), ↓ Hb (9/14 %), F0/F1f: ↓ RBC count (16/25 %), ↓ Hb (8/11 %), ↑:WBC (no change in differential counts) in F0/Flm, F0m: ↑ methaemoglobin (82%); histopathology: in spleen and liver extramedullary haematopoiesis and haemosiderosis in F0 and Fl males and females 10 mg/kg bw/d: clinical signs of toxicity: F0/F1m: rooting in bedding; necropsy: F0m: dark spleens (5/30); blood: F0m: ↓ RBC count (10 %), Hb (6 %); histopathology: in spleen and liver extramedullary haematopoiesis and haemosiderosis in F0/Flm/f **$LOAEL_{m/f}$ = 10 mg/kg bw/d** (haematotoxic an neurobehavioral effects)

5.6.1.2 Repeated dose toxicity: inhalation

For the inhalation route of exposure four repeated dose toxicity studies with butanone oxime were submitted. Of these, one sub-acute study (similar to OECD TG 412) in rats was declared as key study by the registrants. Two studies in mice, a sub-chronic and a sub-acute toxicity study (equivalent to OECD TG 413/412) as supporting studies by the registrants, were available. A further sub-acute study in rats was disregarded by the registrants due to a viral lung infection that occurred in all groups, including the controls. The study results from the combined chronic toxicity/carcinogenicity studies in rats and mice (according to OECD TG 453) were also evaluated regarding non-cancer effects by the registrants.

In all studies butanone oxime (purity 99.98 %) was used as test material.

The results of experimental studies on repeated dose toxicity following inhalation route of exposure are summarised in the following table.

Table 14: Studies on repeated dose toxicity after inhalation exposure

Reference Species; strain; sex; method	Results
TL19 (1990), unpublished report **Rat;** F344; male/female; sub-acute, inhalation: vapour, 6h/d, 5d/wk, whole body; similar to OECD TG 412	• Effects indicative of anaemia: 404 ppm (1440 mg/m^3/6h/d) (m/f): blood: ↓ (10 %): haemoglobin, haematocrit, RBC, MCHC; ↑: methaemoglobin (0.5 %), reticulocytes (threefold), platelets (30 %), leukocytes (13 %); liver and spleen: ↑ weights (30 %) **$LOAEC_{sys, m/f}$ = 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)**
TL19 (1990), unpublished report **Mouse;** CD-1; male/female; sub-acute, inhalation: vapour, 6h/d, 5d/wk, whole body; equivalent to OECD TG 412	400 ppm (1440 mg/m^3/6h/d) (m/f): blood: ↑: methaemoglobin (1-2 %), spleen:↑ weight (30 %) **$NOAEC_{sys}$ = 102 ppm (360 mg/m^3/6h/d)** (effects on blood parameters) **$NOAEC_{local}$** = no data available
TL10 (1995b), unpublished report; Newton et al. (2002) **Mouse;** CD-1; male; effects on the olfactory epithelium and recovery were assessed, inhalation: vapour, 6h/d, 5d/wk, whole body, exposure period: 1, 2, 4, 13 wk, recovery period of 4 or 13 wk, microscopy limited to nasal turbinates; equivalent to OECD TG 413	• 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, full recovery 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)
Newton et al. (2001); TL9 (1994), unpublished report **Rat;** F344; male/female; inhalation: 15, 75, 374 ppm as vapour (particle size distribution: MMAD: 2.3-2.6 µm, GSD: 2.1-2.8), 6h/d, 5d/wk, whole body; carcinogenicity study: interim sacrifice after 3, 12, 18 or 26 months; similar to OECD TG 453	• Effects indicative of anaemia: 3 months: 374 ppm (1346 mg/m^3), m/f: blood: ↑: methaemoglobin (0.4-1.2 %), MCH (2 %), MCV (6 %), platelets (25 %), leukocytes (6 %), ↓: haemoglobin (4 %), RBC (7 %), MCHC (4 %); ↑ weight, m/f, liver: (23/15 %), spleen: (33/33 %), testes: (82 %); necropsy: spleen: ↑: congestion (m); histopathology: pigment in reticuloendothelial cells (assumed to be haemosidering), extramedullary haematopoiesis 12 months: 374 ppm (1346 mg/m^3): blood: m: ↓ haemoglobin, haematocrit, RBC and platelets, females: ↓ haemoglobin, haematocrit, RBC and platelets, MCV, MCH; liver: ↑ weight (m), spleen: ↑ weight (m/f, 33 %); necropsy: spleen: congestion (m/f); histopathology: spleen: extramedullary haematopoiesis (f), liver: basophilic foci in hepatocytes (m), ↓: hyperplasia/proliferation of the biliary duct and peribiliary fibrosis (m/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 (m) • Liver effects: ≥ 75 ppm (270 mg/m^3): basophilic foci and vacuoles in hepatocytes (m) • Effects on the olfactory epithelium in the nasal turbinates ≥ 75 ppm (270 mg/m^3): degeneration on the olfactory epithelium in the nasal turbinates (m/f) **18 months:** • Effects indicative of anaemia: ≥ 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 • Liver effects: 374 ppm (1346 mg/m^3), m: basophilic foci and vacuoles in hepatocytes, ↓: hyperplasia/proliferation of the biliary duct and peribiliary fibrosis • Effects on the olfactory epithelium in the nasal turbinates

	≥ 75 ppm (270 mg/m^3): degeneration of the olfactory epithelium (f) 374 ppm (1346 mg/m^3): degeneration of the olfactory epithelium (m/f) • Effects on testes: ≥ 75 ppm (270 mg/m^3): enlarged testes without corporative findings during histopathology **26 months:** • Liver effects: ≥ 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 olfactory epithelium in the nasal turbinates ≥ 15 ppm (54 mg/m^3): degeneration of the olfactory epithelium (m/f) • Effects on testes: 374 ppm (1346 mg/m^3): ↑ weight (82 %) without corporative findings during histopathology **Reversibility:** haematology parameters after: 18/26 months (m/f) **LOAEC$_{sys, m/f}$ = 15 ppm (54 mg/m^3)** based on spleen effects (congestion, increased pigmentation 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
Newton et al. (2001); TL9 (1993), unpublished report **Mouse**; CD-1; male/female; inhalation: vapour (MMAD: 2.1-2.7 µm, GSD: 2.7-3.4), 6h/d, 5d/wk, whole body; carcinogenicity study: duration: 12, 18 months, similar to OECD TG 453	**12 months:** • Effects indicative of anaemia: ≥ 76 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 %) • Liver effects: ≥ 76 ppm (≥ 274 mg/m^3): centrilobular hepatocellular hypertrophy and necrosis (m) 374 ppm (1346 mg/m^3): ↑ relative liver weight (m/f: 12/17 %) **12/18 months:** • Effects indicative of anaemia: ≥ 15 ppm (54 mg/m^3): liver: ↑ pigment in reticuloendothelial cells • Liver effects: ≥ 15 ppm (54 mg/m^3): centrilobular hypertrophy, granulomatous inflammation, and necrosis (m/f) • Effects on the olfactory epithelium in the nasal turbinates ≥ 15 ppm (54 mg/m^3): degenerative and reparative changes on the olfactory epithelium in the nasal turbinates (m/f) **LOAEC$_{sys, m/f}$ = 15 ppm (54 mg/m^3)** based on effects in the liver **LOAEC$_{local, m/f}$ = 15 ppm (54 mg/m^3)** based on effects of the olfactory epithelium in the nasal turbinates

5.6.1.3 Repeated dose toxicity: dermal

No data submitted.

5.6.1.4 Repeated dose toxicity: other routes

No data submitted.

5.6.2 Human information

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

5.6.3 Summary and discussion of repeated dose toxicity

The evidence for target organ toxicity through repeated exposure to butanone oxime was obtained from animal testing. The data submitted for registration on this endpoint are suitable for evaluation. Sufficient information is available for the evaluation of target organ toxicity through repeated exposure to butanone oxime. No further information required.

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

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 the two-generation toxicity study in rats given butanone oxime by the oral route of exposure.

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 the 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 evaluation of butanone oxime toxicity by the eMSCA.

Major target of butanone oxime toxicity was the 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 extramedullary and medullary haematopoiesis, as well as extramedullary haematopoiesis in the spleen and liver. In studies with rats and mice, the effects have been demonstrated to be only to the anaemia but not to the secondary effects reversible. Effects on the blood increased regarding incidence and severity were observed at doses ≥ 25 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. There were methaemoglobinemia and a responsive Heinz body anaemia, haematopoietic cell proliferation in the spleen, increased incidence of haematopoietic proliferation in the bone marrow, 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 including 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 livers and spleens. Findings of extramedullary haematopoiesis and haemosiderosis in livers and spleens, unaccompanied by any other indications of toxicity were also seen in Fl male and female rats. Based on the haematology and microscopic findings in spleen and liver an increased anaemia

response with a clearly dose relation is suggested. Increased spleen weights and splenic and hepatic extramedullary haematopoiesis (hematopoietic 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. This was accompanied by reduced body weight and weight gain, reduced feed consumption, and clinical signs of toxicity (cyanosis).

In a sub-chronic study in rats, **transient neurobehavioral changes** (cage removal, handling, posture, gait, arousal, salivation, approach response, rearing responses, and aerial righting) 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.

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 and in female mice ≥ 2500 ppm (≥ 755/630 mg/kg bw/d).

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).

The derived No/Lowest observed adverse effect levels (N/LOAEL) for systemic and local effects are summarised in the following table.

Table 15: Oral route of exposure - overview of derived L/NOAEL

Species, strain, sex, duration, administration	LOAEL, effect	NOAEL, effect	Reference
Rat, Crj:CD(SD), m/f, 28 days, gavage	20 mg/kg bw/d Haematotoxicity	4 mg/kg bw/d haematotoxicity	TL18 (1996), unpublished report
Rat, F344, m/f, 13 wk, drinking water	65/100 mg/kg bw/d haematotoxicity	25/30 mg/kg bw/d haematotoxicity 100 mg/kg bw/d degeneration of the nasal olfactory epithelium	NTP (1999)
Rat, Sprague-Dawley, m/f, 13 wk gavage	40 mg/kg bw/d Anaemia	125 mg/kg bw/d neurobehavioral effects	Schulze and Derelanko (1993); TL 21 (1971), unpublished report
Rat, Sprague-Dawley, m/f, 13 wk gavage	25 mg/kg bw/d Haematotoxicity	Not established for effects on the blood	TL2 (1977), unpublished report; TL16 (1988), unpublished report; TL17 (1990), unpublished report
Rat Sprague-Dawley, f, Other GD6-15 gavage	25 mg/kg bw/d Haematotoxicity	Not established for effects on the blood	TL1 (1990a, unpublished report; Derelanko et al. (2003)
Rat, CD Sprague-Dawley (Crl:CD[SD]BR) VAF/Plus), m/f, Other F0: starting from 8 wk of age during 10 wk pre-mating, 3 wk mating period (continued dosing). F1: starting from 11 wk of age in the same regime, gavage	**10 mg/kg bw/d** Haematotoxicity	Not established for effects on the blood	TL15 (1992), unpublished report; Tyl et al. (1996)
Mouse, B6C3F1, m/f, 13 wk, drinking water		515/630 mg/kg bw/d haematopoietic cell	NTP (1999)

		proliferation in the spleen 110/340 mg/kg bw/d changes in the urinary bladder	
Rabbit, New Zealand White, f, Other GDs6-18 gavage	**10 mg/kg bw/d** Haematotoxicity	Not established for effects on the blood	TL1 (1990b), unpublished report; Derelanko et al. (2003)

Inhalation: Repeated exposure of rats and mice to butanone oxime by inhalation produced methaemoglobin formation, compensatory haemolytic anaemia, non-neoplastic liver effects (rats: basophilic foci and hepatocyte vacuoles; mice: hypertrophy and necrosis) increased weight of the testes (rats only), and degenerative and reparative changes of the olfactory epithelium primarily in the dorsal meatus.

The **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) (TL19 1990, unpublished report). A NOAEC of 25 ppm (90 mg/m^3) was derived for effects on the blood. In the inhalation combined chronic toxicity/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 and 12 months in males and females, but not after 18 months in males or after 26 months in both sexes. Spleen effects (increased organ weight, extramedullary haematopoiesis, and haemosiderosis) occurred at 374 ppm (1346 mg/m^3). 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 month sacrifice of the 2-year inhalation combined chronic toxicity/carcinogenicity study in mice the blood effects of butanone oxime occurred less clear. 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.

Liver effects were observed in rats and mice in the life-time studies (combined chronic toxicity/carcinogenicity studies, inhalation) in a dose-related manner. 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 males and females exposed at 374 ppm (1346 mg/m^3). In mice increases in liver hypertrophy and necrosis were noted at 15 ppm (54 mg/m^3) and higher. Accordingly, the LOAEC for systemic effects based on the effects in the liver of mice was 15 ppm (54 mg/m^3).

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

Local effects on the respiratory system were reported from the inhalation combined chronic toxicity/carcinogenicity studies in rats and mice. Mice appear to be more susceptible to the nasal effects of butanone oxime than rats. In the nasal turbinates degeneration of 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 local effects on the respiratory tract in the mouse combined chronic toxicity/carcinogenicity study. In a sub-chronic inhalation toxicity

study in mice designed to investigate the effects of butanone oxime on the olfactory epithelium a NOAEC of 3 ppm (10.8 mg/m^3) was established based on olfactory effects in a small area of tissue in the nose at 10 ppm (36 mg/m^3) and higher. At termination of the study the effects showed reversibility to varying degrees, depending on concentration.

Justification for classification or non-classification

Studies in rats, mice and rabbits indicate that the haematological and neurological systems are targets for the toxicity of butanone oxime.

Haemolytic anaemia was the main toxic effect corresponding with decreased red blood cell parameters and increased breakdown product of haemoglobin, and increased degrees of deposit of iron (haemosiderin) and extramedullary hematopoiesis in spleen and liver. The effects on the erythrocytes were generally less severe with the inhalation exposure. The rabbit and the rat appear more sensitive than the mouse to the haemolytic effects of butanone oxime.

In rats effects on the blood 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. However, serious health effects are caused 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, haemolytic anaemia with concomitant extramedullary haematopoiesis and hemosiderosis in livers and spleens (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 including anaemia. The effects on the blood occurred at ≥ 25 mg/kg bw/d in rats and at ≥ 10 mg/kg bw/d in rabbits. Since mortalities occurred in pregnant rabbits after treatment with two oral doses of 80 mg/kg bw/d butanone oxime during the gestation phase due to the acute toxic action, i.e. methaemoglobin formation, it seems to be most appropriate to cover these toxic effects by classification for acute oral toxicity.

The anaemia is considered to be compensatory, as the degree of anaemia was not progressive with long-life repeated inhalation exposure. In the combined chronic toxicity/carcinogenicity study in rats, adaptation to the haemolytic effects 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. Also the compensatory erythropoiesis points to an adaptive response.

Overall, it is concluded that the observations of haemotoxicity caused by butanone oxime 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 should be considered as ‘adverse’ and at the high dose levels they can equally be considered as ‘severe’. However, findings judged as toxicologically significant toxic effects according to the CLP criteria were 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/carcinogenicity study. 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 the CLP Regulation (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 significant toxic effects according to the CLP criteria. Based on the available data, butanone oxime does not fulfil the criteria for classification for target organ toxicity through repeated exposure (STOT RE 2).

Conclusion: no classification

In the sub-chronic study 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 exposure according to the CLP Regulation.

However, 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 also seen. Data from acute oral, inhalation and dermal toxicity testing have also shown a strong but transient narcotic effect in both sexes following single exposure to butanone oxime. In a developmental toxicity study, rabbits (dams) showed neurological effects, e.g. decreased activity, wobbly gait, at oral doses of 40 mg/kg bw/d and higher. Based on these data and results from acute toxicity testing, butanone oxime meets the criteria for the 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 the CLP Regulation (Annex I, Part 3.8.2.2.2).

Conclusion: narcotic effects as STOT SE 3, H336

The following information is taken into account for hazard / risk assessment:

Oral: target organs: haematological system; neurological systems; other lesions: degeneration of the nasal olfactory epithelium; hyperplasia of the transitional epithelium in urinary bladder.

The lowest oral $LOAEL_{sys}$ for effects on the blood of butanone oxime was 10 mg/kg bw/d, based on histopathological effects in the spleen and the liver of adult male and female rats observed in a two-generation reproduction study (similar to OECD TG 416/B.35) (TL15 1992, unpublished report; 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 of anaemia in adult female rabbits observed in a range-finding developmental study (according to OECD TG 414) (TL1 1990b, unpublished report; Derelanko et al. 2003).

For neurobehavioral effects of butanone oxime a $NOAEL_{sys}$ of 125 mg/kg bw/d was derived from a sub-chronic study (equivalent to OECD TG 408) by gavage with male and female Sprague-Dawley rats (Schulze and Derelanko 1993).

In mice 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) at 110 mg/kg bw/d in males and at 340 mg/kg bw/d in females (NTP 1999).

A NOAEL of 100 mg/kg bw/d for degeneration of the nasal olfactory epithelium of butanone oxime was determined in a sub-chronic drinking water study (equivalent to OECD TG 408) with male and female F344 rats (NTP 1999).

Inhalation: target organs: haematological system; liver effects; local effects on the nasal turbinates

The lowest LOAEC value for haematotoxic effects of butanone oxime was established in rats and mice at 15 ppm (54 mg/m^3) after chronic exposure by inhalation (26/18 months study, whole body, 6h/d, 5d/wk) derived from combined chronic toxicity/carcinogenicity studies (similar to OECD TG 453) in both species (Newton et al. 2001; TL9 1994, 1993, unpublished reports). The LOAEC for

liver effects (hypertrophy and necrosis) of butanone oxime was derived from the mice study at 15 ppm (54 mg/m^3).

For local effects of butanone oxime on the nasal turbinates (degeneration of the olfactory epithelium) a LOAEC at 15 ppm (54 mg/m^3) was derived in mice observed both after 12 and 18 months of exposure by inhalation (similar to OECD TG 453, whole body, 6h/d, 5d/wk) (Newton et al. 2001; Rinehart 1993, unpublished report). For short-term exposures, the lowest LOAEC value of butanone oxime was 30 ppm (108 mg/m^3), based on degeneration of the olfactory epithelium of the nasal cavity of male mice exposed to a butanone oxime exposure regime of 6 hours/day, 5 days/week, for 1 week (5 exposures = 30 total hours of exposure) which is relevant for the acute exposure risk assessment (TL10 1995b, unpublished report; Newton et al. 2002). A NOAEC for these local effects on the nasal turbinates of butanone oxime was observed at 3 ppm (10.8 mg/m^3) identified from a sub-chronic study (equivalent to OECD TG 413, whole body, 6h/d, 5d/wk) in male mice (TL10 1995b, unpublished report; Newton et al. 2002).

Conclusion from SEV:

There is sufficient information available for evaluation of repeated dose toxicity of butanone oxime. No further action is recommended.

5.7 Mutagenicity

5.7.1 Non-human information

5.7.1.1 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), 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), and an UDS test (comparable to OECD TG 482). In addition, in cytogenetic tests with cultured Chinese hamster ovary cells (CHO) the induction of sister chromatid exchanges (comparable to OECD TG 479) and the chromosome aberration (comparable to OECD TG 473) was evaluated both in the presence or absence of S9 activation.

In all studies butanone oxime (purity 99.98 %) was used as test material.

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 report; TL18 1996, unpublished report; 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 (TL20 1995, unpublished report). 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).

5.7.1.2 In vivo data

Butanone oxime was investigated in a Drosophila melanogaster sex-linked recessive lethal (SLRL) test (comparable to OECD TG 477), a chromosome aberration assay in Sprague-Dawley rats (comparable to OECD TG 475), for its clastogenic/genotoxic potential in vivo in a mouse micronucleus test in the peripheral blood (comparable to OECD TG 474), 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 butanone oxime (purity 99.98 %) was used as test material.

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 (TL4 1991, unpublished report). 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 (TL20 1990, unpublished report). 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 mg/kg bw/d butanone oxime via drinking water for 13 weeks (NTP 1999). The potential for the formation of DNA and RNA-modifications 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 modification could not be observed. Increased concentrations of 8-oxodeoxyguanosine, N^2-aminodeoxyguanosine and 8-aminodeoxyguanosine were detected in liver DNA isolated from rats treated with 2-nitropropane as positive control. In liver RNA from butanone oxime exposed rats, a dose, sex and time-dependent formation of 8-aminoguanosine and 8-oxoguanosine was observed. Concentrations of this modification in RNA were approximately 5 times higher in male rats as compared to female rats exposed to identical 8-aminoguanosine concentrations. Concentrations of 8-aminoguanosine were reduced by pre-treatment with inhibitors of presumed pathways of butanone oxime biotransformation (TL21 2000, unpublished report; Friedewald et al. 2001; Völkel et al. 1999).

5.7.2 Human information

No information is available.

5.7.3 Summary and discussion of mutagenicity

The possibility that butanone oxime may induce heritable mutations in the germ cells of humans were examined in tests in vitro and in vivo. Sufficient information is available for the evaluation of the germ cell mutagenicity of butanone oxime. No further information required.

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 guidelines 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 RNA from butanone oxime exposed rats by inhalation for 6 hours, a concentration, sex and time-dependent formation of 8-aminoguanosine and 8-oxoguanosine was observed. DNA modification could not be observed.

Justification for classification or non classification

Data available for studying the germ cell mutagenicity have shown that butanone oxime did not induce heritable mutations in mammals. No classification for germ cell mutagenicity is required according to the CLP Regulation.

Conclusion: no classification

The following information is taken into account for any hazard / risk assessment:

Results from mutagenicity or genotoxicty tests in vitro and in vivo and in mammalian somatic and germ cells in vivo have shown that butanone oxime did not induce heritable mutations in mammals.

Conclusion from SEV:

There is sufficient information available for evaluation of the germ cell mutagenicity of butanone oxime. No further action is recommended.

5.8 Carcinogenicity

5.8.1 Non-human information

5.8.1.1 Carcinogenicity: oral

No information is available.

5.8.1.2 Carcinogenicity: inhalation

Two combined chronic toxicity/carcinogenicity studies (similar to OECD TG 453) considered as key studies by the registrants were available. Results of a 2-year inhalation study (with interim analysis, sacrifices at 3, 12, 18 months) in F344 rats and an 18 months study (with interim analysis, sacrifices at 12 months) in CD-1 mice were submitted.

In both studies butanone oxime (purity 99.98 %) was used as test material.

The results of experimental studies on carcinogenicity after exposure by inhalation are summarised in the following table.

Table 16: Studies on carcinogenicity after inhalation exposure

Reference Species; strain; sex; method	Results Incidence and type of tumour
Newton et al. (2001); TL9 (1994), unpublished report **Rat**; F344; male/female; inhalation: vapour (particle size distribution: MMAD: 2.3-2.6 µm, GSD: 2.1-2.8), 6h/d, 5d/wk, whole body for 26 months, interim sacrifice at 3, 12 and 18 months; similar to OECD TG 453	**Positive:** Liver tumours Carcinomas in males at 374 ppm (1346 mg/m^3), and adenomas dose-related increase in males at 15 ppm (54 mg/m^3) and higer 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 not available**
Newton et al. (2001); TL9 (1993), unpublished report **Mouse**; CD-1; male/female; inhalation: vapour (MMAD: 2.1-2.7 µm, GSD: 2.7-3.4), 6h/d, 5d/wk, whole body for 18 months, interim sacrifice at 12 months; similar to OECD TG 453	**Positive:** Liver tumours Carcinomas in males at 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, but 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**

5.8.1.3 Carcinogenicity: dermal

No information is available.

5.8.2 Human information

No information is available.

5.8.3 Summary and discussion of carcinogenicity

The data on carcinogenicity of butanone oxime were obtained from animal testing. The data submitted for registration to the endpoint carcinogenicity are sufficient for evaluation. No further information required.

The carcinogenic potential of butanone oxime has been studied in two combined chronic toxicity/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/carcinogenicity studies in rats and mice (similar to OECD TG 453) 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 only at 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 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.

No information is available regarding carcinogenicity in humans exposed to butanone oxime.

No species-specific mode of action for butanone oxime carcinogenesis was identified.

The modes of action for induction of the observed tumours in rats and mice have not been fully identified. According to today's state of knowledge the potential mechanisms behind chemical carcinogenesis are highly complex involving genotoxic events (mutations), altered gene expression at the transcriptional translational, and posttranslational levels (epigenetic events), and altered cell survival (proliferation and apoptosis) (Hanahan and Weinberg 2000).

For butanone oxime the results from mutagenicity or genotoxicty tests in vitro and in vivo and in mammalian somatic and germ cells in vivo were mostly negative, including bacterial mutagenicity, unschedulated 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. Based on these results it can be concluded that butanone oxime is not directly to be able to induce directly heritable mutations in the germ cells of humans.

