MINISTRY
OF HUMAN CAPACITIES

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Butan-1-ol

EC No 200-751-6

CAS No 71-36-3

Evaluating Member State(s): Hungary

Dated: 25 June 2018

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2017

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

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Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Butan-1-ol was originally selected for substance evaluation in order to clarify concerns about

-reproductive toxicity with main focus on developmental toxicity

and also considering the following exposure based concerns:

-wide dispersive use,

-consumer use,

-exposure of workers,

-high (aggregated) tonnage.

During the evaluation also another concern was identified. The additional concern was:

developmental neurotoxicity.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Compliance check was performed on the substance and it is also listed in Annex VI of the CLP regulation[2] (Index no.: 603-004-00-6).

The evaluating Member State has no information about other ongoing or completed processes relevant for butan-1-ol.

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION	
Conclusions	**Tick box**
Need for follow-up regulatory action at EU level	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	X

[2] Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures.

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

Not applicable.

4.1.1. Harmonised Classification and Labelling

Not applicable.

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

Table 2

REASON FOR REMOVED CONCERN The concern could be removed because	Tick box
Clarification of hazard properties/exposure	X
Actions by the registrants to ensure safety, as reflected in the registration dossiers(e.g. change in supported uses, applied risk management measures, etc.)	

The initial and additional concerns were removed based on the data in the updated registration dossier and in the publicly available literature.

During the substance evaluation the evaluating Member State found the data on exposure insufficient and this finding was communicated to the Registrant, who updated his registration in this context.

Taking into account the new information and the clarifications provided by the Registrant, the evaluating Member State was able to conclude on every concerned endpoint and found no potential, inadequately controlled risks. Hence the evaluating Member State concludes that currently there is no need for follow-up action at EU level.

5.2. Other actions

Not applicable.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Not applicable.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Butan-1-ol was originally selected for substance evaluation in order to clarify concerns about

-reproductive toxicity with main focus on developmental toxicity

and also considering the following exposure based concerns:

-wide dispersive use,

-consumer use,

-exposure of workers,

-high (aggregated) tonnage.

During the evaluation also another concern was identified. The additional concern was:

-develpomental neurotoxicity.

Table 3

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Acute toxicity	No further action needed. The current harmonised classification is appropriate.
Skin irritation	No further action needed. The current harmonised classification is appropriate.
Eye irritation	No further action needed. The current harmonised classification is appropriate.
Sensitisation	No concern was identified regarding the sensitising property of the substance.
Repeated dose toxicity	The current harmonised classification is appropriate
Mutagenicity	No concern was identified.
Carcinogenicity	No concern was identified.
Toxicity to reproduction	The concern was removed.
Human exposure	No concern was identified for risks posed by butan-1-ol if the current risk management measures are followed.

7.2. Procedure

The evaluating Member State's intention was to conduct a targeted substance evaluation on human health hazards, focusing on the initial concerns, however, evaluating the other human health hazard endpoints as well, in order to exclude any further potential concerns. Environmental hazard endpoints were not examined.

The evaluating Member State conducted a literature search to gather all relevant new information on the concerned endpoints, complementing the results of the previous search conducted in the screening process.

The experts of the evaluating Member State analysed all available information regarding the examined endpoints to conclude on the properties of the substance and the potential EU-level Risk Management Measures warranted by risks controlled inadequately, and to identify any arising needs to ask for further information.

The evaluating Member State found the available data on human exposure in the registration dossier insufficient to draw conclusions. However, after extensive communication between the evaluating Member State and the Registrant, the Registrant updated his registration dossier and provided reliable explanation and clarification on the exposure model used, and thus satisfied the data needs.

In conclusion of the assessment the evaluating Member State did not confirm the initial concerns. Taking into account the new information gathered during the substance evaluation, and the clarification of the exposure, the evaluating Member State was able to conclude on every concerned endpoints and found no potential risk, which was controlled inadequately. Therefore, no further RMM is deemed necessary at the EU-level.

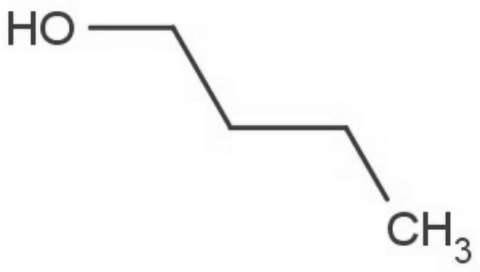
7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	Butan-1-ol
EC number:	200-751-6
CAS number:	71-36-3
Index number in Annex VI of the CLP Regulation:	603-004-00-6
Molecular formula:	C4H10O
Molecular weight range:	74.122
Synonyms:	butanol 1-butanol n-butanol butylalcohol 1-butyl alcohol n-butyl alcohol 1-hydroxybutane butyl hydroxide

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



7.4. Physico-chemical properties

Butan-1-ol is a colorless liquid which has a high water solubility, and due to its vapour pressure and the boiling point it is considered to be a moderately volatile liquid (see Table 5).

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Liquid
Vapour pressure	10 hPa at 20 °C
Water solubility	66 g/L at 20 °C and pH 7
Relative density	0.81 g/cm³ at 20°C
Partition coefficient n-octanol/water (Log Kow)	1 at 25 °C
Melting / freezing point	< -90 °C
Boiling point	119 °C at 101.3 kPa
Surface tension	69.9 mN/m at 20° C
Flash point	35 °C at 101.3 kPa
Autoflammability / self-ignition	355 °C at 101.3kPa
Flammability	Flammable
Explosive properties	Non-explosive
Oxidising properties	Non oxidising
Viscosity	2.947 mPa*s at 20° C (dynamic)

7.5. Manufacture and uses

7.5.1. Quantities

Table 6

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

According to ECHA's dissemination site[3] Butan-1-ol is manufactured and/or imported in the European Economic Area in 100 000 - 1 000 000 tonnes per year.

[3] 4/6/2018.

7.5.2. Overview of uses

The substance is used in the following products: lubricants and greases, coating products, washing and cleaning products, anti-freeze products, adhesives and sealants, polishes and waxes and finger paints.

Table 7

USES	
Uses as intermediate	Use as intermediate in manufacture of substances.
Formulation	Formulation & (re)packing of substances and mixtures. Distribution of substance.
Uses at industrial sites	Use as intermediate. Use in cleaning agents. Use in coatings (paints, ink, toners, adhesives, spin finisher). Use in lubricants. Metal working fluids / rolling oils. Use as process chemical. Metal working/fluids/rolling oils. Manufacture of n-Butanol. Oil and gas field applications. Use in polymer production. Thin film forming for electronics. Use as laboratory agent.
Uses by professional workers	Use in lubricants. Distribution of substance. Metal working fluids/rolling oils. Use in coatings (paints, ink, toners, adhesives). Use in laboratories. Use in cleaning agents. Formulation of substances and mixtures.
Consumer Uses	Use in lubricants. Use in cleaning agents. Use in coatings (paints, ink, toners, adhesives). Use as consumer care product or disinfectant.
Article service life	-

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

According to the harmonised classification and labelling approved by the European Union, butan-1-ol is a flammable liquid and vapour, is harmful if swallowed, causes serious eye damage, causes skin irritation, may cause respiratory irritation and may cause drowsiness or dizziness (see Table 8).

Table 8

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
603-004-00-6	butan-1-ol; n-butanol	200-751-6	71-36-3	Flam. Liq. 3 Acute Tox. 4* Skin Irrit. 2 Eye