As a possible mechanism for the increased incidences of liver tumours in male rats and mice the metabolism of butanone oxime to a carcinogenic agent, mediated by sulfotransferase was discussed. 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.

Justification for classification or non classification

In contrast to the registrants the eMSCA is of the opinion that 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 the CLP Regulation.

Comparison with criteria:

According to the CLP directive a substance shall be classified as carcinogenic if:

Category 1A carcinogen

'It is known to have carcinogenic potential for humans; classification is largely based on human evidence.'

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.

Category 1B carcinogen

'It is presumed to have carcinogenic potential for humans; classification is largely based on animal evidence.'

This category depends on the strength of evidence, which consists of animal experiments for which there is sufficient evidence to demonstrate animal carcinogenicity. This 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 the CLP Regulation butanone oxime fulfils the criteria for Category 1B carcinogen.

There is sufficient evidence of carcinogenicity from studies in experimental 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 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 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.

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 carcinogen

'It is a suspected human carcinogen, but the evidence is not sufficient for Category 1A or 1B.'

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, and nor limited to only promoting activity.

In conclusion, butanone oxime meets the criteria for classification and labelling as category 1B carcinogen, H350 according to the CLP Regulation.

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 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 causes tumours in the liver (adenomas and carcinomas) in both species at all tested exposure concentrations. Statistically significant increases in incidence were observed at the both highest concentrations for liver adenomas in male rats and at the highest concentration for liver carcinomas in male rats and mice. An increased incidence of liver adenomas occurred also in female rats and mice at the both highest concentrations, but was not statistically significant. A statistically significant increased incidence of mammary gland fibroadenomas was also observed in male rats at the highest concentration. As malignancy in both studies was observed and carcinogenicity is not restricted to promoting activities classification as carcinogen 1B carcinogen is most justified.

Conclusion: category 1B carcinogen, H350

The following information is taken into account for hazard / risk assessment:

In combined chronic toxicity/carcinogenicity studies in rats and mice exposed by inhalation to butanone oxime sufficient evidence of animal carcinogenicity was demonstrated. There was an increased incidence of a combination of benign and malignant liver tumours in both sexes of mice and rats at all tested exposure concentrations. A LOAEC of 15 ppm (54 mg/m^3) for carcinogenicity (liver tumour development) was derived for rats and mice. A NOAEC for carcinogenicity was not derived for the rat and also not for the mouse (Newton et al. 2001; TL9 1994, 1993, unpublished report).

The modes of action for induction of the observed liver tumours in rats and mice after long-term exposure by inhalation to butanone oxime have not been fully identified. Although the results of the available in vitro mammalian mutagenicity assays and in vivo heritable germ cell mutagenicity tests in mammals of butanone oxime have shown to be mostly negative, it is postulated that genotoxicity is involved in the tumourigenicity of butanone oxime to the liver. As a possible mechanism the metabolism of butanone oxime to a carcinogenic agent, mediated by sulfotransferase is discussed. Therefore, the possibility cannot be ruled out that butanone oxime may have a genotoxic potential and DNA-damaging activity.

In the REACH requirements it is stated that (ECHA 2012a) "It is to be noted that the decision on a threshold and a non-threshold mode of action may not always be easy to make, especially when, although a biological threshold may be postulated, the data do not allow identification of it. If not clear, the assumption of a non-threshold mode of action would be the prudent choice."

As no thresholds for carcinogenicity can be set, also no DNEL but only DMEL can be derived. Therefore evaluation of the cancer risk from exposure to butanone oxime is carried out by derivation of DMEL.

Conclusion from SEV:

There is sufficient information available for evaluation of carcinogenicity of butanone oxime.

The SEV of butanone oxime has verified the concern that a more severe classification regarding carcinogenicity is needed. Based on the available data on carcinogenicity butanone oxime meets the criteria for classification and labelling as category 1B carcinogen, H350 but not as category 2 according to the CLP Regulation. It leads to the need for an update of the existing harmonised classification and labelling. A proposal for harmonised classification of butanone oxime should be prepared.

5.9 Toxicity for reproduction

5.9.1 Effects on fertility

5.9.1.1 Non-human information

A two-generation toxicity study in rats (similar to OECD TG 416/EU B.35), considered as key study by the registrants, was available. 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 breeding for the F1 to F2 generation.

Butanone oxime (purity 99.98 %) was used as test material.

The results of the experimental study on fertility are summarised in the following table.

Table 17: Study on fertility (two-generation toxicity study in rats)

Reference Species; strain; sex; method	Results
TL15 (1992), unpublished report; Tyl et al. (1996) **Rat**; CD Sprague-Dawley (Crl:CD[SD]BR) VAF/Plus); male/female; two-generation toxicity study, oral: gavage, Exposure: 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); F0 and F1 weanlings were necropsied after 2 wk post wean F1 generation: starting from 11 wk of age in the same regime. (5d/wk); EPA guideline with modifications (similar to OECD TG 416/EU B.35)	**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 m/f; ↓ feed consumption in F0m/f + F1f; F0m: tremors, salivation, slow respiration, mouth breathing, lethargy, staggering, and rooting in bedding (post-dosing); 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: F0 m/f + F1m/f: signs of anaemia with ↓: RBC count, haematocrit, haemoglobin, ↑: 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 haematopoiesis and haemosiderosis 100 mg/kg bw/d: Clinical signs: F0m: lethargy, staggering, 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: signs of anaemia with ↓: RBC count, haematocrit, haemoglobin, ↑: RBC size (MCV), nucleated RBC count, reticulocyte count, MCH; F0m + F1m: ↑: WBC count, methaemoglobin Necropsy: F0m/f + F1m/f: ↑ abs. and rel. (significant) spleen weight; Histology: F0m/f + 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: F0m/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 (hematopoiesis and pigmentation) in both sexes of F0 and F1 adults **Reproductive parameters** - no significant effects of treatment on number of F0 or Fl females, which were cycling, pre- or post-breed, 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 mating and for stillbirth index only in Fl (a + b) mating, but were within the range of the historical control data **Offspring parameter** - no treatment related effects 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 + 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 or F2a weanlings, 10/sex/dose - no histological effects on Fl, F2a, or F2b weanling female mammary glands Overall, no evidence of reproductive organ or mammary gland pathology or of reproductive or postnatal toxicity was found at any dose tested. **NOAEL = 200 mg/kg bw/d for reproductive toxicity**

5.9.1.2 Human information

No information is available.

5.9.2 Developmental toxicity

5.9.2.1 Non-human information

There were developmental toxicity studies (according to OECD TG 414/EU B.31) in the rat and the rabbit available. In both species a preliminary dose range-finding study and a main study were performed. Sprague-Dawley rats received butanone oxime orally by gavage during GDs6–15 and New Zealand White rabbits were treated during GDs6-18, as well orally. The rat study was

considered as key study and the rabbit study as supporting study by the registrants. In both studies butanone oxime (purity 99.98 %) was used as test material.
The results of the experimental studies on developmental toxicity are summarised in the following table.

Table 18 Studies on developmental toxicity

Reference Species; strain; sex; method	Results
TL1 (1990a), unpublished report; Derelanko et al. (2003) **Rat**; Sprague-Dawley; female; developmental toxicity study, oral: gavage, exposure: GDs6-15 (daily), duration: until sacrifice on GD20, according to OECD TG 414/EU B.31	*Preliminary study (dose range-finding study)* **NOAEL = 400 mg/kg bw/d for developmental toxicity**, based on all gestational parameters evaluated during cesarean 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 (toxicity to the haematopoietic system)** based on spleen enlargement
TL1 (1990b), unpublished report; Derelanko et al. (2003) **Rabbit;** New Zealand White; female; developmental toxicity study, oral: gavage, exposure: GDs6-18 (daily), according to OECD TG 414/EU B.31	*Preliminary study (dose range-finding study)* 80 mg/kg bw/d: mortality in 5/5 dams between GDs8-10 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 *Main study* 40 mg/kg bw/d on GDs6-18: mortality in 8/18 dams (44 %) between GDs11-24; 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))

5.9.2.2 Human information

No information is available.

5.9.3 Summary and discussion of reproductive toxicity

Effects on fertility: The data for reproductive toxicity (effects on fertility) was obtained from animal testing. Sufficient information is available for the evaluation of effects on fertility to butanone oxime. No further information required. 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, effects of butanone oxime on 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 by further lesions. A NOAEL for systemic effects of toxicity in adults 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 of the 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.

Developmental toxicity: The data for developmental toxicity was obtained from animal testing. Sufficient information is available for the evaluation of developmental toxicity to butanone oxime. No further information required. Developmental toxicity of butanone oxime was investigated in rats and rabbits. In Sprague-Dawley rats and New Zealand 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 all 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 were established.

Rabbits proved to be more sensitive to butanone oxime toxicity. Butanone oxime was significantly more toxic to rabbits than rats. Three rabbits aborted and 8/18 females, which have received oral doses of 40 mg/kg bw/d by gavage during the gestations phase, were found dead between GDs11-24. 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.

Justification for classification or non classification

Data available for effects on fertility and developmental toxicity in rats and rabbits does not indicate that butanone oxime is either a reproductive or developmental toxicant. Accordingly there is no need for classification of butanone oxime according to the CLP Regulation.

Conclusion: no classification on fertility; no classification on developmental toxicity

The following information is taken into account for hazard / risk assessment:

In **rats** no reproductive toxicity was observed at 200 mg/kg bw/d, the highest dose studied. Toxicity to the haematopoietic system was reported in adults at all doses tested.

$LOAEL_{sys\ rat,\ m/f}$ = 10 mg/kg bw/d for parental toxicity

$NOAEL_{sys,\ rat}$ = 200 mg/kg bw/d for reproductive toxicity

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).

$NOAEL_{sys,\ rat}$ = 600 mg/kg bw/d for developmental toxicity

$LOAEL_{sys,\ rat,\ f}$ = 10 mg/kg bw/d for maternal toxicity (toxicity to the haematopoietic system)

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).

$NOAEL_{sys,\ rabbit}$ = 24 mg/kg bw/d for developmental toxicity

$LOAEL_{sys,\ rabbit}$ = 10 mg/kg bw/d for maternal toxicity (toxicity to the haematopoietic system)

Conclusion from SEV:

There is sufficient information available for evaluation of the toxicity for reproduction (effects on fertility; developmental toxicity) of butanone oxime. No further action is recommended.

5.10 Endocrine disrupting properties

There is no concern for endocrine disrupting properties from the available repeated dose toxicity testing and/or reproduction toxicity studies.

5.11 Other effects

5.11.1 Non-human information

5.11.1.1 Neurotoxicity

The potential of butanone oxime to produce neurotoxicity following acute and sub-chronic exposure was studied in Sprague-Dawley rats. Both studies were considered as key studies by the registrants. In these studies a Functional Observation Battery (FOB), assessment of motor activity, and neuropathology evaluations were conducted in the context of a single and repeated exposure. There were data from three independent studies reported: a pilot time-effect study designed to determine the time course and time peak effect, a single dose neurotoxicity study and a sub-chronic (13-week) repeated dose neurotoxicity study.

In all three studies butanone oxime (purity 99.98 %) was used as test material.

The results of the experimental studies are summarised in the following table.

Table 19: Overview of experimental studies on neurotoxicity

Reference Species; strain; sex; method	Results
Schulze and Derelanko (1993) **Rat**; Sprague-Dawley; m/f; single oral dose: gavage, exploratory time course experiment, EPA OPPTS 870.6200 (Neurotoxicity Screening Battery)	900 mg/kg bw/d, between 30 and 60 min after dosing: ↓ (significant) locomotor activity
Schulze and Derelanko (1993); TL7 (1991), unpublished report **Rat**; Sprague-Dawley; m/f; single oral dose: gavage, acute neurotoxicity study, EPA OPPTS 870.6200 (Neurotoxicity Screening Battery)	900 mg/kg bw, 1h after dosing: ↓ (sign) locomotor activity; behavioural changes: transient changes in ease of cage removal, ease of handling, and in posture and gait 300 mg/kg bw, 1h after dosing: behavioural changes: transient changes (narcoleptic response) in gait, and aerial righting reflex CNS depression reversible within 24 hours **$NOAEL_{sys, m/f}$ = 100 mg/kg bw** (no changes in neurobehavioral function)
Schulze and Derelanko (1993); TL21 (1991), unpublished report **Rat**; Sprague-Dawley; male/female; sub-chronic (13 wk), oral: gavage, 5d/wk, EPA OTS 798.6050 (Neurotoxicity Screening Battery), similar to OECD TG 408	400 mg/kg bw/d, immediately after dosing: behavioural changes: transient changes in ease of cage removal, ease of handling, and in posture, gait, and aerial righting reflex; no effects on locomotor activity; no accumulated neurobehavioral deficits; no microscopic changes in nervous system **$NOAEL_{sys, m/f}$ = 125 mg/kg bw/d** (no transient neurobehavioral changes)

5.11.1.2 Immunotoxicity

No information available.

5.11.1.3 Specific investigations: other studies

No information available.

5.11.2 Human information

No information available.

5.11.3 Summary and discussion of specific investigations

The data for neurotoxicity was obtained from animal testing. Sufficient information is available for the evaluation of neurotoxicity to butanone oxime. No further information required. The potential of butanone oxime to produce neurotoxicity following a single oral dose (acute) and repeated sub-chronic oral exposure was studied in the rat. The observations in the available studies were characterised by transient and reversible functional disturbances in nervous system function consistent with CNS depression. Microscopic changes were not observed in the nervous system. Single oral application of butanone oxime produced significant dose-related decreases in motor activity after one hour following 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 changes (narcoleptic response) in gait, and aerial righting reflex. No progressive long-term, irreversible neurotoxic changes were associated with repeated butanone oxime administration for 13 weeks.

Justification for classification or non classification

Transient neurobehavioral changes were observed in male and female rats immediately after application of butanone oxime. Significant dose-related decreases in motor activity were observed after one hour following single oral dose of butanone oxime which reached statistically significance at 900 mg/kg bw. Data from acute oral, inhalation and dermal toxicity testing and from repeated dose toxicity studies by the oral and inhalation routes have also shown a strong but transient narcotic effect in different animal species of both sexes (for more details see there).

Taking together all data from acute toxicity and repeated dose toxicity testing by oral, inhalation and dermal route of exposure the reasonable suspicion is given that butanone oxime should be classified due to its narcotic effects. Butanone oxime meets the criteria for the 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 the CLP Regulation (Annex I, Part 3.8.2.2.2).

Conclusion: narcotic effects as STOT SE 3, H336

The following information is taken into account for hazard / risk assessment:

Butanone oxime caused transient and reversible changes in neurobehavioral function consistent with CNS depression, but without evidence of cumulative neurotoxicity. Such effects were observed in experimental animals in acute and repeated dose toxicity studies.

Conclusion from SEV:

There is sufficient information available for evaluation of neurotoxicity of butanone oxime.

The SEV has verified the concern that butanone oxime caused transient target organ effects. There were changes in neurobehavioral function including narcotic effects. Based on these data and results from acute toxicity testing, butanone oxime meets the criteria for the 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 the CLP Regulation (Annex I, Part 3.8.2.2.2). The SEV leads to the need for an update of the existing harmonised classification and labelling. A proposal for harmonised classification of butanone oxime should be prepared.

5.12 Combined effects

No information available.

5.13 Derivation of DNEL(s) / DMEL(s)

The process for deriving DNEL and DMEL follows the procedure given in the REACH Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.8: Characterisation of dose [concentration]–response for human health (ECHA 2012a).

According to this Guideline a DNEL for the leading health effect needs to be derived for every relevant human population and every relevant route, duration and frequency of exposure, if feasible.

The derivation of DNEL/C and DMEL/C for workers and general population is based on data from studies with experimental animals.

5.13.1 Overview of typical dose descriptors for all endpoints

The registrants have given an overview of available dose-descriptors per endpoint for workers and the general population. These data were examined.

For the calculation of DNEL/C by the eMSCA the dose-descriptors are gathered from the available and relevant experimental animal studies. Out of this database together with information published in reviews of international bodies (listed above) suitable studies and typical dose descriptors for derivation of DNEL/C and DMEL/C are discussed. In the following table a summary of this evaluation is shown.

Table 20: Dose descriptor(s) per endpoint for derivation of DNEL/C and DMEL/C

Endpoint Route Species	**Dose descriptor /Qualitative assessment**	**Reference Remarks on the study**
Acute toxicity Oral rabbit	LD_{50} = 160 mg/kgbw	**TL1 (1990a), unpublished report; Derelanko et al. (2003)** The data from a developmental toxicity study in rabbits (according to OECD TG 414/EU B.31) have shown that butanone oxime induces acute oral toxicity, e.g. lethality in rabbits from oral doses given in a short time (on 2 days). Mortality was observed in 5/5 rabbits, which were treated with butanone oxime on GD6 and 7 with 80 mg/kg bw (cumulative 160 mg/kg bw). The animals were found dead between the GDs8-10. In the followed main study, the treatment with 40 mg/kg bw during the GDs6 to 10, five days (cumulative 200 mg/kg bw) induced mortality in 8/18 females (GDs11-24). Therefore the oral LD_{50} is 160 mg/kg bw.
Acute toxicity Inhalation mouse	LC_{50} was not established $LOAEC_{local}$ = 30 ppm (108 mg/m^3) (short-term: total: 30h: 6h/d, 5d/wk) $NOAEC_{local}$ = 3 ppm (10.8 mg/m^3) (short-term: 6h/d, 5d/wk)	**TL10 (1995b), unpublished report; Newton et al. (2002)** In rats the LC_{50} was found to be > 13.2 mg/L/4h in male and female rats. For short-term exposures, the lowest LOAEC for local effects was 30 ppm (108 mg/m^3), based on effects in the nasal cavity of male mice. There was degeneration of the olfactory epithelium of the nasal cavity of male mice exposed to butanone oxime after exposure regime of 6 hours/day, 5 days/week (30 total hours of exposure). A NOAEC for these local effects on the nasal turbinates was observed at 3 ppm (10.8 mg/m^3).
Acute toxicity Dermal rabbit	LD_{50} = 1848 mg/kg bw	**TL2 (1984b), unpublished report** Butanone oxime is classified as Acute Tox. 4, H312. The dermal LD_{50} value for male and female rabbits is between 1000 and 1848 mg/kg bw. 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 1848 mg/kg bw all animals died within 48 hours after treatment.
Irritation Corrosivity Skin rabbit	not irritating	**TL2 (1978b), unpublished report** Butanone oxime is slightly irritating to the non-abraded and abraded skin of rabbits.
Irritation Corrosivity Eye rabbit	irreversible effects on the eye/serious damage to the eyes	**TL2 (1978c), unpublished report** Butanone oxime is classified and labelled as 'Irreversible effects on the eye' Category 1: H318. 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. Irreversible effects on the eye were observed in 2/6 rabbits. Conjunctivae necrosis was observed in these rabbits which was not reversible at the end of observation period.
Irritation Corrosivity Respiratory	not irritating	**TL10 (1995b), unpublished report; Newton et al. (2002)** Butanone oxime causes reversible degeneration on the nasal olfactory epithelium after repeated exposure. Based on an exposure regime of 6h/d,

tract Mouse		5d/wk (30 total hours of exposure) a NOAEC for these local effects on the nasal turbinates was observed at 3 ppm (10.8 mg/m^3).
Sensitisation Skin Guinea pig	sensitising	**TL11 (1983), unpublished report; TL12 (1989), unpublished report; TL13 (1989), unpublished report; TL14 (2009), unpublished report** Butanone oxime is a skin sensitizer in guinea pigs and is classified as skin sensitizer 1, H317. Butanone oxime was evaluated by two GPMT and a Buehler assay, which have shown sensitising potential of butanone oxime. In the GPMT the maximum concentration used was: 4 % for intradermal induction, 100 % for topical induction and 50 % for challenge. In the Buehler assay the maximum concentration used was: 25 % for topical induction and 5 % for challenge. In a mouse ear swelling test (MEST) a sensitising response of 40 % and a swelling rate of 120 % for the mouse ears was noted. Based on these animal model systems a moderate potency for skin sensitisation is determined for butanone oxime A LLNA in mice gave a negative result for 50 and 100 % butanone oxime.
Repeated dose toxicity Oral Rat, rabbit, mouse	LOAEL = 10 mg/kg bw/d	**TL15 (1992), unpublished report; Tyl et al. (1996); NTP (1999)** The major target of butanone oxime toxicity was the blood in rats, rabbits, and mice. Further lesions observed included neurobehavioral effects in rats and rabbits and degeneration of the nasal olfactory epithelium in rats and mice and hyperplasia of the urinary bladder transitional epithelium in mice. The lowest oral LOAEL for short-term and sub-chronic exposures was 10 mg/kg bw/d, based on effects in the spleen and liver of adult rats observed in a two-generation reproduction study. At the same dose signs of anaemia in adult female rabbits were observed in a range-finding developmental study.
Repeated dose toxicity Inhalation Rat, mouse	$LOAEC_{sys}$ = 15 ppm (54 mg/m^3) for local and systemic effects in rats and mice $NOAEC_{local}$ = 3 ppm (10.8 mg/m^3) for local effects in male mice	**TL9 (1993, 1994), unpublished reports; TL10 (1995b), unpublished report; Newton et al. (2001); Newton et al. (2002)** Main targets for systemic effects are the haematological system and the liver. Local effects were observed on the nasal turbinates. With respect to non-cancer effects, the lowest LOAEC for local and systemic effects after chronic exposures is 15 ppm (54 mg/m^3), based on degeneration of the olfactory epithelium in the nasal cavities of both mice and rats, liver cell hypertrophy and necrosis in mice, and histopathological effects in the spleen of rats observed in these species. In a sub-chronic inhalation toxicity study in mice designed to investigate the effects of butanone oxime on the olfactory epithelium a $NOAEC_{local}$ of 3 ppm (10.8 mg/m^3) was established based on olfactory effects in a small area of tissue in the nose at 10 ppm (36 mg/m^3). At termination of the study the effects showed reversibility to varying degrees, depending on concentration.
Mutagenicity In vitro In vivo	negative results	**TL2 (1983), unpublished report; Rogers-Back et al. (1988); TL20 (1990), unpublished report; TL4 (1991), unpublished report; TL20 (1995), unpublished report; TL18 (1996), unpublished report; NTP (1999); Völkel et al. (1999); TL3 (2000), unpublished report; Friedewald et al. (2001)** There was no evidence of germ cell mutagenicity of butanone oxime in standard mutagenicity or genotoxicity tests in vitro and in vivo. These results have shown that butanone oxime did not induce directly heritable mutations in mammals.
Carcino-genicity Inhalation Rat, mouse	LOAEC = 15 ppm (54 mg/m^3) for tumour development in the liver	**TL9 (1993, 1994), unpublished reports; Newton et al. (2001)** Butanone oxime causes tumours in the liver (adenomas and carcinomas) in both species at all tested exposure concentrations. Statistically significant increases in incidence were observed at the both highest concentrations for liver adenomas in male rats and at the highest concentration for liver carcinomas in male rats and mice. An increased incidence of liver adenomas occurred also in female rats and mice at the both highest concentrations, but reached no statistically significance. A statistically significant increased incidence of mammary gland fibroadenomas was also observed in male rats at the highest concentration. A NOAEC for carcinogenicity was not derived for rats and mice.
Reproductive toxicity: fertility	NOAEL =200 mg/kg bw/d	**TL15 (1992), unpublished report; Tyl et al. (1996)** In a two-generation toxicity study in rats no reproductive toxicity was observed at 200 mg/kg bw/d, the highest dose studied. Toxicity to the haematopoietic

impairment oral rat		system was observed in adults at all doses studied (≥ 10 mg/kg bw/d). A NOAEL for parental toxicity could not be established.
Reproductive toxicity: fertility impairment inhalation rat	$LOEC_{sys}$ = 75 ppm (270 mg/m^3) for enlarged testis	**TL9 (1994), unpublished report; Newton et al. (2001)** In the combined chronic toxicity/carcinogenicity study enlarged testes in male rats at 75 and 374 ppm (270 and 1346 mg/m^3) were seen, which did not correlate with any microscopic findings.
Reproductive toxicity: developmental toxicity oral rat, rabbit	$NOAEL_{rat}$ =600 mg/kg bw/d $NOAEL_{rabbit}$ =24 mg/kg bw/d	**TL1 (1990a,b), unpublished report; Derelanko et al. (2003)** In rats no developmental toxicity was noted at 600 mg/kg bw/d (the highest dose tested). Maternal toxicity indicative of haemolytic anaemia occurred at all dose tested (LOAEL = 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. Therefore evaluations were conducted at the low and mid dose testing groups. A NOAEL for developmental toxicity in rabbits was set at 24 mg/kg bw/d. For maternal toxicity a NOAEL could not be established due to toxicity on the haematopoietic system observed from the lowest dose tested of 10 mg/kg bw/d.
Neurotoxicity Oral, inhalation, dermal Rat, rabbit	Single exposure: LOEL (oral) rat = 300 mg/kg bw; LOAEC (inhalation) rat = 4.8 mg/m^3 LOEL (dermal) rabbit = 18 mg/kg bw Repeated exposure: NOAEL (oral) rat =125 mg/kg bw/d	**Schulze and Derelanko (1993); TL7 (1991), unpublished report; TL21 (1991), unpublished report** Butanone oxime causes transient and reversible changes in neurobehavioral function consistent with CNS depression, but without evidence of cumulative neurotoxicity. Transient neurobehavioral changes were observed in rats and rabbits immediately after application of butanone oxime by the oral, inhalation and dermal route of exposure. Neurological effects occurred after single and repeated exposure.

A review of all available dose descriptors per each toxicity endpoint indicates that the major concern associated with short-term exposure to butanone oxime are acute oral and dermal toxicity, irreversible effects on the eye, and skin sensitisation.

Based on the results of eye irritation testing in rabbits, calculation of a DNEL for short-term/acute local effects is not possible because no dose-response data are available for the eye effects. The skin sensitisation potential of butanone oxime was evaluated by two GPMT, a Buehler assay and a MEST, which have shown a moderate sensitising potential. Based on the available data on both endpoints it is difficult to identify a DNEL. Therefore, a quantitative risk assessment is neither possible for eye irritation and nor for skin sensitisation. The available data trigger a qualitative risk characterisation for the eye irritation and the moderate skin sensitisation potential of butanone oxime. The general approach when no DNEL for these endpoints is available aims at reducing/avoiding contact with the substance. Eye irritants and moderate skin sensitizers are allocated to the moderate hazard category band on the basis that exposure to these substances should be well-controlled.

Repeated exposure to butanone oxime induces effects on the blood and liver, carcinogenicity, and local effects of the respiratory tract. In addition butanone oxime induces narcotic effects by the oral, inhalation and dermal route of exposure, which occurred after single or repeated exposure.

Overall, two effect types appear potentially relevant for determining the starting points, i.e. those dose descriptors (NOAEL/Cs, LOAEL/Cs) most relevant for setting DNEL/Cs for butanone oxime:

- Acute dermal toxicity
- Toxicity after repeated exposure (non-neoplastic effects); inhalation and dermal.

In addition repeated exposure to butanone oxime induces carcinogenicity. The evaluation of the cancer risk from exposure to butanone oxime aims to provide an estimation of an exposure level for inhalation and dermal exposure with minimal or negligible health risk. The risk level determination is based on a calculation of T25 from experimental data as the dose descriptor for the derivation of DMEL/Cs (derived minimal effect level/concentration).

5.13.2 Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptor for critical health effects

DNEL/Cs have been derived for workers and the general population by the registrants.

DNEL calculation for workers

At the workplace exposure to butanone oxime may occur via inhalation or by dermal contact. Consequently, DNELs have to be derived for both the inhalation and dermal route. The eMSCA derived these values according to the specifications given in the REACH guidance chapter R.8 (ECHA, 2012a).

Data from animal experiments via inhalation indicate exposure to butanone oxime does not only elicit local adverse human health effects in the upper respiratory tract but also systemic effects. Therefore two different long-term DNELs are derived for the inhalation route. A detailed overview on the derivations of the inhalation and dermal DNELs as conducted by the eMSCA is presented in the following three tables.

Table 21: Detailed overview of the derivation of the $DNEL_{worker,\ inhalation,\ long\text{-}term,\ systemic\ effects}$ for butanone oxime conducted by the eMSCA.

DNEL worker – inhalation – long-term – systemic effects		
Description (AF= Assessment factor)	**Value**	**Remark**
Relevant dose descriptor	54.2 mg/m^3 (15 ppm) = LOAEL	The LOAEL results from a chronic (26 months) inhalation toxicity study in Fischer 344 rats (TL9, 1994, unpublished report). At the lowest dose tested (i. e. at 54.2 mg/m^3) a statistically significant decrease in mean hemoglobin concentration (-17 % compared to controls) and mean hematocrit value (-16 % compared to controls) were observed in male rats. In female rats microscopic changes in the spleen were observed (congestion, extramedullary hematopoiesis, pigment in reticuloendothelial cells) indicating haematotoxicity.
Modification of the starting point	(6 h / 8 h)* (6.7 m^3/ 10 m^3) ↓ Overall factor = 0.5025	Due to different exposure conditions in the animal experiment and at the workplace both time scaling and a modification due to different respiratory volumes have to be applied according to the REACH guidance R.8.
Modified dose-descriptor	54.2 mg/m^3 * 0.5025 = 27.236 mg/ m^3 → **27.2 mg/m^3**	
AF for interspecies differences	2.5	Since the dose descriptor is expressed as concentration (in mg/m^3) an assessment factor for allometric scaling is not appropriate. However, a default assessment factor for remaining differences is applied according to the REACH guidance R.8.
AF for	5	The default factor for workers is applied according to the REACH

intraspecies differences		guidance R.8 because no substance-specific information is available for an adjustment.
AF for differences in exposure duration	1	No assessment factor is applied because the dose descriptor is based on a chronic study (26 months for rats).
AF related to dose response relationship	3	The dose descriptor is a LOAEL. Given the overall picture of adverse health effects observed at this concentration, a minimum assessment factor of 3 is applied according to the REACH guidance R.8.
AF related to quality of database	1	-
DNEL	27.2 mg/m^3 / (2.5*5*3) = 0.725 mg/m^3 → **0.7 mg/ m^3**	

Table 22: Detailed overview of the derivation of the DNEL$_{\text{worker, inhalation, long-term, local effects}}$ for butanone oxime conducted by the eMSCA.

DNEL worker – inhalation – long-term – local effects		
Description (AF= Assessment factor)	**Value**	**Remark**
Relevant dose descriptor	10.8 mg/m^3 (3 ppm) = NOAEL	The NOAEL results from a 90-day inhalation study in male CD-1 mice (Newton et al., 2002). The relevant adverse health effects involve degenerative changes of the olfactory epithelium at the next dose level (i. e. at 10 ppm and 36.1 mg/m^3, respectively).
Modification of the starting point	-	Data indicate that the relevant toxic effects are mainly driven by the exposure concentration. In such a case both time scaling and a modification due to different respiratory rates are not appropriate according to the REACH guidance R.8.
Modified dose-descriptor	10.8 mg/m^3	
AF for interspecies differences	2.5	According to the REACH guidance R.8 no assessment factor for allometric scaling is applied because degeneration of the olfactory epithelium is a local adverse health effect. However, a default factor of 2.5 for remaining differences is applied because no substance specific data are available for an adjustment.
AF for intraspecies differences	5	The default factor for workers is applied according to the REACH guidance R.8 because no substance-specific information is available for an adjustment.
AF for differences in exposure duration	1	Data indicate that incidence and severity of the degenerative changes of the olfactory epithelium depend rather on the air concentration of butanone oxime than on the duration of repeated exposure. In this case, an assessment factor is not justified.
AF related to dose response relationship	1	No assessment factor is applied because i) the dose descriptor is a NOAEL, ii) the LOAEL is characterised by low incidence (3 out of 10 animals) and low severity (minimal olfactory degeneration) of the relevant adverse health effects, and iii) the data do not point to a steep slope of the dose-response curve.
AF related to quality of database	1	-
DNEL	10.8 mg/m^3 / (2.5 * 5) = 0.864 mg/m^3 → **0.9 mg/m^3**	

Table 23: Detailed overview of the derivation of the $DNEL_{worker, dermal, long-term, systemic effects}$ for butanone oxime conducted by the eMSCA.

DNEL worker – dermal – long-term – systemic effects		
Description (AF= Assessment factor)	**Value**	**Remark**
Relevant dose descriptor	0.7 mg/m^3	No experimental data on repeated dermal exposure is available. Therefore, the $DNEL_{worker, inhalation, long-term, systemic effects}$ is used as relevant dose descriptor.
Modification of the starting point	70 kg bw, 10 m^3/d	Route-to-route extrapolation is needed from the inhalation to the dermal route. For this purpose a default body weight of 70 kg and a respiratory volume of 10 m^3 per person and day are applied for workers according to the REACH guidance R.8. The absorption rate via inhalation is not known for butanone oxime and set at 100 % by default assumption. Experimental data on dermal absorption rates is available for butanone oxime (Burka et al., 1998). However, due to low total recovery rates specifically in the low dose range (i. e. only about 50 % recovery at the 2.7 mg/kg dose), the experimentally available absorption rates are not considered sufficiently reliable. Consequently, dermal absorption of butanone oxime is set at 100 % by default assumption. This approach is supported by the REACH guidance R.8.
Modified dose-descriptor	0.7 mg/m^3 * 10 m^3 / 70 kg = **0.1 mg/kg bw/d**	
AF for interspecies differences	-	Not applicable.
AF for intraspecies differences	-	Not applicable.
AF for differences in exposure duration	-	Not applicable.
AF related to dose response relationship	-	Not applicable.
AF related to quality of database	-	Not applicable.
DNEL	**0.1 mg/kg bw/d**	

It is pointed out that in September 2013 a German national occupational limit value for butanone oxime was officially published in the German Joint Ministerial Gazette (BMAS, 2013) for inclusion in the Technical Rules for Hazardous Substances No. 900 (AGS, 2013b). The value that must be complied with in Germany is 1 mg/m^3 (0.3 ppm) and relates to an 8-hour time-weighted average concentration in the workplace air. The hazard based value is derived from a 90-day inhalation study in male CD-1-mice in which adverse effects on the respiratory tract following exposure to butanone oxime were specifically investigated (Newton et al., 2002). Degenerative changes of the olfactory epithelium were identified as the most sensitive endpoint and the lowest concentration tested was defined as NOAEC, i. e. 10.8 mg/m^3 (3 ppm).

For butanone oxime the German Committee on Hazardous Substances who is in charge of the derivation of national occupational limit values applied a benchmark-dose model to the study results and obtained by this means a BMD of 6.66 mg/m^3 (1.84 ppm). This value was then adjusted to a human equivalent concentration of 3.33 mg/m^3 (0.92 ppm). Since severity and incidence of the degenerative changes of the olfactory epithelium were predominantly dependent on the concentration of butanone oxime and not on the exposure duration, no assessment factor for duration extrapolation was used. Concerning intra- and interspecies differences a total assessment factor of 5 was applied. Finally, the value of 3.33 mg/m^3: 5 = 0.66 mg/m^3 (0.184 ppm) was rounded

up to 1 mg/m^3 (0.3 ppm). The criteria document on the derivation of the occupational limit value for butanone oxime is publicly available in German language (AGS, 2013a).

DMEL calculation for workers

For the calculation of derived minimal effect levels (DMELs) for workers the study of Newton (2001) (rats, inhalation route, 26 months duration) was used. At a concentration of 75 ppm (270 mg/m^3) the incidence of liver adenomas was significantly increased in male rats. Incidence of liver adenomas in the control group was 0/50 and in the 75 ppm group 5/51, which is equivalent to a 10 % increase in liver tumour formation. For the calculation of the DMELs T25 value was used as starting point. T25 value indicates the dose, at which 25 % of testing animals show occurrence of in this case liver adenomas. As the dose for 10 % incidence of liver adenomas in male rats was experimentally determined as 75 ppm (270 mg/m^3), T25 value for developing hepatocellular carcinomas and liver adenomas in male rats was calculated as 675 mg/m^3. DMELs were derived according to the REACH Guidance chapter R.8 (ECHA 2012a). Using T25 as a starting point for the derivation of $DMEL_{inhalation}$ and $DMEL_{dermal}$ values some modifications and extrapolations had to be applied. A detailed overview on the derivations of both DMELs as conducted by the eMSCA is presented in Table 24 and

Table 25.

Table 24: Detailed overview of the derivation of $DMEL_{worker, inhalation, liver adenomas}$ for butanone oxime conducted by the eMSCA

DMEL Calculation – worker – inhalation		
Description (AF= Assessment factor)	**Value**	**Remark**
Relevant dose descriptor	675 mg/m^3	T25 for developing hepatocellular carcinomas and liver adenomas in rats was used as relevant dose descriptor.
Modification of the starting point	(6 h/8 h) * (6.7 m^3/10 m^3) * (5 d/5 d) * (52 w/48 w) * (75 y/40 y) ↓ Overall factor = 1.02	Due to different exposure conditions in the animal experiment and at the workplace both time scaling and a modification due to different respiratory volumes have to be applied according to the REACH guidance R.8. Differences between occupational and lifetime exposition have also been included.
Modified dose-descriptor	675 mg/m^3 * 1.02 = **688.5 mg/ m^3**	
AF for interspecies differences	1	According to the REACH guidance R.8 an assessment factor for allometric scaling is not needed here because the dose unit of the dose descriptor is expressed as concentration.
Extrapolation to a 10^{-5} risk level	$\frac{688.5 \text{ mg/m}^3}{1 * 25000}$	0.02754 mg/m^3 → 28 µg/m^3
$DMEL_{inhalation}$ for workers (based on T25)	**28 µg/m^3** (1:100 000, linear)	

Table 25: Detailed overview of the derivation of $DMEL_{worker, dermal, liver adenomas}$ for butanone oxime conducted by the eMSCA.

DMEL Calculation – worker – dermal		
Description (AF= Assessment factor)	**Value**	**Remark**
Relevant dose descriptor	**28 µg/m³** (1:100 000, linear)	$DMEL_{inhalation}$ value for workers (based on T25) was used as relevant dose descriptor.
Extrapolation from inhalation to dermal exposition	28 µg/m³ * 10 m³/d / 70 kg bw	For extrapolation of the inhalation to dermal DMEL it was necessary to apply modifications (respiration rate 10 m³/d; 70 kg body weight).
$DMEL_{dermal}$ for workers (based on T25)	**4 µg/kg bw/d** (1:100 000, linear)	

DNEL/C calculation for the general population

According to the CSRs butanone oxime is used as an anti-skinning agent in paints. The relevant routes of exposure to butanone oxime for the general population are inhalation and dermal contact, exposure to the eyes is possible as well. Exposure via the oral route is considered to be not relevant for consumers due to the nature of the product. Accordingly the registrants have derived DNEL/Cs for the inhalation and dermal route of exposure. For the inhalation route DNECs for long-term systemic and local effects were derived and for the skin contact DNELs for short-term/acute and long-term systemic effects. In the following table an overview of data are given which were selected by the registrants for the DNEL/C calculation for the general population.

Table 26: Registrants data base for calculation of DNEL for the general population

Exposure pattern	Dose descriptor	Remark
Dermal, short-term/acute - systemic effects	NOAEL = 18 mg/kg bw/d	Acute dermal toxicity study, rabbit: transient methaemoglobinaemia, splenic effects; narcotic effects
Dermal, long-term - systemic effects	$DNEC_{long-term-systemic effects}$ for inhalation = 2.7 mg/m³	Extrapolation from DNEC inhalation, long-term → DNEL dermal
Inhalation, long-term - systemic effects	NOAEC = 54 mg/m³	Combined chronic/carcinogenicity studies, rat and mouse: liver effects
Inhalation, long-term - local effects	NOAEC = 10 mg/m³	Sub-chronic study, male mouse: nasal lesions

Based on the available toxicity data of butanone oxime for the general population the eMSCA has selected dose descriptors different to that used by the registrants for the subsequent derivation of DNEL/C. In view of the exposure routes, the eMSCA is of the opinion that DNEL/C for short-term/acute systemic effects by inhalation should also be derived.

Dermal, short-term/acute exposure

For derivation of the DNEL for short-term/acute – dermal, systemic effects the registrants have used as starting point the NOAEL of 18 mg/kg bw/d based on effects on the blood (transient methaemoglobinaemia, splenic effects) and narcotic effects from the acute dermal toxicity study in rabbits. As an alternative approach this dose descriptor was also used for derivation of the DNEL for this exposure pattern by the eMSCA. However, butanone oxime is legally classified and labelled for its acute dermal toxicity as Acute Tox. 4, H312 according to the CLP Regulation. According to REACH Guidance, Chapter R.8 a DNEL for acute toxicity should be derived if an acute toxicity hazard (leading to C&L) has been identified and there is a potential for high peak exposures.

Therefore, the DNEL for short-term/acute, systemic effects by the dermal route of exposure was derived from the **LD_{50} value of 1848 mg/kg bw in rabbits** observed from the same study (TL2 1984b, unpublished report).

Inhalation, short-term/acute exposure

The registrants have not derived a DNEC for short-term/acute systemic effects by inhalation. For derivation of the DNEC for short-term/acute – inhalation, systemic effects the eMSCA has used as starting point the **NOAEC of 3 ppm (10.8 mg/m^3)** based on effects on the nasal turbinates (degeneration of the olfactory epithelium) derived from a sub-chronic study (13 wk, 6h/d, 5d/wk) in **male mice** (TL10 1995b, unpublished report; Newton et al. 2002).

Inhalation, long-term exposure, systemic effects

The most sensitive non-cancer effects induced by butanone oxime was haemotoxicity observed as haemolytic anaemia with concomitant extramedullary haematopoiesis and hemosiderosis in liver and spleen after repeated exposure by the oral and inhalation route, and in addition the toxic effects on the liver after repeated exposure by inhalation.

For derivation of the DNEC for long-term – inhalation, systemic effects the registrants have used as starting point the same concentration as the eMSCA. But the eMSCA has identified the concentration of **15 ppm (54 mg/m^3)** as LOAEC and not as NOAEC. At this concentration toxic effects on the blood in **rats and mice**, and liver effects (hypertrophy and necrosis) in male mice were observed after chronic exposure by inhalation (26/18 months, combined chronic toxicity/carcinogenicity studies; whole body, 6h/d, 5d/wk). This concentration was identified as the most appropriate starting point for DNEC derivation for systemic effects following long-term exposure by inhalation (TL9 1994, 1993, unpublished reports; Newton et al. 2001)

Inhalation, long-term exposure, local effects

For local effects on the nasal turbinates (degeneration of the olfactory epithelium) a LOAEC at 15 ppm (54 mg/m^3) was derived in mice observed both after 12 and 18 months of exposure by inhalation in the combined chronic toxicity/carcinogenicity study (Rinehart 1993, unpublished report; Newton et al. 2001). However, the NOAEC for these local effects on the nasal turbinates of **3 ppm (10.8 mg/m^3)**, derived from a sub-chronic study (13-wk study, whole body, 6h/d, 5d/wk) **in male mice**, was identified as the most appropriate starting point for DNEC derivation for local effects following long-term exposure by inhalation by the registrants and the eMSCA (TL10 1995b, unpublished report; Newton et al. 2002).

Dermal, long-term exposure, systemic effects

For butanone oxime no long-term dermal studies are available which would allow for a direct conclusion on a ‚safe' dermal dose with respect to the systemic effects. The calculation of DNEL for systemic effects after long-term dermal exposure to butanone oxime has been undertaken by **using route-to-route extrapolation from the derived $DNEC_{long\text{-}term\text{-}systemic\ effects}$ for inhalation deduced in rats**.

Based on the evaluation of all available toxicity data to butanone oxime a calculation of DNEL/Cs for the general population was performed. The following table shows the selected dose descriptors and/or corrected dose descriptors for the derivation of DNEL/Cs.

Table 27: Dose descriptors selected for DNEL/C calculation for the general population by the eMSCA

Exposure pattern	Dose descriptor/corrected dose descriptor/Reference
Inhalation, short-term/acute – systemic effects	NOAEC = 3 ppm (10.8 mg/m^3), sub-chronic (13 wk) study; 6h/d, 5d/wk); male mice (TL10 1995b, unpublished report; Newton et al. 2002)
Dermal, short-term/acute – systemic effects	LD_{50} (dermal) = 1848 mg/kg bw; rabbit, acute dermal toxicity study (TL2 1984b, unpublished report) Alternative: NOAEL (dermal) = 18 mg/kg bw/d for transient methaemoglobinaemia, splenic effects; narcotic effects derived from the same study in rabbits
Inhalation, long-term – systemic effects	LOAEC = 15 ppm (54 mg/m^3; 6h/d, 5d/wk), combined chronic toxicity/carcinogenicity studies, inhalation; rats and mice (TL9 1993, 1994, unpublished reports; Newton et al. 2001) LOAEC correction to the exposure pattern in the human exposure scenario, default: exposure duration: a) 6h→24h; b) 5d/wk→7d/wk : (6/24) * (5/7) * 54 mg/m^3 = 9.64 mg/m^3 ($LOAEC_{corr}$)
Inhalation, long-term – local effects	NOAEC = 3 ppm (10.8 mg/m^3; 6h/d, 5d/wk), sub-chronic (13-week) study; male mice (TL10 1995b, unpublished report; Newton et al. 2002) NOAEC correction to the exposure pattern in the human exposure scenario, default: exposure duration: a) 6h→24h; b) 5d/wk→7d/wk : (6/24) * (5/7) * 10.8 mg/m^3 = 1.93 mg/m^3 ($NOAEC_{corr}$)
Dermal, long-term – systemic effects	Extrapolation from DNEC inhalation→DNEL dermal: LOAEC = 15 ppm (54 mg/m^3; 6h/d, 5d/wk), combined chronic toxicity/carcinogenicity study, inhalation; rats and mice (TL9 1993, 1994 unpublished reports; Newton et al. 2001) LOAEC correction to the exposure pattern in the human exposure scenario, default: exposure duration: a) 6h→24h; b) 5d/wk→7d/wk : (6/24) * (5/7) * 54 mg/m^3 = 9.64 mg/m^3 ($LOAEC_{corr}$)

The registrants have calculated the following DNELs for the general population to butanone oxime:

$DNEL_{short\text{-}term/acute\text{-}systemic\ effects}$ for dermal exposure = 1.5 mg/kg bw/d

$DNEL_{long\text{-}term\text{-}systemic\ effects}$ for dermal exposure = 0.78 mg/kg bw/d

$DNEC_{long\text{-}term\text{-}systemic\ effects}$ for inhalation = 2.7 mg/m^3

$DNEC_{long\text{-}term\text{-}local\ effects}$ for inhalation = 2.0 mg/m^3.

The eMSCA has judged the registrant's derivation of DNEL/Cs for the general population as not valid regarding the application of the assessment factor (AF) for intraspecies differences. The registrants have used an intraspecies AF of 5 for the general population instead of the default value of 10 according to the REACH Guidance Chapter R.8 (ECHA 2012a). The lead registrant has not given substance-specific grounds for the application of this lower AF. As reasons for preferring a AF of 5 the lead registrant has cited the publications on the differences of human variability in the fate of the chemical in the body (kinetics) and target organ sensitivity (dynamics) by Renwick and Lazarus (1998), the interindividual variability in parameters related to health risks by Hattis et al.

(1999), and the merits and disadvantages of a specific proposal for a numeric calculation of the reference dose by Hattis et al. (2002). Each of the aspects described in these publications is recognised and is reflected in a default AF of 10 for the general population with an even subdivision into $10^{0.5}$ (3.16) for toxicokinetic variability and $10^{0.5}$ (3.16) for toxicodynamic variability according to the REACH Guidance Chapter R.8 (ECHA 2012a). Further it is considered that information on intraspecies variation for local effects is very scarce and it is therefore generally suggested not to refine these default factors. This is consistent with the REACH Guidance: *"Therefore, when the available data do not allow the derivation of a substance-specific or analogue-specific AF, the default AF should be applied according to the REACH Guidance document."* Accordingly, an alternative calculation of the DNEL/C for the general population was performed and is presented in the following table.

Table 28: Alternative calculation of DNEL/C for the general population by the eMSCA

Exposure pattern	DNEL/C Calculation
	Starting point is a NOAEC of 3 ppm (10.8 mg/m^3) based on degeneration of the olfactory epithelium on the nasal cavity of mice exposed to an exposure regime of 6h/d, 5d/wk, in a sub-chronic (13 wk) study in male mice (TL10 1995b, unpublished report; Newton et al. 2002).
Inhalation Short-term/acute – systemic effects	NOAEC = 3 ppm (10.8 mg/m^3) Modification of the relevant dose descriptor to need the everyday concentration per mouse during the exposure period: everyday vs. 5d/wk = (5/7) * 10.8 mg/m^3 = 7.72 mg/m^3 DNEC for other exposure durations can be observed by time extrapolation using the modified Haber's law: $C^n * t = const$. For extrapolation from shorter to longer durations, n is set to 1, and for extrapolation from longer to shorter durations, n is set to 3. DNEC calculation for the following time periods: 4h, and 1.3, 5, 20, 25, 60, 66 and 132 min Discussion of the application of AF to get the DNEC is for all time periods the same described in the time-scaling for 4 hours. **Time-scaled NOAEC (4 hours)** $C^n * t = const$; n = 3 (from longer to shorter) $C^3 = (7.72 mg/m^3)^3 = 460.1 mg/m^3$ 460.1 mg/m^3 * 6h = [NOAEC (4h)]^3 * (6/4) NOAEC (4h) = $\sqrt[3]{}$ 460.1 mg/m^3 * 1.5 NOAEC (4h) = $\sqrt[3]{}$ 690.15 mg/m^3 1. NOAEC (4h) = 8.84 mg/m^3 Discussion of the application of AF to get the DNEL: AF for interspecies differences: 1 for allometric scaling (for inhalation NOAEC is compared directly) AF for remaining uncertainties: 2.5 (default; for other interspecies differences, i.e. significant quantitative differences in deposition; airflow patterns, clearance rates and protective mechanisms between humans and animals; humans would be more sensitive than animals) AF for intra species differences: 10 (default for general population) AF for quality of whole database: 1 Total AF: 1 * 2.5 * 10 * 1 = 25 **$DNEC_{short\text{-}term/acute\text{-}systemic\ effects}$ for inhalation of 4 hours:** 8.84/25 = **0.353 mg/m^3/4h** **Time-scaled NOAEC (1.3 min); 1.3 min = 0.022h** 460.1 mg/m^3 * 6h = [NOAEC (1.3 min)]^3 * (6/0.022) **NOAEC (1.3 min) = $\sqrt[3]{}$ 460.1 mg/m^3 * 272.73** **NOAEC (1.3 min) = 50.06 mg/m^3** **$DNEC_{short\text{-}term/acute\text{-}systemic\ effects}$ for inhalation of 1.3 minutes: 50.06 mg/m^3/25 = 2.0 mg/m^3/1.3 minutes** **Time-scaled NOAEC (5 min); 5 min = 0.08h** 460.1 mg/m^3 * 6h = [NOAEC (5 min)]^3 * (6/0.08) 2. NOAEC (5 min) = 32.56 mg/m^3

	$DNEC_{short\text{-}term/acute\text{-}systemic\ effects}$ for inhalation of 5 minutes: 32.56 mg/m^3/25 = 1.3 mg/m^3/5 minutes **Time-scaled NOAEC (20 min); 20 min = 0.33h** 460.1 mg/m^3 * 6h = [NOAEC (20 min)]^3 * (6/0.33) **$DNEC_{short\text{-}term/acute\text{-}systemic\ effects}$ for inhalation of 20 minutes: 20.30 mg/m^3/25 = 0.81 mg/m^3/20 minutes** **Time-scaled NOAEC (25 min); 25 min = 0.42h** 460.1 mg/m^3 * 6h = [NOAEC (25 min)]^3 * (6/0.42) **$DNEC_{short\text{-}term/acute\text{-}systemic\ effects}$ for inhalation of 25 minutes: 18.73 mg/m^3/25 = 0.749 mg/m^3/25 minutes** **Time-scaled NOAEC (60 min); 60 min = 1h** 460.1 mg/m^3 * 6h = [NOAEC (60 min)]^3 * (6/1) **$DNEC_{short\text{-}term/acute\text{-}systemic\ effects}$ for inhalation of 60 minutes: 14.028 mg/m^3/25 = 0.561 mg/m^3/60 minutes** **Time-scaled NOAEC (66 min); 66 min = 1.1h** 460.1 mg/m^3 * 6h = [NOAEC (66 min)]^3 * (6/1.1) **$DNEC_{short\text{-}term/acute\text{-}systemic\ effects}$ for inhalation of 66 minutes: 13.59 mg/m^3/25 = 0.543 mg/m^3/66 minutes** **Time-scaled NOAEC (132 min); 132 min = 2.2h** 460.1 mg/m^3 * 6h = [NOAEC (132 min)]^3 * (6/2.2) **$DNEC_{short\text{-}term/acute\text{-}systemic\ effects}$ for inhalation of 132 minutes = 10.786 mg/m^3/25 = 0.431 mg/m^3/132 minutes**
	Alternative: Starting point is the derived $DNEC_{long\text{-}term\text{-}systemic\ effects}$ for inhalation from a LOAEC observed from combined chronic toxicity/carcinogenicity studies (inhalation) in rats and mice (LOAEC = 15 ppm (54 mg/m^3; 6h/d, 5d/wk); TL9 1993, 1994, unpublished reports; Newton et al. 2001) (see below details of derivation the $DNEC_{long\text{-}term\text{-}systemic\ effects}$ for inhalation)
	Derived $DNEC_{long\text{-}term\text{-}systemic\ effects}$ for inhalation = 0.128 mg/m^3 The acute DNEC for systemic effects by inhalation to butanone oxime is set by default as 3 times the long-term DNEC (REACH Guidance Chapter R.8, 2012). $DNEC_{long\text{-}term\text{-}systemic\ effects}$ for inhalation: 0.128 mg/m^3 * 3 = 0.384 mg/m^3 **$DNEC_{short\text{-}term/acute\text{-}systemic\ effects}$ for inhalation = 0.384 mg/m^3**
	Starting point is a LD50 value of 1848 mg/kg bw derived from an acute dermal toxicity study in rabbits (TL2 1984b, unpublished report).
Dermal Short-term/acute – systemic effects	LD50 = 1848 mg/kg bw Discussion of the application of AF to get the DNEL: AF for severe of effects (LD50): 100 (default) AF for interspecies differences: 2.4 AF for intra species differences: 10 (default for general population) AF for quality of whole database: 1 Total AF: 100 * 2.4 *10 * 1 = 2400 **$DNEL_{short\text{-}term/acute\text{-}systemic\ effects}$ for dermal exposure:** 1848/2400 = **0.77 mg/kg bw**

	Alternative: Starting point is a NOAEL of 18 mg/kg bw for transient methaemoglobinaemia, splenic effects; narcotic effects derived from the same acute dermal toxicity study in rabbits (TL2 1984b, unpublished report).
	NOAEL = 18 mg/kg bw Discussion of the application of AF to get the DNEL: AF for severe of effects (NOAEL): 1 (default) AF for interspecies differences: 2.4 AF for intra species differences: 10 (default for general population) AF for quality of whole database: 1 Total AF: 1 * 2.4 *10 * 1 = 24 **$DNEL_{short\text{-}term/acute\text{-}systemic\ effects}$ for dermal exposure:** 18/24 = **0.75 mg/kg bw**
	Starting point is the corrected $LOAEC_{corr}$ for systemic effects of 9.64 mg/m³ derived from combined chronic toxicity/carcinogenicity studies (inhalation) in rats and mice (LOAEC = 15 ppm (54 mg/m³; 6h/d, 5d/wk); TL9 1993, 1994, unpublished reports; Newton et al. 2001)
Inhalation Long-term – systemic effects	$LOAEC_{corr}$ = 9.64 mg/m³ Discussion of the application of AF to get the DNEC: AF for difference in duration of exposure: 1 (LOAEC is based on chronic studies, 26/18 months) AF for interspecies differences: 1 for allometric scaling (for inhalation LOAEC is compared directly) AF for remaining uncertainties: 2.5 (default; for other interspecies differences, i.e. significant quantitative differences in deposition; airflow patterns, clearance rates and protective mechanisms between humans and animals; humans would be more sensitive than animals) AF for intra species differences: 10 (default for general population) Dose response: 3 (from LOAEC to NOAEC) AF for quality of whole database: 1 Total AF: 1 * 1 * 2.5 * 10 * 3 * 1 = 75 **$DNEC_{long\text{-}term\text{-}systemic\ effects}$ for inhalation:** 9.64/75 = **0.128 mg/m³**
	Starting point is the corrected $NOAEC_{corr}$ for local effects of 1.93 mg/m³ derived from a sub-chronic (13-week) inhalation toxicity study in male mice (NOAEC = 3 ppm (10.8 mg/m³; 6h/d, 5d/wk); TL10 1995b, unpublished report; Newton et al. 2002).
Inhalation Long-term – local effects	$NOAEC_{corr}$ for local effects = 1.93 mg/m³ Discussion of the application of AF to get the DNEC: AF for difference in duration of exposure: 2 (NOAEC is based on a sub-chronic study, 3 months) AF for interspecies differences: 1 for allometric scaling (for inhalation NOAEC is compared directly) AF for remaining uncertainties: 2.5 (default; for other interspecies differences, i.e. significant quantitative differences in deposition; airflow patterns, clearance rates and protective mechanisms between humans and animals; humans would be more sensitive than animals; no chemical specification available) AF for intra species differences: 10 (default for general population) AF for quality of whole database: 1 (default) Total AF: 2 * 1 * 2.5 * 10 * 1 = 50 **$DNEC_{long\text{-}term\text{-}local\ effects}$ for inhalation:** 1.93 mg/m³/50 = **0.0386 mg/m³**
	Extrapolation from DNEC inhalation, systemic effects → DNEL dermal, modification according REACH Guidance Chapter R.8
Dermal Long-term – systemic effects	Derived $DNEC_{long\text{-}term\text{-}systemic\ effects}$ for inhalation = 0.128 mg/m³ 0.128 mg/m³ * (20 m³ amount general population in 24h exposure/60 kg bw default for general population; 100 % bioavailability) = 0.0427 mg/kg bw/d **$DNEL_{long\text{-}term\text{-}systemic\ effects}$ for dermal exposure = 0.0427 mg/kg bw/d**

An overview of the derived DNEL/C for the general population by the eMSCA is given in the following table.

Table 29: Overview of the derived DNEL/C of butanone oxime for the general population

Hazard information	Value	Unit
Inhalation DNEC – short-term/acute – systemic effects	0.353	mg/m^3/4h
	2.0	mg/m^3/1.3 min
	1.3	mg/m^3/5 min
	0.81	mg/m^3/20 min
	0.749	mg/m^3/25 min
	0.561	mg/m^3/60 min
	0.543	mg/m^3/66 min
	0.431	mg/m^3/132 min
Inhalation DNEC – short-term/acute – systemic effects (alternative calculation from the long-term DNEC)	0.384	mg/m^3
Dermal DNEL – short-term/acute – systemic effects	0.77	mg/kg bw
Dermal DNEL – short-term/acute – systemic effects (alternative calculation based on NOAEL = 18 mg/kg bw/d)	0.75	mg/kg bw
Inhalation DNEC – long-term – systemic effects	0.128	mg/m^3
Inhalation DNEC – long-term – local effects	0.0386	mg/m^3
Dermal DNEL – long-term – systemic effects	0.0427	mg/kg bw/d

The derived DNEL/Cs for the general population by the eMSCA are lower than those used by the registrants in the CSRs.

DMEL/C calculation for the general population

The registrants have not considered whether risks of cancer from exposure to butanone oxime are adequately controlled for the general population known to be exposed. Butanone oxime is a human carcinogen and is legally classified as a carcinogen of category 2; H351. During the SEV the classification of butanone oxime as category 1B carcinogen, H350 according to the CLP Regulation was identified as a concern. The relevant routes of exposure to butanone oxime for the general population are inhalation and dermal contact. Therefore, the eMSCA has derived DMEL/Cs for both exposure routes.

Dose descriptor for the derivation of DMEL/Cs

The carcinogenic potential of butanone oxime has been investigated in two studies (combined chronic toxicity/carcinogenicity studies, similar to OECD TG 453) and in two species. Butanone oxime was administered by whole-body inhalation as a vapour 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.

In the combined chronic toxicity/carcinogenicity studies in rats and mice exposed by inhalation to butanone oxime sufficient evidence of animal carcinogenicity was demonstrated. A causal relationship has been established between butanone oxime and an increased incidence of a combination of benign and malignant tumours in both animal species. The combined chronic toxicity/carcinogenicity studies in rats and mice have demonstrated that tumour development in the liver was noted following inhalation of relative small concentrations in rats and mice. Butanone oxime causes an increased incidence of liver tumours (adenomas and carcinomas) in both species at

all tested exposure concentrations. However, statistically significant increases in incidence were observed only at the two highest concentrations for liver adenomas in male rats and at the highest concentration for liver carcinomas in male rats and mice. An increased incidence of liver adenomas occurred also in female rats and mice at the two highest concentrations, but was not statistically significant. In the rat control groups no tumours were found in the liver. A statistically significant increase in the incidence of mammary gland fibroadenomas was also observed in male rats at the highest concentration (TL9 1994, 1993, unpublished report; Newton et al. 2001). A NOAEC for carcinogenicity was not derived for butanone oxime in the mouse and rat study. For carcinogenicity (liver tumour development) a LOAEC of 15 ppm (54 mg/m^3) was derived for rats and mice from these studies.

The modes of action for induction of the liver tumours in rats and mice have not been fully identified. According to today's state of knowledge the potential mechanisms behind chemical carcinogenesis are highly complex involving genotoxic events (mutations), altered gene expression at the transcriptional translational, and posttranslational levels (epigenetic events), and altered cell survival (proliferation and apoptosis) (Hanahan and Weinberg 2000).

For butanone oxime, in vitro and in vivo mutagenicity or genotoxicity tests and tests in mammalian somatic and germ cells were mostly negative. These results support the assumption that butanone oxime is not able to induce directly heritable mutations in the germ cells of humans.

As a possible mechanism for the induction of liver tumours in rats and mice the metabolism of butanone oxime to a carcinogenic agent, mediated by sulfotransferase was discussed. 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.

Overall, the modes of action for induction of liver tumours in rats and mice after long-term exposure by inhalation have not been fully identified.

In the REACH Guidance documents on information requirements, Chapter R.8 (ECHA 2012a) it is stated that "It is to be noted that the decision on a threshold and a non-threshold mode of action may not always be easy to make, especially when, although a biological threshold may be postulated, the data do not allow identification of it. If not clear, the assumption of a non-threshold mode of action would be the prudent choice."

As no thresholds for carcinogenicity can be set, also a DMEL/C instead of a DNEL/C can be derived. Therefore the evaluation of the cancer risk from exposure to butanone oxime is carried out by derivation of DMEL/C.

Evaluation of cancer risk from exposure to butanone oxime

The purpose of this evaluation is to provide an estimation of an exposure level for inhalation and dermal route of exposure to butanone oxime with minimal or negligible health risk. This level depends on the risk of acquiring disease associated with a dose level. Establishing an acceptable risk level is a public health policy issue and is often related to other comparable health risks in our society.

The REACH Guidance Chapter R.8 (ECHA 2012a) states that cancer risk levels of 10^{-5} and 10^{-6} could be seen as indicative of tolerable risks levels when setting DMEL/C for workers and the general population, respectively. In summary, the cancer risk decision points used for lifetime exposure of the general population are generally in the range of 10^{-5} to 10^{-6}. This means that lifelong exposure at the indicated levels would give an excess lifelong risk of acquiring cancer of

either 10 (10^{-5}) or 1 (10^{-6}) in a million. A risk of one in a million is considered negligible. A risk of 10 in a million is considered as minimal; however, measures to reduce it should be considered.

Choice of the dose descriptor for calculation of risk estimates

According to the REACH Guidance Chapter R.8 (ECHA 2012a) the T25 should be used as a default dose-descriptor unless the dose-response curve is clearly sub- or supra-linear. For derivation of DMEL/C for the carcinogen butanone oxime the **"Linearised" approach** is applied. According to the REACH Guidance Chapter R.8 (ECHA 2012a) the chronic dose rate, T25 is used as a default dose descriptor.

Calculation of risk estimates using the dose-descriptor T25

The risk level determination is based on a calculation of T25 from experimental data as the dose descriptor (Dybing et al. 1997) and a linear extrapolation to 10^{-5} and 10^{-6} risk levels.

Calculation of T25 for developing hepatocellular carcinomas and adenomas in rats

The data of liver tumour development in male rats were assessed as suitable for the T25 approach. Liver tumours occurred in all of the three tested concentration groups (15, 75, 374 ppm) at the incidences of 2/51, 5/51, and 18/51, respectively. In the control group none (0/50) was found. The lowest concentration with a significantly increased incidence of liver adenomas was used for calculation. This concentration was 75 ppm (270 mg/m^3).

Adjustment of background tumour incidences is needed (Dybing et al., 1997):

Liver adenoma: 75 ppm (270 mg/m^3) butanone oxime exposed by whole-body inhalation as a vapour 6h/day, 5 days/week for 26 months; Control: 0/50; 75 ppm: 5/51; net% = 10 %

Modification of the starting point: Conversion of the rat LOAEC into a corrected human LOAEC:

Correction of the exposure conditions from the rat study into human exposure conditions:

- 6h/day to default consumer 24h/day, and
- 5 days/week to default consumer 7 days per week:

$LOAEC_{corr}$ = (6/24) * (5/7) * 270 mg/m^3 = 48.21 mg/m^3

The chronic dose rate giving liver tumours in 25 % of the animals (T25) for butanone oxime is calculated from 48.21 mg/m^3: T25 = (25/10) * 48.21 mg/m^3 = 120.52 mg/m^3

The relevant dose descriptor is **T25 = 120.52 mg/m^3** (based on results from a combined chronic toxicity/carcinogenicity study by inhalation in rats; Rinehart 1994; Newton et al. 2001).

DMEL/C calculation for the general population

For evaluation of cancer risk from exposure to butanone oxime and derivation of tolerable risks levels DMEL/C for the general population were deduced.

The steps of DMEL/C calculation for the general population exposed to butanone oxime are shown in the following table.

Table 30: Calculation of DMEL/C for the general population exposed to butanone oxime

Route	DMEL/C Calculation
	Starting point is the derived T25 value of 120.52 mg/m^3 based on the results from a combined chronic toxicity/carcinogenicity study by inhalation in rats (TL9 1994; Newton et al. 2001). The T25 for developing of liver tumours (hepatocellular carcinomas and adenomas) is used as Point of Departure (PoD).
Inhalation	PoD = 120.52 mg/m^3 Discussion of the application of AF to get the DMEC: AF for interspecies extrapolation: 1 for allometric scaling AF for intraspecies extrapolation: not applied AF for remaining uncertainties: 1 Total AF: 1 Extrapolation (high to low dose): 25,000 (linearity, 1:100000) 250,000 (linearity, 1:1000000) Calculation of DMEC: corrected T25 divided by overall assessment factor of 1 120.52 mg/m^3/25,000 = 0.00482 mg/m^3 = 4.82 µg/m^3 120.52 mg/m^3/250,000 = 0.000482 mg/m^3 = 0.482 µg/m^3 Summing up, the following DMECs (based on T25) associated with a lifetime cancer risk of very low concern were obtained: **Linearised approach, 10^{-5} risk level (1:100,000): 4.82 µg/m^3** **Linearised approach, 10^{-6} risk level (1:1000000): 0.482 µg/m^3**
	Extrapolation from DMEC inhalation → DMEL dermal; modification according REACH Guidance Chapter R.8 from 'µg/m^3 to 'µg/kg bw/d'
Dermal	DMEL, linearised approach, 10^{-5} risk level (1:100000): 4.82 µg/m^3 * (20 m^3 amount general population in 24h exposure/60 kg bw default for general population; 100 % bioavailability) = 1.61 µg/kg bw/d DMEL, linearised approach, 10^{-6} risk level (1:1000000): 0.482 µg/m^3 * (20 m^3 amount general population in 24h exposure/60 kg bw default for general population; 100 % bioavailability) = 0.161 µg/kg bw/d **Linearised approach, 10^{-5} risk level (1:100,000): 1.61 µg/kg bw/d** **Linearised approach, 10^{-6} risk level (1:1000000): 0.161 µg/kg bw/d**

An overview of the derived DMEL/C (based on T25 calculation) associated with a lifetime cancer risk of very low concern for butanone oxime for the general population by inhalation and dermal exposure is given in the following table.

Table 31: Overview of the derived DMEL/C of butanone oxime for the general population

Hazard information	Value
DMEC, inhalation exposure	4.82 µg/m^3 (linearity, 1:100000) 0.482 µg/m^3 (linearity, 1:1000000)
DMEL, dermal exposure	1.61 µg/kg bw/d (linearity, 1:100000) 0.161 µg/kg bw/d (linearity, 1:1000000)

5.14 Conclusions of the human health hazard assessment and related classification and labelling

In the following table conclusions for classification or non classification of butanone oxime based on the examination of the existing toxicity data for the human health endpoints are given.

Table 32: Conclusions for classification or non classification of butanone oxime

Endpoint	Route Species	Value/Effect, Reference	Classification, criteria
Acute toxicity	Oral rabbit	LD_{50} = 160-200 mg/kg bw (TL1 1990b, unpublished report; Derelanko et al. 2003)	Classification proposal: Acute Tox. 3, H301: Toxic if swallowed (50 < ATE ≤ 300 mg/kg bw)
Acute toxicity	Inhalation rat	LC_{50} assumed to be higher than 13.2 mg/L/4h (TL8 1971a, unpublished report)	No classification (legal classification) It is assumed that the real LC_{50} value exceeds the limit value, vapours of 20 mg/L/4h for Acute Tox. 4
Acute toxicity	Dermal rabbit	LD_{50} = 1848 mg/kg bw (TL2 1984b, unpublished report)	Legal classification confirmed: Acute Tox. 4, H312: Harmful in contact with skin (1000 < ATE ≤ 2000 mg/kg bw)
Narcotic effect	Oral, inhalation, dermal Rat, rabbit, mouse	Transient and reversible changes in neurobehavioral function consistent with CNS depression, but no evidence of cumulative neurotoxicity	Classification proposal: STOT SE 3, H336: May cause drowsiness or dizziness (Annex I, Part 3.8.2.2.2)
Irritation	Skin rabbit	Not irritating to skin (TL2 1978b; TL8 1971b, unpublished report)	No classification (legal classification)
Irritation corrosivity	Eye rabbit	irreversible effects on the eye/serious damage to the eyes (TL2 1978c, unpublished report)	Legal classification confirmed: Irreversible effects on the eye category 1, H318: Causes serious eye damage
Sensitisation	Skin guinea pig	Skin sensitizer (TL11 1983, unpublished report; TL12 1989, unpublished report; TL13 1989, unpublished report; TL14 2009, unpublished report)	Classification proposal for sub-category: Skin sensitizer sub-category 1B, H317: May cause an allergic skin reaction
Repeated dose toxicity	Oral rat, rabbit, mouse	Targets: haematological system (rat, rabbit, mouse); transient neurobehavioral changes (rat, rabbit); degenerative effects on the nasal olfactory epithelium (rat, mouse); hyperplasia of the urinary bladder transitional epithelium (mouse)	No classification (legal classification) Borderline case for classification for target organ toxicity (haematotoxicity) as STOT RE 2 Cut off: ≥100 mg/kg bw/d effects on the haematological system (rat; two-generation toxicity study), not significant toxic effects according CLP Regulation (oral, rat: 10 < C ≤ 100 mg/kg bw/d)
Repeated dose toxicity	Inhalation rat, mouse	Targets: haematological system (rat, mouse); liver effects (rat, mouse); degenerative effects on the nasal olfactory epithelium (rat, mouse)	No classification (legal classification) Borderline case for classification for target organ toxicity (haematotoxicity) as STOT RE 2 374 ppm (1.346 mg/L/6h/d; rat; combined chronic toxicity/carcinogenicity study), above the cut-off concentration for classification according the CLP Regulation: inhalation, vapour, rat: 0.2 < C ≤ 1.0 mg/L/6h/d)
Mutagenicity	Other: in vitro, in vivo	Negative in standard mutagenicity/genotoxicity tests	No classification (legal classification) Negative in mutagenicity and genotoxicity studies in vitro and in vivo
Carcinogenicity	Inhalation rat, mouse	LOAEC = 15 ppm (54 mg/m^3) for liver tumour development (TL9 1993, 1994, unpublished reports; Newton et al. 2001)	Classification proposal as: category 1B carcinogen, H350: May cause cancer (legal classification: carcinogen category 2, H351) liver tumours (adenomas and carcinomas) in rats and mice at all tested exposure

			concentrations; statistically significant increases in incidence at the both highest concentrations for liver adenomas in male rats and at the highest concentration for liver carcinomas in male rats and mice; increased incidence of liver adenomas occurred also in female rats and mice at the both highest concentrations, but was not statistically significant; statistically significant increased incidence of mammary gland fibroadenomas in male rats at the highest concentration
Reproductive toxicity: fertility impairment	Oral rat	NOAEL = 200 mg/kg bw/d for reproductive toxicity (TL15 1992, unpublished report; Tyl et al. 1996) LOAEL ≥ 10 mg/kg bw/d for parental toxicity (TL15 1992, unpublished report; Tyl et al. 1996)	No classification (legal classification) two-generation toxicity study: No evidence of reproductive organ or mammary gland pathology or of reproductive or postnatal toxicity up to the highest dose tested Parental toxicity (F0+F1 males and females adults) at all doses tested (toxicity to the haemotopoietic system)
Reproductive toxicity: developmental toxicity	Oral rat, rabbit	NOAEL (rat) = 600 mg/kg bw/d (TL1 1990a, unpublished report; Derelanko et al. 2003) NOAEL (rabbit) = 24 mg/kg bw/d (TL1 1990b, unpublished report; Derelanko et al. 2003)	No classification (legal classification) Rat: no developmental toxicity; maternal toxicity: LOAEL = 10 mg/kg bw/d (effects on the blood) Rabbit: 40 mg/kg bw/d: excessive mortality and abortions in 3/10 adult pregnant rabbits; maternal toxicity: LOAEL = 10 mg/kg bw/d (effects on the blood)
Neurotoxicity	Oral, inhalation, dermal rat, rabbit	Single exposure: LOEL (oral, rat) = 300 mg/kg bw (Schulze and Derelanko 1993); LOAEC (inhalation, rat) = 4.8 mg/m^3 (TL2 1984a, unpublished report) LOEL (dermal, rabbit) = 18 mg/kg bw (TL2 1984b, unpublished report) Repeated exposure: NOAEL (oral, rat) = 125 mg/kg bw/d (Schulze and Derelanko 1993; TL21 (1991), unpublished report)	Classification proposal: STOT SE 3, H336: May cause drowsiness or dizziness (Annex I, Part 3.8.2.2.2) Neurological effects occurred after single and repeated exposure; transient and reversible changes in neurobehavioral function consistent with CNS depression, but without evidence of cumulative neurotoxicity; such changes were observed in rats and rabbits immediately after application of butanone oxime by the oral, inhalation and dermal route of exposure.

6 HUMAN HEALTH HAZARD ASSESSMENT OF PHYSICO CHEMICAL PROPERTIES

Not evaluated.

7 ENVIRONMENTAL HAZARD ASSESSMENT

Not evaluated.

8 PBT AND VPVB ASSESSMENT

Not evaluated.

9 EXPOSURE ASSESSMENT

9.1 Human Health

9.1.1 Exposure assessment for worker

Butanone oxime is used primarily as an anti-skinning agent in liquid coating materials containing drying oils and fatty acid derivatives such as alkyd paints, varnishes or primers (Danish Environmental Protection Agency, 2003; Government of Canada, 2010; U.S.Department of Health and Human Services, 1999).

Butanone oxime is also used in the production of oxime silanes as well as blocked diisocyanates. Oxime silanes are used as a curing agent (crosslinker) in silicone sealant formulations. During the curing process in the presence of atmospheric moisture the oxime is released and evaporates. In the case of isocyanates typically diisocyanates are reversibly blocked by reaction with butanone oxime from polymerisation. Exposure to butanone oxime released during curing and hardening from oxime silanes or blocked diisocyanates is not covered by the registration dossiers.

The use of butanone oxime as an intermediate for the synthesis of silanes is registered. According to the registration dossier butanone oxime fulfils the criteria as a transported isolated intermediate under strictly controlled conditions for the complete process. Therefore no exposure to butanone oxime was assessed for the synthesis of oxime silanes.

9.1.1.1 Overview of uses and exposure scenarios

According to the registration dossiers following uses were identified:

- Manufacture
- Intermediate use of butanone oxime
- Intermediate for the synthesis of butanone oxime-silanes
- Formulation of liquid paints containing butanone oxime
- Manufacturing liquid paints containing butanone oxime
- Industrial application of coatings containing butanone oxime

- Industrial application of paints containing butanone oxime
- Professional application of coatings containing butanone oxime
- Professional application of paints containing butanone oxime

9.1.1.2 Scope and type of exposure

Manufacture of butanone oxime is within the scope of the registered uses. However, after consultations with the registrants no manufacturing is taking place in the EU but all of the quantities used are imported. In addition, the manufacturing process would take place at industrial sites where high levels of risk management can be expected and exposure can be expected to be adequately controlled. Therefore the exposure scenarios for manufacturing are not taken into account for this substance evaluation under REACH.

As mentioned above the most prevalent use of butanone oxime is as an additive (anti skinning agent) in alkyd paints and liquid coating materials containing drying oils and fatty acid derivatives. There is wide dispersive use of such materials both in industrial and professional applications and a large number of employees with occupational exposure on a regular basis can be assumed in the EU.

9.1.1.2.1 Monitoring data

The eMSCA is aware of just one evaluation report on occupational exposure to butanone oxime in Germany (IFA, 2012). The study is provided by the Institute for Occupational Safety and Health of the German Social Accident Insurance (IFA). The measured data for workplace exposure in Germany were collected over the period 1998-2011 and documented in accordance with the measurement system of the German Social Accident Insurance Institutions for exposure assessment (MGU).

86% of the measurements are representative for exposure times equal to or over 6 hours and the samplings were taken in 35 branches of industry and 74 work areas. The data are therefore highly representative and highly valid for the situation in Germany and deemed to be equally representative for similar work areas in the EU.

Table 33 provides an overview of the measured values while tables 36 and 37 summarize the statistic evaluations for industry groups and for work area groups respectively.

Table 33**:** Overview of the measured values collected in the MGU, data period 1998 to 2011 (IFA, 2012).

General description	Number of measured values (%)
Total	289
Type of sampling: Stationary Personal	 147 (51%) 142 (49%)
Number of data < quantification limit	167 (58%)
Sampling representative for: Exposure time ≥ 6 h Exposure time < 6 h	 248 (86%) 35 (12%)
Examples: Exposure conditions	
Measurement plan: Workplace measurements Interior measurements	 250 (87%) 39 (13%)
Reason for measurement: investigation in case of suspected occupational disease	11 (4%)
Without mechanical ventilation With mechanical ventilation No details	88 (30%) 167 (58%) 34 (12%)
Without local exhaust ventilation With local exhaust ventilation No details	102 (35%) 122 (42%) 56 (19%)

General description of measurements of butanone oxime in: 35 branches of industry and 74 work areas

The criteria for inclusion of measured data in the evaluation are:

- Data period 1998 to 2011
- Standard method in the MGU
- Sampling is representative for exposure duration.
- Exposure duration ≥ 6 hours or < 6 hours
- If any single value fell below the measurement method´s analytical quantification limit (a. q.), half of each value was adopted in the evaluation
- Data sets comprising fewer than ten measured data were disregarded.
- The evaluation is performed according to industry groups and work area groups
- Owing to the small number of measured values available, a distinction is made between
    - Stationary measurements and personal measurements, and
    - Measured values with or without local exhaust ventilation for all data

The following abbreviations and indices are used in the evaluation tables:

Frequency < values	Number of measured values below the analytical quantification limit
a. q.	Analytical quantification limit (limit of quantification)
*	If any single value fell below the measurement methods analytical quantification limit (a. q.), half of each value was adopted in the evaluation.
+	The distribution value is below the largest analytical quantification limit (a. q.) in the data set. The quantification limit may deviate from the quantification limit quote in the introduction, e.g. depending on sampling duration or flow rate.
!	The number of measured values below the analytical quantification limit (a. q.) is greater than the number of measured values represented by this cumulative frequency value. No concentration is therefore given for this cumulative frequency value.
$	With reference to the given limit value, the percentage of values below the limit value is given.

Table 34 provides the statistic evaluation differentiated according to the industry groups regarded.

Table 34: Statistic evaluation differentiated according to the industry groups: sampling representative for exposure time ≥ 6 h (IFA, 2012).

Designation Branch of industry	Number of measured data	Number of firms	Frequency < (number of values %)	Largest quantification limit in mg/m³	Concentrations in mg/m³		
					50 per-centile	90 per-centile	95 per-centile
Designation	248	113	143 (57.7)	4	! a.q.	+ 2	+ 3.2
Manufacture and processing of coating materials	43	28	29 (67.4)	4	! a.q.	+ 3	4.46
Chemical and plastics industry	12	7	8 (66.7)	0.4	! a.q.	1.24	2.18
Electrical engineering and fine mechanics	58	35	37 (63.8)	0.6	! a.q.	0.72	0.91
Processing of metals and mechanical engineering	69	27	42 (60.9)	1.6	! a.q.	1.64	3.275
Interior work, parquet laying (wood floors)	13	6	5 (38.5)	0.7	+ 0.6	4.12	5.44
# Schools and administration	39	3	14 (35.9)	0.4	+ 0.4	# 1.47	# 3.105
Other branches of industry	14	6	8 (57.1)	0.5	! a.q.	3.8	5.3

Measured values above the quantification limit were encountered in classrooms and teachers' staff rooms in which sealing work had previously been undertaken on the windows. A month after the first measurements, the measured values were back below the quantification limit.

Table 35 provides the statistic evaluation according to the different work area groups.

Table 35: Statistic evaluation according to the different work area groups: sampling representative for exposure time ≥ 6h (IFA, 2012).

D.No = Data set number/ Designation	Number of measured Data	Number of firms	Frequency < (number of values %)	Largest quantification limit in mg/m³	Concentrations in mg/m³		
					50 per-centile	90 per-centile	95 per-centile
No limitation	248	113	143 (57.7)	4	! a.q.	+ 2	+ 3.2
Gluing	18	7	8 (44.4)	0.4	+ 0.4	1	1.2
Surface coating, general	28	20	21 (75)	0.4	! a.q.	0.98	2.62
Brushing/ Rolling	26	17	13 (50)	4	+ 0.5	+ 3.8	5
Spraying/Painting	51	35	40 (78.4)	1.6	! a.q.	+ 0.8	+ 1.135
Immersion/Flow coating	34	15	20 (58.8)	0.5	! a.q.	1.06	1.29
# Classroom/Office	31	3	11 (35.5)	0.4	+ 0.35	# 1.07	# 1.66
Work area, miscellaneous	60	32	30 (50)	0.7	+ 0.3	3.5	4.7

Measured values above the quantification limit were encountered in classrooms and teachers' staff rooms in which sealing work had previously been undertaken on the windows. A month after the first measurements, the measured values were back below the quantification limit.

9.1.1.2.2 Modelled data

Exposure assessments in the CSRs include five exposure scenarios (ES) out of which four are related to worker exposure and one is related to consumer use.

Table 36: Overview of worker related exposure scenarios according to CSR

ES number	Exposure scenario name
1	Intermediate use of MEKO
2	Formulation of liquid paints containing MEKO
3	Industrial application of paints containing MEKO
4	Professional application of paints containing MEKO

According to the CSR the worker exposure estimates have been assessed using ECETOC TRAv2 with some modifications. The modifications include:

- Adjusted efficacy values for gloves as adopted by CEFIC.
- Linear correction for concentration of the substance (0.8%) instead of the broad default TRA categories.

Use of drum pumps results in an 80% lower exposure, as adopted by CEFIC.

A linear exposure modifying factor of 0.008 (0.8%) was applied to ECETOC TRA v2 for all contributing scenarios where butanone oxime is used as part of a formulation/paint by the registrant. (This factor is applied for all CS in ES 3: Industrial applications of paints containing MEKO and ES 4: Professional application of paints containing MEKO).

In the opinion of the eMSCA a "linear correction" is not applicable within the ECETOC TRA model for inhalation exposure. ECETOC TRA explicitly does not take into account the amount of product used for the exposure estimation. In ECETOC Technical Report No. 93 (European Centre for Ecotoxicology and Toxicology of Chemicals, 2004) (page 19) is stated: "The prime determinant of what a population's exposure to a chemical is likely to be is not where a substance is used but how it is used". Instead of including the amount directly in the model ECETOC TRA v2 applies modifiers (1; 0.6; 0.2; 0.1) which are linked to concentration bands (>25%; 5-25%; 1-5%; <1%). (A

rationale is given in Section 2.1.6 (and Appendix D-2) of ECETOC Technical Report No. 107 (European Centre for Ecotoxicology and Toxicology of Chemicals, 2009). The correct modifier in ECETOC TRA for concentrations <1% therefore is 0.1 (instead of 0.008).

The eMSCA deems measured data to be more appropriate. Therefore the eMSCA does not provide any modelled inhalation data.

The following table gives an overview of the highest predicted dermal exposure values within each exposure scenario according to the CSR.

Table 37: Overview of highest estimates of dermal exposure in exposure scenarios 1-4 (according to CSR)

ES number	Highest predicted dermal exposure
1 - Intermediate use of MEKO	0.69 mg/kg bw/d
2 - Formulation of liquid paints containing MEKO	0.69 mg/kg bw/d
3 - Industrial application of paints containing MEKO	0.34 mg/kg bw/d
4 - Professional application of paints containing MEKO	0.86 mg/kg bw/d

9.1.1.2.3 Comparison of monitoring and modelled data

Comparison of the monitoring data with modelled estimates is not trivial since the measured data are not evaluated and presented within the REACH use descriptor system. Assignment of CS (i. e. PROCs) to work area groups is not always possible or clear. (Apparently assignment of industry groups to PROCs would be highly speculative for industry groups are represented by SU descriptors). The eMSCA deems valid measured data to be more appropriate than modelled data.

The following charts show the 95th, the 90th and 50th percentile of measured exposures to butanone oxime assigned to either industry groups or work area groups according to the data evaluated by IFA (2012).

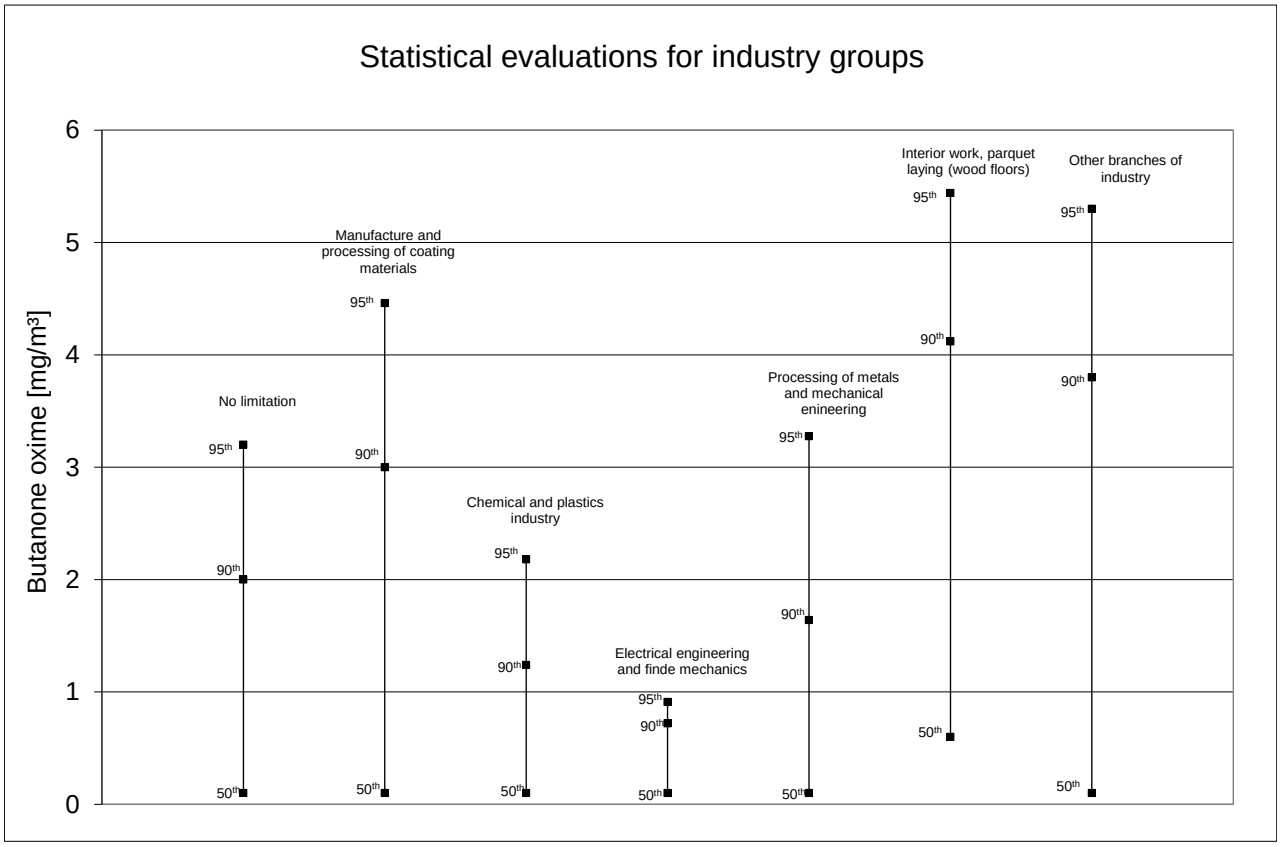


Chart 1: Statistical evaluations for industry groups according to IFA (2012).

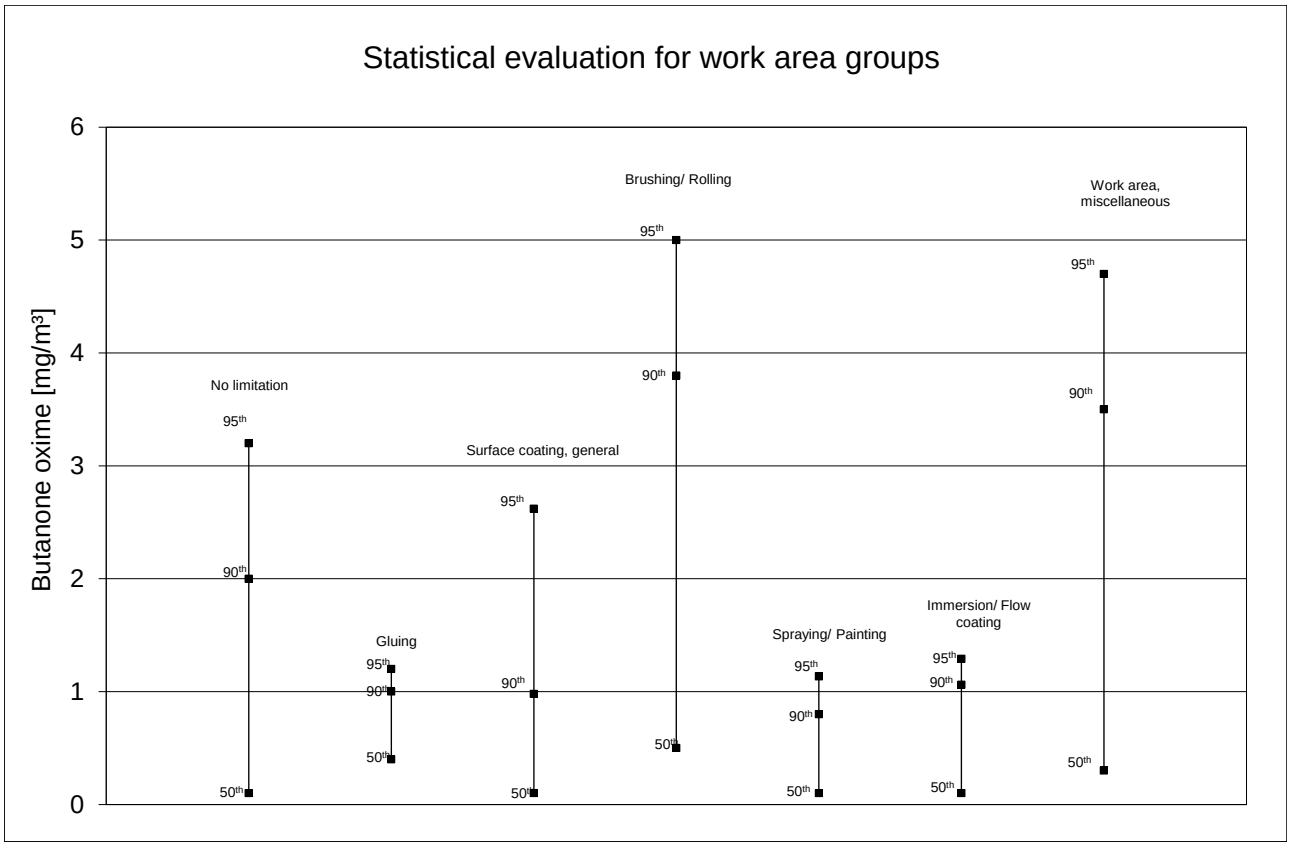


Chart 2: Statistical evaluation for work area groups according to IFA (2012).

In the case of the statistical evaluation of industry groups the data suggest that for all industry groups but 'electrical engineering and fine mechanics' exposure levels above 2 mg/m³ were regularly reached in the time frame of the evaluation (1998-2011). Two of the industry groups stand out with particularly high exposure levels. This is in one case 'manufacture and processing of coating materials' which can be assigned to exposure scenario 2 presented in the CSR. The 90th and 95th percentiles of the measured exposures are 3 and 4.46 mg/m³ respectively in this case. In the case of the industry group 'interior work, parquet laying' even higher exposures were measured with 4.12 and 5.44 mg/m³ for the 90th and the 95th percentile respectively. The industry group 'interior work, parquet laying' is best compared with ES 4 - Professional application of paints containing MEKO. When looking at the statistical evaluation for work area groups the outstanding group is 'brushing/rolling' with the highest exposure. 'Brushing/rolling' is clearly best described by PROC 10. The actual measured data are for the 90th percentile 3.8 mg/m³ and 5 mg/m³ for the 95th percentile.

9.1.2 Exposure assessment for consumers

9.1.2.1 Overview of uses and exposure scenarios

According to the CSRs, butanone oxime is used in consumer application of coatings. There are no consumer uses advised against. The corresponding use descriptors in the CSRs are:

Product category:	PC 9a Coatings and paints, thinners, paint removers
Environmental release categories:	ERC 8a: Wide dispersive indoor use of processing aids in open systems,
	ERC 8d: Wide dispersive outdoor use of processing aids in open systems,
	Other: CEPE SPERC 11 and 13

Subsequent service life relevant for that use: No.

In order to identify possible consumer uses of butanone oxime not described in the CSRs the following literature, websites and databases have been searched in addition to a general internet search:

Table 38: Websites and databases

Hazardous Substances Data Bank (HSDB)	http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB
RÖMPP Online	http://www.roempp.com/prod/
National Toxicology Programm	http://ntpsearch.niehs.nih.gov/index.html?col=010stat
Spin - Substances in Products in Nordic Countries	http://90.184.2.100/DotNetNuke/default.aspx
Danish Environmental Protection Agency - Danish surveys on chemicals in consumer products	http://www.mst.dk/English/Chemicals/consumers_consumer_products/danish_surveys_consumer_products/
OECD-SIDS Initial Assessment Report	http://webnet.oecd.org/hpv/ui/Search.aspx
WHO-Concise International Chemical Assessment Document (CICAD)	http://www.who.int/ipcs/publications/cicad/cicads_alphabetical/en/index.html
ATSDR – Toxicological Proflile	http://www.atsdr.cdc.gov/toxprofiles/index.asp
WHO-International Programme on Chemical Safety (IPCS)	http://www.who.int/ipcs/en/
CDC Centers for Disease Control and Prevention	http://www.cdc.gov/exposurereport/
Danish Environmental Protection Agency	http://www.mst.dk/English/
Kemi – Swedish Chemicals Agency	http://www.kemi.se/en/
Environment Canada: Management of Toxic Substances	https://www.ec.gc.ca/toxiques-toxics/default.asp?lang=En&n=6B9B6B28-1
Scorecard	http://scorecard.goodguide.com/chemical-profiles/
RIVM - National Institute for Public Health and the Environment	http://www.rivm.nl/English

In addition, the product registers from Germany, Slovenia and Switzerland were asked for information on butanone oxime in registered products.

Some non-professional products with butanone oxime registered in the German and the Slovenia product registers were construction products, adhesives and sealants with a maximum content of

5 % butanone oxime. However, none of the registration dossiers supported use of butanone oxime in adhesives and sealants. Therefore, the lead registrant was asked by the eMSCA whether use of butanone oxime in products like filling materials or sealants is supported by the registration. The lead registrant limited his answer to his own registration and confirmed that it was the intention to only register the use of butanone oxime as an anti-skinning agent in solvent-borne paints and as an intermediate. One of these intermediate uses would be use of butanone oxime as endcapping agent in the production of for instance "Butan-2-one O,O',O''- (methylsilylidyne) trioxime" or "Methyl Oximo Silane" (MOS), a silane used as a crosslinking agent in first generation oxime silicone sealants. Small quantities of free butanone oxime would be found as impurity in the final silane material (typically < 1 %). The lead registrant also referred to the similar "intermediate use" in endcapped isocyanates for use in the polyurethane industry. Both product lines, silicones and polyurethanes, could end up in adhesives and glues.

This is in line with the main uses described in a Product Stewardship Summary found in the Internet (Honeywell 2007), according to which butanone oxime "*is used as an anti-skinning agent in paints and lacquers, as a blocking-agent for isocyanate in polyurethanes, and in the manufacture of oxime silanes (that are used as crosslinkers for silicone sealants)*".

According to product information found in the Internet, butanone oxime can be released from neutral moisture curing silicone sealants as a cleavage product from the oxime silane based crosslinkers (Evonic Industries 2013; Henkel Corporation 2012). There have been reports on complaints of the general public after butanone oxime releases from silicone sealants in a public school (Landesgesundheitsamt 2004).

Exposures of the general public that may result as an indirect consequence from intermediate uses of butanone oxime are not covered by the registrations. The eMSCA decided to limit the scope of this consumer exposure evaluation to exposure to butanone oxime from its registered consumer uses. Health risks for the general population from release of butanone oxime upon curing of silicone sealants or polyurethanes are not covered by this substance evaluation.

9.1.2.2 Scope and type of exposure

For the registered consumer uses of butanone oxime in paints and coatings, oral exposure is not considered relevant. Accidental consumer exposure is not covered by this substance evaluation. It is supposed that consumer coatings are not used by small children. Adult exposure from hand to mouth contact with paints cannot be excluded, but it is supposed to be insignificant compared to exposures by the dermal and the inhalation route.

Short-term/ acute exposure

Butanone oxime is classified for acute dermal toxicity (Acute Tox. 4; H312: Harmful in contact with skin). In the CSRs, dermal exposure is expressed as amount (per kg bw) per day. The registrants stated that acute dermal exposure (peaks; in mg/kg bw/day) would not be higher than a calculated total exposure per day (chronic; in mg/kg bw/day). This argument is accepted by the eMSCA.

The registrants did not estimate short-term inhalation exposure nor did they derive DNECs for short-term local and systemic effects by inhalation. However, in the view of the eMSCA, short-term effects by inhalation cannot be excluded. Therefore mean event concentrations (in mg/m³) have been calculated for all contributing exposure scenarios by the eMSCA.

Long term exposure
Long-term dermal exposure was calculated as the amount (per kg bw) per day for the day of exposure by both, registrants and eMSCA. In addition, the eMSCA calculated the dermal load (in mg/cm²) on the day of exposure. Long-term inhalation exposure was calculated as the mean concentration on the day of exposure (in mg/m³) by both, registrants and eMSCA.

9.1.2.2.1 Monitoring data

The following information is taken from the Canadian Screening Assessment report (Environment Canada, Health Canada 2010, citing Environment Canada 2009): *"A limited unpublished study measured butanone oxime concentrations of up to 9.9 ppm (30 mg/m³) during a simulation using an indoor painting scenario with an alkyd paint containing approximately 0.2 % butanome oxime."*

Chang et al. (1998) conducted small environmental chamber tests on the emissions of butanone-oxime from three different alkyd paints. "*It was found that MEKO emissions occurred almost immediately after each alkyd paint was applied to a pine board. Due to the fast emission pattern, more than 90 % of the MEKO emitted was released within 10 hours after painting. The peak concentrations of MEKO in chamber air correlated well with the MEKO content in the paint. Material balance showed that good recovery (more than 68 %) was achieved between the MEKO applied with the paint and the MEKO emitted. The chamber data were simulated by a first order decay emission model assuming the MEKO emissions were mostly gas-phase mass transfer controlled. The model was used to predict indoor MEKO concentrations during and after painting in a test house. It was found that the predicted test house MEKO concentrations during and after the painting exceeded a suggested indoor exposure limit of 0.1 mg/m^3 for all three paints. The predicted MEKO concentrations exceeded even the lower limit of a suggested sensory irritation range of 4 to 18 mg/m^3 with two of the three paints tested.* "

It should be noted that the maximum concentration of butanone oxime determined in the tested paints was 0.293 %, while the concentrations in paints reported in the CSRs range up to 1 %.

There is no monitoring information on indoor air concentrations during mixing and loading operations of consumer paints and coatings containing butanone oxime.

Analyses of volatile organic compounds in indoor air performed by 19 institutes of the Association of Ecological Research Institutes (AGÖF) in the years 2002 to 2006 have been sampled in a common database (Hofmann and Plieninger 2008). The samples were taken from office and private buildings in Germany and Austria. Butanone oxime was determined in 18 from 130 analyses. The 50th percentile was below the determination limit of about 1 µg/m³, and the 90th percentile was 3.6 µg/m³. These data are in line with the assumption that butanone oxime emissions from indoor sources decline quickly and do not produce prolonged contaminations of indoor air.

9.1.2.2.2 Modelled data

All contributing scenarios from the existing CSR versions have been compiled and recalculated in this substance evaluation.

Consumer exposure estimations have been performed with ConsExpo 4.1 by both, registrants and eMSCA. Several registrants used the ECETOC (v2) worker model to calculate exposure from yacht paint and spray uses. This model is not accepted for consumer exposure estimations by the eMSCA (see there).

The following product types and contributing scenarios have been considered in the exposure assessments:

High solid paint:	Mixing and loading of two component high solid paint
	Brushing or roller painting of high solid paint
Waterborne wall paint:	Mixing and loading of two component waterborne wall paint
	Brushing or roller painting of waterborne wall paint
Waterborne paint:	Brushing or roller painting of waterborne paint
Spray Products:	Spraying paint with a spray can
	Pneumatic spraying
General coating (floor):	Mixing and loading of general coating (floor)
	Application of general coating (floor)
Artist paint:	Brushing or roller painting of artist paint
Paint paste tube:	Mixing and loading of a paint paste tube
Yacht paint:	Mixing and loading yacht paint
	Yacht painting indoor
	Yacht painting outdoor

In the Confidential Annex I, details on the consumer exposure calculations by the registrants taken from the CSRs are given. The ConsExpo Reports of the consumer exposure calculations by the eMSCA are documented in the Confidential Annex II.

In the following, some problems found in the registrants´ consumer exposure assessments are discussed on a general level:

Exposure models used in the Consumer exposure assessments for yacht paints and for spray uses

In several CSRs estimations of consumer exposure from use of butanone oxime in spray cans and from use of butanone oxime by brushing and rolling of yacht paints have been performed with the ECETOC TRA Worker Tool v.2. This was justified by the assumption of a "semiprofessional use". However, there is no "semiprofessional use" under the REACH Regulation. The exposure predictions of the ECETOC TRA Worker Tool v.2 (ECETOC 2004 and 2009) are based on a modified EASE model. The EASE model categorises occupational exposure with reference to historical data collected in the UK's National Exposure Database (NEDB) (Health and Safety Executive 2003) and was developed to predict workplace exposure to chemical substances. The underlying data thus are occupational exposure measurements supported by occupational hygiene experts' judgement. Any validation of the resulting exposure estimates (ranges in the original model) was performed by comparison to occupational exposure data (Tickner et al. 2005) and experts' experience using the model in the industry. All modifications to EASE predictions by the ECETOC model and the adaptations of the original use scenarios to the REACH process categories (PROC'S) were performed to represent workplace situations. Moreover the PROC'S are

representations of techniques and processes categorized *inter alia* upon "… the principal level of containment and engineering controls to be expected" (ECHA 2010, Use descriptor system). Containment levels, engineering controls and operational conditions (e.g. average room size, industrial hygiene) resulting in specific, empirical data on exposure levels at the workplace are not representative for conditions under which consumers would generally use a substance/mixture. Based on these considerations the model used to predict exposure for use of butanone oxime in spray cans and yacht paints is not suitable to give realistic or sufficiently conservative estimates for consumer uses and exposure may be underestimated.

In some CSRs consumer exposure estimations for spray uses of butanone oxime were based on spray use scenarios provided in the RIVM Paint Products Fact Sheet (Bremmer et al. 2007). However, according to this Fact Sheet, the "*ConsExpo spray model is developed on the basis of the results of experimental work and describes the indoor inhalation exposure to slightly evaporating or non-volatile compounds in droplets that are released from a spray can or pump spray (Delmaar et al. 2005 and 2009). For volatile compounds, the evaporation model is more appropriate. If the spray model is used for volatile compounds, inhalation exposure will be underestimated, because exposure to vapour is not considered in the spray model. 'Volatile' is defined as compounds with vapour pressure > 0.1 Pa, 'non-volatile' < 0.01 Pa and 'slightly volatile' between 0.01 and 0.1 Pa.*"

Butanone oxime has to be regarded as a volatile substance. Therefore consumer exposure to butanone oxime from spray uses is underestimated with the ConsExpo spray model.

For the exposure calculations of the spray use scenarios by the eMSCA, the general assumptions were taken from the spray can paint scenario in the RIVM Paints Product Fact Sheet, but the model used for the calculation was the ConsExpo 4.1 evaporation model. For indoor painting of yacht paints, it was assumed that a surface of a little boat was painted in a garage. Details are documented in the respective ConsExpo reports in Confidential Annex II.

Use of personal protection

In some CSRs, the registrants have assumed the use of gloves in the exposure estimation for consumer use of butanone oxime in yacht paints. However, the ECHA Guidance Chapter R.15 v.2.1 (ECHA 2012) states:

"There are limited circumstances for consideration of personal protective equipment (PPE) in consumer exposure, because people will not necessarily use PPE even though recommended by the manufacturer. Even when PPE is provided with the product (e.g., gloves with a hair dye), it cannot be ensured that consumers will use it. The exposure estimation needs to consider the reasonable worst-case situation which indicates no use of gloves or other PPE."

Assuming the use of gloves is expected to underestimate real life consumer exposure.

In the consumer exposure calculations by the eMSCA, no use of personal protection was assumed.

Input parameters based on consumer behavior

Most scenarios of the CSRs rely on the respective scenarios in correspondent RIVM Fact Sheets. However, in contrast to the standard assumptions in these Fact Sheets, open windows and higher ventilation rates were assumed in several exposure calculations, and the advice "*Do not use when windows closed*" has been

introduced in the correspondent scenarios as a risk management measure. In one scenario of some CSRs, also the advice "*Avoid using in room with closed doors*" has been introduced.

However, the ECHA Guidance R.15 v.2.1 states (ECHA 2012b):

"*Effective risk management measures for consumers are usually product-integrated measures (see Chapter R.13). For quantitative exposure estimation, only those RMMs which can be controlled by the manufacturer of the product should be applied. This means that RMMs may be implemented by changing operational conditions or product composition, e.g.: maximum concentration used in the product, change of the product form (pellets or granules instead of powder) or maximum amount of product used (package size). The use of consumer instructions as RMMs cannot be expected to be highly effective, unless consumer behavioural data provide evidence that a sufficient degree of compliance can be assumed. The adherence to instructions is fundamentally different for consumers by comparison to that in occupational settings where the employer has the duty to ensure good operational conditions and use of RMMs. Consumer RMMs based on instructions should be introduced only when the use of such RMMs can be shown to be effective and be well adhered to by consumers.*"

Also, in several scenarios the amount of product, the application time and the release area have been reduced in comparison to the correspondent RIVM Fact Sheets. In some CSRs, the parameters were changed without communicating a specific RMM. In other CSRs, the advice "*For each use, avoid using for more than 1 hour*" has been introduced in the correspondent scenarios as a RMM.

No data have been provided by the registrants that show the advices on application ventilation and application time to be effective and well adhered to by consumers, as required by the REACH Guidance. Thus, these assumptions are expected to lead to an underestimation of the reasonably foreseeable consumer exposure.

Therefore, the eMSCA has calculated the consumer exposure estimates for all these scenarios using the ConsExpo standard scenarios, the product concentrations of butanone oxime provided in the CSRs and RIVM standard assumptions.

Mass transfer rate

The following explanation is given in the RIVM Paint Products Fact Sheet (Bremmer et al. 2007) for the mass transfer rate, which is used in the evaporation models of ConsExpo 4.1:

"*The mass transfer rate is determined by the rate at which the compound is transported away from the evaporation surface. In general this transport will depend on the rate of diffusion of the compound through air, and the rate of air movement above the product-air surface.*
Langmuir's method effectively assumes that diffusion of the compound is infinitely fast. It will as a rule highly overestimate the evaporation rate and predict higher peak concentrations than the Thibodeaux approximation. Thibodeaux' method is a simple approximation of the ore elaborate Liss-Slater two-layer model, describing the evaporation of a compound from water.

Mass transfer rates calculated using the Thibodeaux' method will be lower than the ones calculated by Langmuir's method, but it should be remembered that this method is only an approximation of a specific system (evaporation of a solute from water) and has limited validity outside the domain for which it was derived. Therefore the Langmuir's method is set as default method, except in waterborne systems, then Thibodeaux' method is chosen."

The ConsExpo default mass transfer rates are 4000 m/min for Langmuir´s method and 0.296 m/min for Thibodeaux´ method. Some registrants used a much lower mass transfer rate in all their calculations with the ConsExpo evaporation model. No justification was given for this change,

which may result in an underestimation of exposure. In the calculations by the eMSCA the mass transfer rate defaults were used as proposed in the RIVM Paint Products Fact Sheet.

In the following, the exposure assessments are discussed by product groups. Most registrants adhered to two CSR versions which are called CSR A and CSR B. Results of the exposure estimations are given as rough estimates in order to protect confidential information.

Solvent rich paint

The scenario for brushing or roller painting of solvent rich paint was only provided in CSR A. As no detailed justification was given for several differences of the operational conditions to RIVM standard assumptions, the eMSCA performed a calculation using RIVM standard assumptions. The following table gives a rough overview on the results. Details of the eMSCA calculations are documented in the Confidential Annex II.

Table 39: Exposure estimates for brushing and rolling of solvent rich paint

Author	Product Concen-trations	Other Parameters	Mean Event Concentration	Mean concentration on Day of Exposure	Dermal Load	Dermal External Dose
	%		mg/m³	mg/m³	mg/cm²	mg/kg bw
CSR A	CSR A	CSR A	-	0.1-1	-	0.1-1
eMSCA	CSR A	CSR A	10-100	0.1-1	0.01-0.1	0.1-1
eMSCA	CSR A	RIVM Paint Product Fact Sheet	10-100	0.1-1	0.01-0.1	0.1-1

The following values were calculated by Environment Canada (2010) assuming a concentration of 1 % butanone oxime in solvent rich paint:

Inhalation mean event concentration: 72.7 mg/m^3
Dermal load: 98.1 mg/cm^2
Dermal external dose: 0.508 mg/kg bw

High solid paint

Only CSR B provided a scenario for mixing and loading high solid paint, while both CSR versions provided scenarios for application by brushing and rolling. As no detailed justification was given for several differences of the operational conditions to RIVM standard assumptions, the eMSCA performed calculations using RIVM standard assumptions. The following tables give a rough overview on the results. Details of the eMSCA calculations are documented in the Confidential Annex II.

Table 40: Exposure estimates for mixing and loading of high solid paint

Author	Product Concen-trations	Other Parameters	Mean Event Concentration	Mean concentration on Day of Exposure	Dermal Load	Dermal External Dose
	%		mg/m³	mg/m³	mg/cm²	mg/kg bw
CSR B	CSR B	CSR B	-	0.1-1	-	0.001-0.01
eMSCA	CSR B	CSR B	10-10	0.1-1	0.0001-0.001	0.001-0.01
eMSCA	CSR B	RIVM Fact Sheets	>1000	1-10	0.0001-0.001	0.001-0.01

Table 41: Exposure estimates for brushing and rolling of high solid paint

Author	Product Concen-trations	Other Parameters	Mean Event Concentration	Mean concentration on Day of Exposure	Dermal Load	Dermal External Dose
	%		mg/m³	mg/m³	mg/cm²	mg/kg bw
CSR B	CSR B	CSR B	-	0.1-1	-	0.1-1
eMSCA	CSR B	CSR B	1-10	0.1-1	0.01-0.1	0.1-1
CSR A	CSR A	CSR A	-	1-10	-	0.1-1
eMSCA	CSR A	CSR A	10-100	1-10	0.01-0.1	0.1-1
eMSCA	CSR B	RIVM Fact Sheet	100-1000	10-100	0.01-0.1	0.1-1
eMSCA	CSR A	RIVM Fact Sheets	100-1000	10-100	0.01-0.1	0.1-1

The following values were calculated by Environment Canada (2010) assuming a concentration of 1 % butanone oxime in high solid paint:

Inhalation mean event concentration: 113 mg/m^3
Dermal load: 0.009 81 mg/cm^2
Dermal external dose: 0.508 mg/kg bw

Waterborne wall paint

Only CSR A contained this product group. As no detailed justification was given for several differences of the operational conditions to RIVM standard assumptions, the eMSCA performed calculations using RIVM standard assumptions. The following tables give a rough overview on the results. Details of the eMSCA calculations are documented in the Confidential Annex II.

Table 42: Exposure estimates for mixing and loading of waterborne wall paint

Author	Product Concen-trations	Other Parameters	Mean Event Concentration	Mean concentration on Day of Exposure	Dermal Load	Dermal External Dose
	%		mg/m³	mg/m³	mg/cm²	mg/kg bw
CSR B	CSR B	CSR B	-	0.001-0.01	-	0.001-0.01
eMSCA	CSR B	CSR B	1-10	0.001-0.01	0.0001-0.001	0.001-0.01
eMSCA	CSR B	RIVM Fact Sheets	1-10	0.001-0.01	0.0001-0.001	0.001-0.01

Table 43: Exposure estimates for brushing and rolling of waterborne wall paint

Author	Product Concen-trations	Other Parameters	Mean Event Concentration	Mean concentration on Day of Exposure	Dermal Load	Dermal External Dose
	%		mg/m³	mg/m³	mg/cm²	mg/kg bw
CSR B	CSR B	CSR B	-	1-10	-	-
eMSCA	CSR B	CSR B	10-100	1-10	0.001-0.01	0.1-1
eMSCA	CSR B	RIVM Fact Sheets	10-100	1-10	0.01-0.1	0.1-1

Waterborne paint

Both CSR versions contained this product group. The concentrations given were 0.8 % (older version) and 0.3 % (updated version). While the product amount and the application time were reduced compared to RIVM standards from the RIVM Paint products fact sheet in the old version, this was not the case in the updated version. Instead, the mass transfer rate was reduced. As no detailed justification was given for these changes, the eMSCA performed a calculation with RIVM standard assumptions. The following table gives an overview on the results. Details of the eMSCA calculations are documented in the Confidential Annex II.

Table 44: Exposure estimates for brushing and rolling of waterborne paint

Author	Product Concen-trations	Other Parameters	Mean Event Concentration	Mean concentration on Day of Exposure	Dermal Load	Dermal External Dose
	%		mg/m³	mg/m³	mg/cm²	mg/kg bw
member CSR	0.8	member CSR	-	0.983	-	0.222
eMSCA	0.8	member CSR	21.5	0.984	0.0167	0.24
Lead CSR	0.3	Lead CSR	-	1.35	-	0.18
eMSCA	0.3	Lead CSR	14.7	1.35	0.0126	0.18
eMSCA	0.8	RIVM Fact Sheet	67	6.14	0.0335	0.48
eMSCA	0.3	RIVM Fact Sheets	25.1	2.3	0.0126	0.18

Spray paint

Both CSR versions contained this product group but only CSR B included pneumatic spraying. In the CSR A, the ECETOC worker TRA was used to calculate consumer exposure to butanone oxime from spray uses. In CSR B the ConsExpo Spray model was used for this purpose. Both models were not considered suitable by the eMSCA for the reasons explained above.

Therefore, the eMSCA constructed another ConsExpo model for spray paints. The general assumptions were taken from the spray paint scenarios in the RIVM Paint products fact sheet. For spraying with a spray can it was assumed that a radiator is painted in a garage using 300 g paint. For pneumatic spraying it was assumed that two radiators were sprayed in a garage using 400 g paint. However, due to the volatility of butanone oxime, the model used for the calculation was the ConsExpo 4.1 evaporation model. The follwing tables give an overview on the results. The dermal load is not given here because the contaminated dermal area cannot be specified. Details of the eMSCA calculations are documented in the Confidential Annex II.

Table 45: Exposure estimates for spraying paint with a can

Author	Product Concen-trations	Other Parameters	Mean Event Concentration	Mean concentration on Day of Exposure	Dermal External Dose
	%		mg/m³	mg/m³	mg/kg bw
CSR B	CSR B	CSR B	-	0.01-0.1	0.1-1
CSR A	CSR A	CSR A	0.1-1	-	0.1-1
eMSCA	CSR B	adapted from RIVM Fact Sheets	10-100	0.1-1	0.1-1
eMSCA	CSR A	adapted from RIVM Fact Sheets	10-100	0.1-1	0.01-0.1

Table 46: Exposure estimates for pneumatic spraying

Author	Product Concen-trations	Other Parameters	Mean Event Concentration	Mean concentration on Day of Exposure	Dermal External Dose
	%		mg/m³	mg/m³	mg/kg bw
CSR B	CSR B	CSR B	-	0.001-0.01	0.1-1
eMSCA	CSR B	adapted from RIVM Fact Sheets	10-100	0.1-1	0.1-1
eMSCA	CSR B	adapted from RIVM Fact Sheets	10-100	0.1-1	0.01-0.1

General coating (floor)

Both CSR versions contained this product group. In the CSR B, a correspondent mixing and loading scenario was included, but not in CSR A. As no detailed justification was given for several differences of the operational conditions to RIVM standard assumptions, the eMSCA performed calculations using RIVM standard assumptions (ter Burg et al. 2007). The following tables give a rough overview on the results. Details of the eMSCA calculations are documented in the Confidential Annex II.

Table 47: Exposure estimates for mixing and loading of general coating (floor)

Author	Product Concen-trations	Other Parameters	Mean Event Concentration	Mean concentration on Day of Exposure	Dermal Load	Dermal External Dose
	%		mg/m³	mg/m³	mg/cm²	mg/kg bw
CSR B	CSR B	CSR B	-	0.1-1	-	<0.001
eMSCA	CSR B	CSR B	100-1000	0.1-1	E-6 – E-5	E-5 – E-4
eMSCA	CSR A	RIVM Fact Sheets	100-1000	1-10	E-4 – E-3	E-3 – E-2

Table 48: Exposure estimates for application of general coating (floor)

Author	Product Concen-trations	Other Parameters	Mean Event Concentration	Mean concentration on Day of Exposure	Dermal Load	Dermal External Dose
	%		mg/m³	mg/m³	mg/cm²	mg/kg bw
CSR B	CSR B	CSR B	-	1-10	-	0.01-0.1
eMSCA	CSR B l	CSR B	10-100	1-10	0.001-0.01	0.01-0.1
CSR A	CSR A	CSR A	-	1-10	-	0.01-0.1
eMSCA	CSR A	CSR A	10-100	1-10	0.01-0.1	0.01-0.1
eMSCA	CSR B	RIVM Fact Sheet	10-100	1-10	0.001-0.01	0.01-0.1
eMSCA	CSR A	RIVM Fact Sheets	100-1000	1-10	0.01-0.1	0.01.-0.1

The following values were calculated by Environment Canada (2010) assuming a concentration of 1 % butanone oxime in an alkyd coating:

Inhalation mean event concentration: 223 mg/m^3
Dermal load: 0.0231 mg/cm^2
Dermal external dose: 0.0353 mg/kg bw

Artist paint

Brushing or roller painting of artist paint was included in both CSR versions. There is no scenario for artist paint in the RIVM Paint Products Fact Sheet. Details on the exposure scenarios of the registrants are regarded as confidential. The eMSCA used RIVM standard assumptions for room volume, ventilation rate and temperature from the RIVM General fact Sheet in his exposure scenario. The product amount was set at 125 g, the release area was 10000 cm² , the exposure duration was 132 minutes , the application duration was 120 minutes, the mol weight of the matrix was 550 g/mol The mass transfer rate was 4000 m/min. For dermal exposure, the eMSCA used the constant rate model with a contact rate of 30 mg/min and a surface area of 860 cm² for both hands which are RIVM standard assumptions for painting downwards and to the side. The following table gives an overview on the results. Details of the eMSCA calculations are documented in the Confidential Annex II.

Table 49: Exposure estimates for brushing and rolling of artist paint

Author	Product Concen-trations	Other Parameters	Mean Event Concentration	Mean concentration on Day of Exposure	Dermal Load	Dermal External Dose
	%		mg/m³	mg/m³	mg/cm²	mg/kgBW
CSR B	CSR B	CSR B	-	1-10	-	0.1-1
eMSCA	CSR B	CSR B	10-100	1-10	0.1-1	0.1-1
CSR A	CSR A	CSR A	-	0.1-1	-	0.1-1
eMSCA	CSR A	CSR A	1-10	0.1-1	0.01-0.1	0.1-1
eMSCA	CSR B	adapted from RIVM Fact Sheets	10-100	1-10	0.01-0.1	0.1-1
eMSCA	CSR A	adapted from RIVM Fact Sheets	1-10	0.1-1	0.01-0.1	0.1-1

Paint paste tube

A scenario for mixing and loading of a paint paste tube was included in CSR A. Details on the exposure scenario of the registrant are regarded as confidential. In the exposure scenario of the eMSCA, standard assumptions of the RIVM Paint Product Factsheet for mixing and loading two component paints were applied together with an amount of product of 250g. The mole weight of the matrix was set at 550 g/mol, the mass transfer rate was 4000 m/min which is the RIVM standard for all paints except waterbased paints. The following table gives an overview on the results. Details of the eMSCA calculations are documented in the Confidential Annex II.

Table 50: Exposure estimates for mixing and loading a paint paste tube

Author	Product Concen-trations	Other Parameters	Mean Event Concentration	Mean concentration on Day of Exposure	Dermal Load	Dermal External Dose
	%		mg/m³	mg/m³	mg/cm²	mg/kg bw
CSR A	CSR A	CSR A	-	0.01-0.1	-	0.001-0.01
eMSCA	CSR Al	CSR A	10-100	0.01-0.1	0.0001-0.001	0.001-0.01
eMSCA	CSR A	adapted from RIVM Paint Product Fact Sheet	1000-10000	1-10	0.0001-0.001	0.001-0.01

Yacht paint

A ConsExpo scenario for mixing and loading yacht paint was included in CSR A. As no detailed justification was given for several differences of the operational conditions to RIVM standard assumptions, the eMSCA performed a calculation for this scenario based on RIVM standard assumptions.

Exposure from indoor and outdoor yacht painting was assessed in CSR A using the ECETOC worker TRA (v2) and assuming use of personal protection. Neither the model nor the assumption of personal protection is considered suitable for consumer exposure estimations by the eMSCA for the reasons discussed above. Therefore, the eMSCA constructed new ConsExpo scenarios for mixing and loading yacht paint and for indoor yacht painting. It was assumed that a little boat was painted in a garage with a room volume of 34 m³, a ventilation rate of 1.5/h and a temperature of 15 °C (Bremmer et al. 2006; ter Burg et al. 2007). As a suitable surface area to be painted in a garage 10 m² or 100000 cm² were assumed. For painting this area, product amounts between 1000 g and 1300 g are needed depending on the paint type according to the RIVM Paint Products Fact Sheet (Bremmer et al. 2007). The amount of 1300 g for a high solid paint was chosen as a worst case. The concentration of butanone oxime was set at 0.5 % according to the updated CSR. The other defaults were taken from the mixing and loading scenario for two component paints and from the brushing and rolling scenario for high solid paints in the Paint Products Fact Sheet. For the calculation of dermal exposure, 50 % overhead painting was assumed. Thus, the contact rate was calculated as 75 mg/min (mean of the RIVM standard contact rates of 30 mg/min for downward painting and painting directed to the side and 120 mg/min for overhead painting). The following tables give an overview on the results. Details of the eMSCA calculations are documented in the ConfidentialAnnex II.

Table 51: Exposure estimates for mixing and loading yacht paint

Author	Product Concen-trations	Other Parameters	Mean Event Concentration	Mean concentration on Day of Exposure	Dermal Load	Dermal External Dose
	%		mg/m³	mg/m³	mg/cm²	mg/kg bw
CSR A	CSR A	CSR A	-	0.1-1	-	0.001-0.01
eMSCA	CSR A	CSR A	10-100	0.1-1	0.0001-0.001	0.001-0.01
eMSCA	eMSCA	adapted from RIVM Paint Product Fact Sheet	100-1000	0.1-1	0.0001-0.001	0.001-0.01

Table 52: Exposure estimates for brushing and rolling yacht paint indoor

Author	Product Concen-trations	Other Parameters	Mean Event Concentration	Mean concentration on Day of Exposure	Dermal Load	Dermal External Dose
	%		mg/m³	mg/m³	mg/cm²	mg/kg bw
CSR A	CSR A	CSR A	1-10	-	-	0.01-0.1 (with PPE)
eMSCA	CSR A	adapted from RIVM Paint Product Fact Sheet	10-100	1-10	0.01-0.1	0.1-1

The registrants also provided exposure estimates for yacht painting outdoor: 1.044 mg/m³ as mean event concentration and 0.04 mg/kg bw as dermal external dose. However, these estimates are not accepted by the eMSCA because they were derived using the ECETOC worker TRA (v2) and assuming use of gloves. However, neither the REACH Guidance R.15 (ECHA 2012b) nor the ConsExpo tool provides any model for the calculation of inhalation exposure from outdoor uses. According to RIVM, *"weather conditions, highly variable and affecting ventilation rate and temperature, and an infinitely large 'room' volume prevent any sensible estimate of outdoor exposure using ConsExpo"* (ter Burg 2007). Therefore, the eMSCA did not perform a ConsExpo calculation for this scenario.

9.1.2.2.3 Comparison of monitoring and modelled data

No monitoring data have been found on mixing and loading operations with consumer paints and coatings containing butanone oxime. For indoor paint applications, the existing monitoring data on consumer exposure to butanone oxime are too scarce to allow for a thorough comparison. However, the order of magnitude of the mean event concentrations that result from the ConsExpo 4.1 modelling by the eMSCA and by Environment Canada (2010) is supported by the reported monitoring value of 30 mg/m³ (Environment Canada 2010) and by the monitoring based modelling value of more than 18 mg/m³ (Chang et al. 1998).

On the other side, the consumer exposure models and assumptions provided in the CSRs and by RIVM include some uncertainties on processes and conditions. In order to cover a broad range of situations, many of these conditions have been chosen on a conservative level. This may imply some overconservatism in the light of detailed knowledge on use characteristics of the consumer products that are actually on the market. Therefore, the eMSCA does not exclude in general that if

data on products and consumer use habits could be documented in a detailed and transparent way and combined with monitoring studies or refined modelling exercises, further refining of the estimations of consumer exposure to butanone oxime could be performed.

10 RISK CHARACTERISATION

10.1 Human Health

10.1.1 Workers

Quantitative risk characterisation

Exposure to butanone oxime at the workplace is considered safe when the total risk characterisation ratio (RCR) of each contributing scenario within an exposure scenario yields values below 1. A RCR is defined as the ratio of the external exposure concentration of butanone oxime to its relevant DNEL. At the workplace exposure to butanone oxime may occur via inhalation or by dermal contact. Consequently, single RCRs need to be calculated for both exposure routes and subsequently summed up to a total RCR.

In the case of butanone oxime the $DNEL_{worker,\ inhalation,\ long\text{-}term,\ systemic\ effects}$ equivalent to 0.7 mg/m^3 is compared to external air concentration values of the substance to yield RCRs for the inhalation route and long-term exposure. In order to obtain RCRs for long-term exposure via the dermal route the substance-specific $DNEL_{worker,\ dermal,\ long\text{-}term,\ systemic\ effects}$ equivalent to 0.1 mg/kg bw/d is used as reference value. A detailed overview of how the eMSCA derived these two DNELs is given in chapter 5.13.2.

As already presented in chapter 9.1.1.2.1, air monitoring data are available for butanone oxime at the workplace.

Table 53 below gives an overview of the RCRs which are calculated for the 90^{th} and 95^{th} percentile values depending on the branch of industry and work area group, respectively. None of the RCRs yields a value below 1.

Table 53: Overview of the RCRs for air monitoring data of butanone oxime. The air concentration values are taken from IFA (2012) and compared to 0.7 mg/m^3 (= $DNEL_{worker, inhalation, long-term, systemic effects}$ as calculated by the eMSCA). The sampling for the air monitoring data is representative for an exposure time of ≥ 6 hours/day. RCR values are rounded up or down to one decimal.

	Air concentration measured (mg/m³)		**RCR**	
	90th percentile	**95th percentile**	**90th percentile**	**95th percentile**
Branch of industry				
No limitation	2[a]	3.2[a]	2.9	4.6
Manufacture and processing of coating materials	3[a]	4.46	4.3	6.4
Chemical and plastics industry	1.24	2.18	1.8	3.1
Electrical engineering and fine mechanics	0.72	0.91	1.0	1.3
Processing of metals and mechanical engineering	1.64	3.275	2.3	4.7
Interior work, parquet laying (wood floors)	4.12	5.44	5.9	7.8
Schools and administration	1.47[b]	3.105[b]	2.1	4.4
Other branches of industry	3.8	5.3	5.4	7.6
Work area group				
No limitation	2[a]	3.2[a]	2.9	4.6
Gluing	1	1.2	1.4	1.7
Surface coating, general	0.98	2.62	1.4	3.7
Brushing/rolling	3.8[a]	5	5.4	7.1
Spraying/painting	0.8[a]	1.135[a]	1.1	1.6
Immersion/flow coating	1.06	1.29	1.5	1.8
Classroom/office	1.07[b]	1.66[b]	1.5	2.4
Work area, miscellaneous	3.5	4.7	5.0	6.7

[a] The distribution value is below the largest analytical quantification limit in the data set. The quantification limit may deviate from 0.2 mg/m^3 in 40 litres sampling air volume, e.g. depending on sampling duration or flow rate.

[b] Measured values above the quantification limit were encountered in classrooms an teachers' staff rooms in which sealing work had previously been undertaken on the windows. A month after the first measurements, the measured values were back below the quantification limit.

For the purpose of risk characterisation valid monitoring data are considered of higher relevance than modelled data in accordance with REACH Guidance R.14 (ECHA, 2012c). However, the available air monitoring data have some deficiencies. It is not clear at what percentage butanone oxime was contained in the formulations used. This information is crucial because the eMSCA learned during the substance evaluation process that there is (at least in Germany) considerable reduction in the concentration of butanone oxime in nowadays formulations (0.5 – 0.8 %) compared to typical concentrations used some years ago (up to 3 % and above). This development is allegedly ascribed to the national implementation of the EU Decopaint Directive 2004/42/CE (EU, 2004). Consequently, even though the available air monitoring data cover a rather recent collecting period (1998-2011) it cannot be excluded that the data are not representative anymore for current exposure situations at the workplaces. In this respect the eMSCA is informed that a new field campaign is conducted in Germany at present which is supposed to provide more robust air monitoring data of butanone oxime with respect to paints and varnishes containing butanone oxime manufactured and used by now.

The registrants have provided estimated dermal exposure values for butanone oxime at the workplace by applying the ECETOC TRAv2 model with modifications. Based on these modelled data the eMSCA calculated single RCRs for each exposure scenario. For each exposure scenario just the contributing scenario with the highest predicted dermal exposure value was taken into

account. Table 54 shows that based on this tier 1 modelled no safe exposure scenario can be demonstrated: each RCR is above 1.

Table 54: Overview of the RCRs for modelled dermal exposure data of butanone oxime. The modelled exposure data are taken from the registrants' CSR. Only the highest predicted dermal exposure levels per exposure scenario are presented here. The predicted exposure levels are compared to 0.1 mg/kg bw/d (= $DNEL_{worker, dermal, long-term, systemic effects}$ as calculated by the eMSCA).

Exposure scenario	**Highest predicted dermal exposure value (mg/kg bw/d)**	**RCR**
Intermediate use of butanone oxime	0.69	6.9
Formulation of liquid paints containing butanone oxime	0.69	6.9
Industrial application of paints containing butanone oxime	0.34	3.4
Professional application of paints containing butanone oxime	0.86	8.6

For the purpose of risk characterisation single RCRs of each exposure route need to be summed to a total RCR. In this case this is not possible because comparison of the monitoring data with modelled estimates is not trivial since the measured data are not evaluated and presented within the REACH use descriptor system. Assignment of contributing scenarios (i. e. PROCs) to work area groups is not always possible or clear. Apparently assignment of industry groups to PROCs would be highly speculative for industry groups are represented by SU descriptors. However, it is shown that already single RCRs of each exposure route yield values above 1.

Besides as described in chapter 5.13.2 the inhalation and dermal DMELs for workers which are associated with cancer risks of 1:100 000 are significantly lower than the long-term DNELs. DNELs and DMELs differ by a factor of around 25.

As outlined in the hazard assessment of this report, the eMSCA's evaluation leads to the need of an update of the existing harmonised classification and labelling of butanone oxime concerning carcinogenicity. Therefore the eMSCA will await the discussion on classification and the outcome of the current field campaign, before drawing a final conclusion on the risk assessment for workers.

10.1.2 Consumers

According to the information requirements for risk characterisation for human health, a risk characterisation has to be conducted only for those toxicological effects that result in the most critical DNEL (or DMEL) (ECHA 2008).

This SEV is based on the exposure estimates and exposure scenarios reported by the registrants. Butanone oxime is used in consumer application of coatings. The product category PC9a includes coatings and paints, thinners, and paint removers. No consumer uses advised against are available.

In order to identify possible risks the CSRs were checked whether the risk characterisation including recorded RCRs and qualitative descriptions is exhaustive, plausible and well documented regarding consumer exposure scenarios and the DNEL/Cs for all relevant endpoints.

A review of all available data per each toxicity endpoint indicates that the major concerns associated with short-term exposure to butanone oxime are acute oral and dermal toxicity, irreversible effects on the eye, and skin sensitisation. Repeated exposure to butanone oxime induces

effects on the blood and liver, carcinogenicity, and local effects in the respiratory tract. In addition butanone oxime induces narcotic effects by the oral, inhalation and dermal route of exposure which occurred after single or repeated exposure.

Based on the high vapour pressure of butanone oxime and its half-life in air, butanone oxime is expected to exist primarily as a vapour and to persist in ambient air. The most likely route of exposure to butanone oxime for the general population is probably from inhalation of indoor air immediately following the application of consumer products containing the substance. Further the use of butanone oxime can lead to consumer exposure by dermal contact. Exposure via the oral route is considered not to be relevant for consumers due to the nature of the products.

Butanone oxime is classified as Skin Sens. 1, H317 and Eye Dam. 1, H318. The eMSCA considers that based on the available data on both endpoints it is difficult to identify a DNEL. Therefore, a quantitative risk assessment is neither possible for eye irritation nor for skin sensitisation. The available data trigger a qualitative risk characterisation for the eye irritation and the moderate skin sensitisation potential of butanone oxime. According to the REACH guidance on information requirements and chemical safety assessment, Part E (ECHA, 2008) the general approach when no DNEL for these endpoints is available aims at reducing/avoiding contact with the substance. Eye irritants and moderate skin sensitizers are allocated to the moderate hazard category band on the basis that exposure to these substances should be well-controlled.

The registrants are also of the opinion that such effects need a qualitative risk assessment other than a quantitative assessment. They state that all consumer products contain < 1 % butanone oxime which are below the generic concentration limit of components of a mixture classified for irreversible eye effects category 1 and as skin sensitizer category 1.

Risk for short-term/acute exposure

For the dermal exposure route, the registrants have derived a DNEL for short-term/acute systemic effects.

The eMSCA also proposes a DNEC for short-term/acute inhalation exposure, since some consumer exposure estimations were documented for a short period of time (from minutes to a few hours). These exposure conditions, which are likely for the identified uses, are not covered by the risk assessment of the registrants.

In the present case, there is concern on acute toxicity. Butanone oxime has a moderate acute dermal toxicity and is classified for this endpoint. In addition, butanone oxime is classified for serious eye damage/eye irritation. It is supposed that the long-term DNEL/C is not sufficient to ensure that effects occurring after a single exposure of a few minutes up to 24 hours do not occur. Therefore, a DNEL/C for acute toxicity is derived for effects of short-term exposures as these exposures can be significantly higher than the average daily exposure and the long-term DNEL/C may be insufficient to limit them. As in the consumer exposure estimations single and rare uses of butanone oxime with a relatively short duration are reported DNEL/Cs for short-term/acute systemic effects are derived for the general population by the eMSCA (see chapter 5.13 Derivation of DNEL(s)/DMEL(s)).

Inhalation

The derivation of acute inhalation DNECs for butanone oxime is based on the NOAEC of 3 ppm (10.8 mg/m^3) for effects on the respiratory tract (degeneration of the olfactory epithelium in the nasal cavity) derived from a sub-chronic inhalation toxicity study in male mice. Exemplified acute

DNECs for butanone oxime were derived for the following time periods: 1.3, 5, 20, 25, 60, 66, and 132 minutes and 4 hours.

According to Guidance on information requirements and chemical safety assessment Chapter R.8: Characterisation of dose [concentration]-response for human health (2012), it can be assumed that effects occurring after short-term exposure are prevented if the long-term DNEL is not exceeded, and further the acute DNEL/C can by default be set as 1-5 times (default 3) the long-term DNEL/C. The risk characterisation of butanone oxime by short-term/acute inhalation for the general population has been performed based on the DNELs presented in the following table.

Table 55: Overview of DNECs for butanone oxime obtained for the inhalation route of exposure for varying time durations of single, acute exposure (calculated by the eMSCA)

Hazard information	Value	Unit
Inhalation DNEC – short-term/acute – systemic effects	0.353	mg/m^3/4h
	2.0	mg/m^3/1.3 min
	1.3	mg/m^3/5 min
	0.81	mg/m^3/20 min
	0.749	mg/m^3/25 min
	0.561	mg/m^3/60 min
	0.543	mg/m^3/66 min
	0.431	mg/m^3/132 min
Inhalation DNEC – short-term/acute – systemic effects (alternative calculation from the long-term DNEC)	0.384	mg/m^3

Dermal

For systemic effects by short-term dermal exposure the derivation of DNELs for butanone oxime have been performed by using the LD_{50} value of 1848 mg/kg bw observed from the acute dermal toxicity study in rabbits (TL2 1984b, unpublished report). Alternatively, the dose descriptor used by the registrants of 18 mg/kg bw/d (NOAEL based on effects on the blood (transient methaemoglobinaemia, splenic effects) and narcotic effects) from the same study was also used for derivation of the DNEL for this exposure pattern by the eMSCA. For the general population the risk characterisation of butanone oxime by short-term/acute dermal exposure has been performed based on the DNELs presented in the following table.

Table 56: Overview of DNELs for butanone oxime obtained for the dermal route of exposure by single, acute exposure (calculated by the eMSCA)

Hazard information	Value	Unit
Dermal DNEL – short-term/acute – systemic effects	0.77	mg/kg bw
Dermal DNEL – short-term/acute – systemic effects (alternative calculation using NOAEL = 18 mg/kg bw/d)	0.75	mg/kg bw

Risk for repeated long-term exposure

For the inhalation route the registrants and the eMSCA have derived DNECs for long-term systemic and local effects, and for the skin contact a DNEL for long-term systemic effects. The eMSCA has checked the derivation of the long-term DNEL/Cs by the registrants for the general population and has concluded that they are not valid (see chapter 5.13 Derivation of DNEL/C(s)/DMEL/C(s)).

Based on the evaluation of all available data on butanone oxime a calculation of DNEL/Cs was carried out by the eMSCA. In the following table an overview is given on the DNEL/Cs derived by

the eMSCA for local and systemic effects by long-term exposure for the general population which are used for the risk characterisation of butanone oxime.

Table 57: Overview of DNEL/Cs for long-term systemic and local effects for butanone oxime for the general population (calculated by the eMSCA)

Hazard information	Value	Unit
Inhalation DNEC – long-term – systemic effects	0.128	mg/m^3
Inhalation DNEC – long-term – local effects	0.0386	mg/m^3
Dermal DNEL – long-term – systemic effects	0.0427	mg/kg bw/d

Risk characterisation for the consumer exposure scenarios in the CSR

A quantitative risk characterisation of consumer exposures to butanone oxime regarding short-term/rare use and repeated/regular uses has been conducted based on exposure estimates given in chapter 9.1.2.2.2 Modelled data, tables 45-58 and the DNEL/Cs for inhalation and dermal route given in the tables 61-63 and described in the text module above.

The following overview shows the product types and contributing scenarios which have been considered in the risk assessment.

Table 58: Overview of the assessed product types and contributing scenario

Product types	Contributing scenario
High solid paint	- Mixing and loading, high solid paint - Brushing and rolling, high solid paint
Waterborne wall paint	- Mixing and loading, waterborne wall paint - Brushing and rolling, waterborne wall paint
Waterborne paint	- Brushing and rolling, waterborne paint
Spray Products	- Spraying paint with a can - Pneumatic spraying
General coating (floor)	- Mixing and loading, general coating (floor) - Application of general coating (floor)
Artist paint	- Brushing and rolling, artist paint
Paint paste tube	- Mixing and loading, paint paste tube
Yacht paint	- Mixing and loading, yacht paint - Brushing and rolling, yacht paint indoor

The eMSCA has evaluated the consumer exposure scenarios and estimates provided by the registrants with the result that there is concern that the identified uses of butanone oxime may pose health risks for the general population by the inhalation and by the dermal route.

In detail, the eMSCA has calculated the RCRs by using the exposure scenarios for product subcategories and the product concentrations of butanone oxime provided in the CSRs. As described in chapter 9, additional exposure estimates by the eMSCA have been mainly based on standard assumptions in the respective RIVM fact sheets. A sample of recalculated exposure estimates has shown deviations between the values obtained by the eMSCA and the estimates provided by the registrants.

For the calculations, the DNEL/Cs derived by the eMSCA were selected according to the exposure patterns in the respective product types and contributing scenarios. In order to evaluate potential short-term/acute effects from inhalation, the eMSCA has also calculated mean event concentrations. The mean event concentrations were compared to a short-term/ acute systemic DNEC calculated by the eMSCA and to a value resulting from multiplication of the registrants' DNEC for long-term systemic and local effects by a factor of 3.

A review of dermal and inhalation exposure levels and the corresponding RCRs for the available contributing scenarios for consumer exposure can be found in the following tables. Shading indicates RCRs >1.

Table 59: RCRs for consumer contributing scenarios, solvent rich paint

Solvent rich paint, dermal exposure								
Author	Product conc. [%]	Other para-meters	Dermal load [mg/cm^2]	Dermal external dose [mg/kg bw]	RCR short-term/acute-sys.	RCR long-term-sys.	RCR short-term/ac.-sys. (**DNEL reg**.)	RCR long-term-sys. (**DNEL reg**.)
Scenario: Brushing and rolling, solvent rich paint								
CSR A	CSR A	CSR A	-	0.1-1	0.1-1	1-10	0.1-1	0.1-1
eMSCA	CSR A	CSR A	0.01-0.1	0.1-1	0.1-1	1-10	0.1-1	0.1-1
eMSCA	CSR A	RIVM Fact Sheet	0.01-0.1	0.1-1	0.1-1	1-10	0.1-1	0.1-1

Solvent rich paint, inhalation											
Author	Pro-duct conc. [%]	Other para-meters	Mean event conc. [mg/m^3]	Mean conc. on day of expo-sure [mg/m^3]	RCR short-term/ acute sys.	RCR long-term sys.	RCR long-term-local	RCR long-term/ sys. **DNEC reg.**	RCR long-term-local **DNEC reg**.	RCR short-term sys. **3xDNEC reg.**	RCR short-term local **3xDNEC reg.**
Scenario: Brushing and rolling, solvent rich paint											
CSR A	CSR A	CSR A	-	1-10	-	1-10	10-100	0.1-1	0.1-1	-	-
eMSCA	CSR A	CSR A	10-100	1-10	10-100	1-10	10-100	0.1-1	0.1-1	1-10	1-10
eMSCA	CSR A	RIVM Fact Sheet	10-100	1-10	100-1000	10-100	100-1000	1-10	1-10	1-10	1-10

Table 60: RCRs for consumer contributing scenarios, high solid

High solid paint, dermal exposure								
Author	Product conc. [%]	Other para-meters	Dermal load [mg/cm^2]	Dermal external dose [mg/kg bw]	RCR short-term/ac.-sys.	RCR long-term-sys.	RCR short-term/ac.-sys. (**DNEL reg**.)	RCR long-term-sys. (**DNEL reg**.)
Scenario: Mixing and loading, high solid paint								
CSR B	CSR B	CSR B	-	0.001-0.01	0.001-0.01	0.1-1	0.001-0.01	0.001-0.01
eMSCA	CSR B	CSR B	0.0001-0.001	0.001-0.01	0.001-0.01	0.1-1	0.001-0.01	0.001-0.01
eMSCA	CSR B	RIVM Fact Sheet	0.0001-0.001	0.001-0.01	0.001-0.01	0.1-1	0.001-0.01	0.001-0.01
Scenario: Brushing and rolling, high solid paint								
CSR B	CSR B	CSR B	-	0.1-1	0.1-1	1-10	0.1-1	0.1-1
eMSCA	CSR B	CSR B	0.01-0.1	0.1-1	0.1-1	1-10	0.1-1	0.1-1
CSR A	CSR A	CSR A	-	0.1-1	0.1-1	1-10	0.1-1	0.1-1
eMSCA	CSR A	CSR A	0.01-0.1	0.1-1	0.1-1	1-10	0.1-1	0.1-1
eMSCA	CSR B	RIVM Fact Sheet	0.01-0.1	0.1-1	0.1-1	10-100	0.1-1	0.1-1
eMSCA	CSR A	RIVM Fact Sheet	0.01-0.1	0.1-1	0.1-1	1-10	0.1-1	0.1-1

High solid paint, inhalation											
Author	Pro-duct conc. [%]	Other para-me-ters	Mean event conc. [mg/m^3]	Mean conc. on day of expo-sure [mg/m^3]	RCR short-term/ acute sys.	RCR long-term sys.	RCR long-term-local	RCR long-term/ sys. **DNEC reg**.	RCR long-term-local **DNEC reg.**	RCR short-term sys. **3xDNEC reg.**	RCR short-term local **3xDNEC reg**.
Scenario: Mixing and loading, high solid paint											
CSR B	CSR B	CSR B	-	0.1-1	-	0.1-1	1-10	0.01-0.1	0.01-0.1	-	-
eMSCA	CSR B	CSR B	10-100	0.1-1	10-100	0.1-1	1-10	0.01-0.1	0.01-0.1	1-10	1-10
eMSCA	CSR B	RIVM Fact Sheet	1000-10000	1-10	1000-10000	10-100	100-1000	1-10	1-10	100-1000	100-1000
Scenario: Brushing and rolling, high solid paint											
CSR B	CSR B	CSR B	-	0.1-1	-	1-10	10-100	0.1-1	0.1-1	-	-
eMSCA	CSR B	CSR B	10-100	0.1-1	10-100	1-10	10-100	0.1-1	0.1-1	1-10	1-10
CSR A	CSR A	CSR A	-	1-10	-	10-100	10-100	0.1-1	0.1-1	-	-
eMSCA	CSR A	CSR A	10-100	1-10	10-100	10-100	10-100	0.1-1	0.1-1	1-10	1-10
eMSCA	CSR B	RIVM Fact Sheet	100-1000	10-100	100-1000	100-1000	100-1000	1-10	1-10	10-100	10-100
eMSCA	CSR A	RIVM Fact Sheet	100-1000	10-100	100-1000	100-1000	100-1000	1-10	1-10	10-100	10-100

Table 61: RCRs for consumer contributing scenarios, waterborne wall paint

Waterborne wall paint, dermal exposure								
Author	Product conc. [%]	Other parameters	Dermal load [mg/cm^2]	Dermal external dose [mg/kg bw]	RCR short-term/ac.-sys.	RCR long-term-sys.	RCR short-term/ac.-sys. (**DNEL reg**.)	RCR long-term-sys. (**DNEL reg**.)
Scenario: Mixing and loading, waterborne wall paint								
CSR B	CSR B	CSR B	-	0.001-0.01	0.001-0.01	0.001-0.1	0.001-0.01	0.001-0.01
eMSCA	CSR B	CSR B	0.0001-0.001	0.001-0.01	0.001-0.01	0.01-0.1	0.001-0.01	0.001-0.01
eMSCA	CSR B	RIVM Fact Sheet	0.0001-0.001	0.001-0.01	0.001-0.01	0.01-0.1	0.001-0.01	0.001-0.01
Scenario: Brushing rolling, waterborne wall paint								
CSR B	CSR B	CSR B	-	0.1-1	0.1-1	1-10	0.01-0.1	0.1-1
eMSCA	CSR B	CSR B	0.001-0.01	0.1-1	0.1-1	1-10	0.01-0.1	0.1-1
eMSCA	CSR B	RIVM Fact Sheet	0.01-0.1	0.1-1	0.1-1	1-10	0.1-1	0.1-1

Waterborne wall paint, inhalation											
Author	Product conc. [%]	Other parame-ters	Mean event conc. [mg/m^3]	Mean conc. on day of expo-sure [mg/m^3]	RCR short-term/ acute sys.	RCR long-term sys.	RCR long-term-local	RCR long-term/ sys. **DNEC reg**.	RCR long-term-local **DNEC reg**.	RCR short-term sys. **3xDNEC reg.**	RCR short-term local **3xDNEC reg**.
Scenario: Mixing and loading, waterborne wall paint											
CSR B	CSR B	CSR B	-	0.001-0.01	-	0.01-0.1	0.1-1	0.001-0.01	0.001-0.01	-	-
eMSCA	CSR B	CSR B	1-10	0.001-0.01	1-10	0.01-0.1	0.1-1	0.001-0.01	0.001-0.01	0.1-1	0.1-1
eMSCA	CSR B	RIVM Fact Sheet	1-10	0.001-0.01	1-10	0.01-0.1	0.1-1	0.001-0.01	0.001-0.01	0.1-1	0.1-1
Scenario: Brush/roller painting, waterborne wall paint											
CSR B	CSR B	CSR B	-	1-10	-	10-100	10-100	0.1-1	0.1-1	-	-
eMSCA	CSR B	CSR B	10-100	1-10	10-100	10-100	10-100	0.1-1	0.1-1	1-10	1-10
eMSCA	CSR B	RIVM Fact Sheet	10-100	1-10	100-1000	10-100	100-1000	1-10	1-10	10-100	10-100

Table 62: RCRs for consumer contributing scenarios, waterborne paint

Waterborne paint, dermal exposure								
Author	Product conc. [%]	Other para-meters	Dermal load [mg/cm^2]	Dermal external dose [mg/kg bw]	RCR short-term/ac.-sys.	RCR long-term-sys.	RCR short-term/ac.-sys. (**DNEL reg**.)	RCR long-term-sys. (**DNEL reg**.)
Scenario: Brushing and rolling, waterborne paint								
CSR B	CSR B	CSR B	-	0.1-1	0.1-1	1-10	0.1-1	0.1-1
MSCA	CSR B	CSR B	0.01-0.1	0.1-1	0.1-1	1-10	0.1-1	0.1-1
CSR A	CSR A	CSR A	-	0.1-1	0.1-1	1-10	0.1-1	0.1-1
eMSCA	CSR A	CSR A	0.01-0.1	0.1-1	0.1-1	1-10	0.1-1	0.1-1
eMSCA	CSR B	RIVM Fact Sheet	0.01-0.1	0.1-1	0.1-1	10-100	0.1-1	0.1-1
eMSCA	CSR A	RIVM Fact Sheet	0.01-0.1	0.1-1	0.1-1	1-10	0.1-1	0.1-1

Waterborne paint, inhalation											
Author	Pro-duct conc. [%]	Other parame-ters	Mean event conc. [mg/m^3]	Mean conc. on day of expo-sure [mg/m^3]	RCR short-term/ acute sys.	RCR long-term sys.	RCR long-term-local	RCR long-term/ sys. **DNEC reg.**	RCR long-term-local **DNEC reg**.	RCR short-term sys. **3xDNEC reg.**	RCR short-term local **3xDNEC reg.**
Scenario: Brushing and rolling, waterborne paint											
CSR B	CSR B	CSR B	-	0.1-1	-	1-10	10-100	0.1-1	0.1-1	-	-
MSCA	CSR B	CSR B	10-100	0.1-1	10-100	1-10	10-100	0.1-1	0.1-1	1-10	1-10
CSR A	CSR A	CSR A	-	1-10	-	10-100	10-100	0.1-1	0.1-1	-	-
eMSCA	CSR A	CSR A	10-100	1-10	10-100	10-100	10-100	0.1-1	0.1-1	1-10	1-10
eMSCA	CSR B	RIVM Fact Sheet	10-100	1-10	100-1000	10-100	100-1000	10-100	1-10	1-10	10-100
eMSCA	CSR A	RIVM Fact Sheet	10-100	1-10	10-100	10-100	10-100	0.1-1	1-10	1-10	1-10

Table 63: RCRs for consumer contributing scenarios, spray paint

Spray paint, dermal exposure								
Author	Product conc. [%]	Other para-meters	Dermal load [mg/cm^2]	Dermal external dose [mg/kg bw]	RCR short-term/ac.-sys.	RCR long-term-sys.	RCR short-term/ac.-sys. (**DNEL reg**.)	RCR long-term-sys. (**DNEL reg**.)
Scenario: Spraying paint with a can								
CSR B	CSR B	CSR B	-	0.1-1	0.1-1	1-10	0.1-1	0.1-1
CSR A	CSR A	CSR A	-	0.1-1	0.1-1	1-10	0.1-1	0.1-1
eMSCA	CSR B	adapted from RIVM Fact Sheet	-	0.1-1	0.1-1	1-10	0.1-1	0.1-1
eMSCA	CSR A	adapted from RIVM Fact Sheet	-	0.01-0.1	0.01-0.1	1-10	0.01-0.1	0.01-0.1
Scenario: Pneumatic spraying								
CSR B	CSR B	CSR B	-	0.1-1	0.1-1	1-10	0.1-1	0.1-1
eMSCA	CSR B	adapted from RIVM Fact Sheet	-	0.1-1	0.1-1	1-10	0.1-1	0.1-1
eMSCA	CSR A	adaptd from RIVM Fact Sheet	-	0.01-0.1	0.01-0.1	1-10	0.01-0.1	0.01-0.1

Spray paint, inhalation											
Author	Pro-duct conc. [%]	Other parame-ters	Mean event conc. [mg/m^3]	Mean conc. on day of expo-sure [mg/m^3]	RCR short-term/ acute sys.	RCR long-term sys.	RCR long-term-local	RCR long-term/ sys. **DNEC reg.**	RCR long-term-local **DNEC reg.**	RCR short-term sys. **3xDNEC reg**.	RCR short-term local **3xDNEC reg**.
Scenario: Spraying paint with a can											
CSR B	CSR B	CSR B	-	0.01-0.1	-	0.1-1	1-10	0.01-0.1	0.01-0.1	-	-
CSR A	CSR A	CSR A	0.1-1	-	1-10	-	-	-	-	0.1-1	0.1-1
eMSCA	CSR B	adapted from RIVM Fact Sheet	10-100	0.1-1	10-100	1-10	10-100	0.1-1	0.1-1	1-10	1-10
eMSCA	CSR A	adapted from RIVM Fact Sheet	10-100	0.1-1	10-100	1-101	1-10	0.01-0.1	0.01-0.1	1-10	1-10
Scenario: Pneumatic spraying											
CSR B	CSR B	CSR B	-	0.001-0.01	-	0.001-0.01	0.01-0.1	0.0001-0.001	0.0001-0.001	-	-
eMSCA	CSR B	CSR B	10-100	0.1-1	10-100	10-100	10-100	0.1-1	0.1-1	1-10	1-10
eMSCA	CSR A	adapted from RIVM Fact Sheet	10-100	0.1-1	10-100	1-10	1-10	0.1-1	0.1-1	1-10	1-10

Table 64: RCRs for consumer contributing scenarios, general coating (floor) paint

General coating (floor), dermal exposure								
Author	Product conc. [%]	Other parameters	Dermal load [mg/cm^2]	Dermal external dose [mg/kg bw]	RCR short-term/ac.-sys.	RCR long-term-sys.	RCR short-term/ac.-sys. (**DNEL reg**.)	RCR long-term-sys. (**DNEL reg**.)
Scenario: Mixing and loading: general coating (floor)								
CSR B	CSR B	CSR B	-	<0.001	<0.001	<0.023	<0.0006	<0.0012
eMSCA	CSR B	member CSR	1.0E-06 – 1.0E-05	1.0E-05 – 1.0E-04	1.0E-05 – 1.0E-04	1.0E-04 – 1.0E-03	1.0E-0g – 1.0E-04	1.0E-05- - 1.0E-04
eMSCA	CSR B	RIVM Fact sheet	1.0E-04 – 1.0E-03	1.0E-03 – 1.0E-03	1.0E-03 - 1.0E-02	0.01-0.1	0.001-0.01	0.001-0.01
Scenario: Application of general coating (floor)								
CSR B	CSR B	CSR B	-	0.01-0.1	0.01-0.1	0.1-1	0.01-0.1	0.01-0.1
eMSCA	CSR B	CSR B	0.001-0.01	0.01-0.1	0.01-0.1	0.1-1	0.001-0.01	0.01-0.1
CSR A	CSR A	CSR A	-	0.01-0.1	0.01-0.1	0.1-1	0.01-0.1	0.01-0.1
eMSCA	CSR A	CSR A	0.01-0.1	0.01-0.1	0.01-0.1	0.1-1	0.01-0.1	0.01-0.1
eMSCA	CSR B	RIVM Fact Sheet	0.001-0.01	0.01-0.1	0.01-0.1	0.1-1	0.001-0.01	0.01-0.1
eMSCA	CSR A	RIVM Fact Sheet	0.01-0.1	0.01-0.1	0.01-0.1	0.1-1	0.01-0.1	0.01-0.1

General coating (floor), inhalation											
Author	Product conc. [%]	Other parameters	Mean event conc. [mg/m^3]	Mean conc. on day of exposure [mg/m^3]	RCR short-term/ acute sys.	RCR long-term sys.	RCR long-term-local	RCR long-term/ sys. **DNEC reg.**	RCR long-term-local **DNEC reg.**	RCR short-term sys. **3xDNEC reg.**	RCR short-term local **3xDNEC reg**.
Scenario: Mixing and loading, general coating (floor)											
CSR B	CSR B	CSR B	-	0.1-1	-	1-10	1-10	0.01-0.1	0.1-1	-	-
eMSCA	CSR B	member CSR	10-100	0.1-1	10-100	1-10	1-10	0.01-0.1	0.1-1	10-100	10-100
eMSCA	CSR B	RIVM Fact sheet	100-1000	1-10	100-1000	10-100	10-100	0.1-1	1-10	10-100	100-1000
Scenario: Application of general coating (floor)											
CSR B	CSR B	CSR B	-	1-10	-	10-100	10-100	0.1-1	0.1-1	-	-
eMSCA	CSR B	CSR B	10-100	1-10	10-100	10-100	10-100	0.1-1	0.1-1	1-10	1-10
CSR A	CSR A	CSR A	-	1-10	-	10-100	10-100	0.1-1	0.1-1	-	-
eMSCA	CSR A	CSR A	10-100	1-10	10-100	10-100	10-100	0.1-1	0.1-1	1-10	1-10
eMSCA	CSR B	RIVM Fact Sheet	10-100	1-10	100-1000	10-100	10-100	1-10	1-10	10-100	10-100
eMSCA	CSR A	RIVM Fact Sheet	100-1000	1-10	100-1000	10-100	100-1000	1-10	1-10	10-100	10-100

Table 65: RCRs for consumer contributing scenarios, artist paint

Artist paint, dermal exposure								
Author	Product conc. [%]	Other para-meters	Dermal load [mg/cm^2]	Dermal external dose [mg/kg bw]	RCR short-term/ac.-sys.	RCR long-term-sys.	RCR short-term/ac.-sys. (**DNEL reg**.)	RCR long-term-sys. (**DNEL reg**.)
Scenario: Brushing and rolling, artist paint								
CSR B	CSR B	CSR B	-	0.1-1	0.1-1	1-10	0.1-1	0.1-1
eMSCA	CSR B	CSR B	0.1-1	0.1-1	0.1-1	1-10	0.1-1	0.1-1
CSR A	CSR A	CSR A	-	0.1-14	0.1-1	1-10	0.1-1	0.1-1
eMSCA	CSR A	CSR A	0.01-0.1	0.1-1	0.1-1	1-10	0.1-1	0.1-1
eMSCA	CSR B	adapted from RIVM Fact Sheet	0.01-0.1	0.1-1	0.1-1	10-100	0.1-1	0.1-1
eMSCA	CSR A	adapted from RIVM Fact Sheet	0.01-0.1	0.1-1	0.1-1	1-10	0.1-1	0.1-1

Artist paint, inhalation											
Author	Pro-duct conc. [%]	Other parame-ters	Mean event conc. [mg/m^3]	Mean conc. on day of expo-sure [mg/m^3]	RCR short-term/ acute sys.	RCR long-term sys.	RCR long-term-local	RCR long-term/ sys. **DNEC reg.**	RCR long-term-local **DNEC reg.**	RCR short-term sys. **3xDNEC reg**.	RCR short-term local **3xDNEC reg.**
Scenario: Brushing and rolling, artist paint											
CSR B	CSR B	CSR B	-	1-10	-	10-100	10-100	0.1-1	0.1-1	-	-
eMSCA	CSR B	CSR B	10-100	1-10	10-100	10-100	10-100	0.1-1	0.1-1	1-10	1-10
CSR A	CSR A	CSR A	-	0.1-1	-	1-10	1-10	0.01-0.1	0.1-1	-	-
eMSCA	CSR A	CSR A	1-10	0.1-1	1-10	1-10	1-10	0.01-0.1	0.1-1	0.1-1	0.1-1
eMSCA	CSR B	adapted from RIVM Fact Sheet	10-100	1-10	10-100	10-100	10-100	0.1-1	0.1-1	1-10	1-10
eMSCA	CSR A	adapted from RIVM Fact Sheet	1-10	0.1-1	10-100	1-10	10-100	0.1-1	0.1-1	1-10	1-10

Table 66: RCRs for consumer contributing scenarios, paint past tube

Paint paste tube, dermal exposure								
Author	Product conc. [%]	Other para-meters	Dermal load [mg/cm^2]	Dermal external dose [mg/kg bw]	RCR short-term/ac.-sys.	RCR long-term-sys.	RCR short-term/ac.-sys. (**DNEL reg.)**	RCR long-term-sys. (**DNEL reg**.)
Scenario: Mixing and loading, paint paste tube								
CSR A	CSR A	CSR A	-	0.001-0.01	0.001-0.01	0.01-0.1	0.001-0.01	0.001-0.01
eMSCA	CSR A	CSR A	0.0001-0.001	0.001-0.01	0.001-0.01	0.01-0.1	0.001-0.01	0.001-0.01
eMSCA	CSR A	adapted from RIVM Fact Sheet	0.0001-0.001	0.001-0.01	0.001-0.01	0.01-0.1	0.001-0.01	0.001-0.01

Paint paste tube, inhalation											
Author	Pro-duct conc. [%]	Other para-meters	Mean event conc. [mg/m^3]	Mean conc. on day of expo-sure [mg/m^3]	RCR short-term/ acute sys.	RCR long-term sys.	RCR long-term-local	RCR long-term/ sys. **DNEC reg.**	RCR long-term-local **DNEC reg.**	RCR short-term sys. **3xDNEC reg**.	RCR short-term local **3xDNEC reg**.
Scenario: Mixing and loading, paint paste tube											
CSR A	CSR A	CSR A	-	0.01-0.1	-	0.1-1	0.1-1	0.01-0.1	0.01-0.1	0.001-0.01	0.001-0.01
eMSCA	CSR A	CSR A	10-100	0.01-0.1	1-10	0.1-1	0.1-1	0.01-0.1	0.01-0.1	0.001-0.01	0.001-0.01
eMSCA	CSR A	adapted from RIVM Fact Sheet	1000-10000	1-10	1000-10000	10-100	100-1000	1-10	1-10	100-1000	100-1000

Table 67: RCRs for consumer contributing scenarios, Yacht paint

Yacht paint, dermal exposure								
Author	Product conc. [%]	Other para-meters	Dermal load [mg/cm^2]	Dermal external dose [mg/kg bw]	RCR short-term/ac.-sys.	RCR long-term-sys.	RCR short-term/ac.-sys. (**DNEL reg**.)	RCR long-term-sys. (**DNEL reg**)
Scenario: Mixing and loading, yacht paint								
CSR A	CSR A	CSR A	-	0.001-0.01	0.01-0.1	0.1-1	0.001-0.01	0.01-0.1
eMSCA	CSR A	CSR A	0.0001-0.001	0.001-0.01	0.01-0.1	0.1-1	0.001-0.01	0.01-0.1
eMSCA	eMSCA	adapted from RIVM Fact Sheet	0.0001-0.001	0.001-0.01	0.001-0.01	0.01-0.1	0.001-0.01	0.001-0.01
Scenario: Brushing and rolling, yacht paint indoor								
lead CSR	CSR A	CSR A	-	0.01-0.1 (with gloves)	0.01-0.1	0.1-1	0.01-0.1	0.01-0.1
eMSCA	CSR A	adapted from RIVM Fact Sheet	0.01-0.1	0.1-1	0.1-1	10-100	0.1-1	0.1-1

Yacht paint, inhalation											
Author	Pro-duct conc. [%]	Other para-meters	Mean event conc. [mg/m^3]	Mean conc. on day of expo-sure [mg/m^3]	RCR short-term/ acute sys.	RCR long-term sys.	RCR long-term-local	RCR long-term/ sys. **DNEC reg**.	RCR long-term-local **DNEC reg.**	RCR short-term sys. **3xDNEC reg**.	RCR short-term local **3xDNEC reg.**
Scenario: Mixing and loading, yacht paint											
CSR A	CSR A	CSR A	-	0.1-1	-	1-10	10-100	0.1-1	0.1-1	-	-
eMSCA	CSR A	CSR A	10-100	0.1-1	10-100	1-10	10-100	0.1-1	0.1-1	1-10	1-10
eMSCA	eMSCA	adapted from RIVM Fact Sheet	100-1000	0.1-1	100-1000	1-10	10-100	0.1-1	0.1-1	10-100	10-100
Scenario: Brushing and rolling, yacht paint indoor											
lead CSR	CSR A	CSR A	1-10	-	1-10	-	-	-	-	0.1-1	0.1-1
eMSCA	CSR A	adapted from RIVM Fact Sheet	10-100	1-10	10-100	10-100	100-1000	1-10	1-10	1-10	1-10

The calculation of RCRs for short-term/acute effects from skin contact for activities associated with consumer application resulted in values below 1. The control of such risks is guaranteed for the evaluated scenarios of consumer exposure to butanone oxime. However, comparing the inhalation DNEC for short-term/acute systemic effects with the external mean event concentrations, RCRs >1 were calculated for all scenarios that comprise brushing and rolling or spraying. RCRs >1 were also found for the scenarios that cover mixing and loading of high solid paint, waterborne wall paint, general coating (floor), paint paste tube and yacht paint and for application of general coating (floor). These RCRs indicate that the corresponding risks are not adequately controlled.

Comparing the corrected long-term dermal DNEL with the dermal external dose on the day of exposure as calculated by the eMSCA, the RCRs exceed 1 in all scenarios that comprise brushing and rolling or spraying, indicating that the corresponding risks are not adequately controlled. The comparison of the long-term inhalation DNEC for local and systemic effects with the mean concentration on day of exposure resulted in RCRs >1 in all scenarios that comprise brushing and rolling or spraying. Also these RCRs indicate that the corresponding risks are not adequately controlled. RCRs >1 were also found for the scenarios that cover mixing and loading of high solid paint, general coating (floor), paint paste tube and yacht paint and for the application of general coating (floor).

Based on these data it is assumed that a combined risk characterisation via inhalation and the dermal route by summation of the respective RCRs results also in RCRs that all exceed 1.

These RCRs >1 indicate that the corresponding risks are not adequately controlled.

If butanone oxime will be included in Annex VI to the CLP Regulation as carcinogen 1B, H350, as proposed by the eMSCA this will imply a restriction according to generic entry 28 of Annex XVII of the REACH Regulation. This will affect sales to the general public of butanone oxime as a substance, as a constituent of other substances or in mixtures at concentrations ≥0.1 %. The registered concentrations of butanone oxime in coatings for consumer use currently would exceed this generic concentration limit. As a consequence of a harmonised classification of butanone oxime as carcinogen 1B, H350 the use pattern of butanone oxime is expected to change and the assumed risks for the general population as currently estimated may not continue to exist. Therefore the result of a harmonised classification of butanone oxime should be awaited and the need of further community–wide regulatory risk management measures for the consumer uses should be re-assessed.

Evaluation of cancer risk from exposure to butanone oxime

Carcinogenicity was not considered in the risk assessment by the registrants, although butanone oxime is a human carcinogen and is legally classified as a carcinogen category 2; H351. Accordingly the registrants have not considered whether risks of cancer from exposure to butanone oxime are adequately controlled for the general population known to be exposed. During the SEV, the classification of butanone oxime as category 1B carcinogen, H350 according to the CLP Regulation revealed appropriate.

The purpose of evaluation of risks of butanone oxime on cancer induction for the general population is to obtain an estimate of an exposure level for inhalation and dermal route of exposure to butanone oxime with minimal or negligible health risk. This level depends on the risk of acquiring disease associated with a dose level. For evaluation of cancer risk from exposure to butanone oxime and derivation of tolerable risks levels, DMEL/Cs for the general population were derived by the eMSCA. An overview of the derived DMEL/C (based on T25 calculation) associated with a lifetime cancer risk of very low concern for butanone oxime for the general population by inhalation and dermal exposure is given in the following table.

Table 68: Overview of the derived DMEL/C of butanone oxime for the general population

Hazard information	Value
DMEC, inhalation exposure	4.82 µg/m^3 (linearity, 1:100000) 0.482 µg/m^3 (linearity, 1:1000000)
DMEL, dermal exposure	1.61 µg/kg bw/d (linearity, 1:100000) 0.161 µg/kg bw/d (linearity, 1:1000000)

As described in chapter 5.13.2 the values for DMEL/Cs for general population for both routes, inhalation and dermal, are significantly lower than the DNEL/Cs. DNEL/Cs and DMEL/C differ about by a factor of 100 which would yield in RCR values significantly above 1.

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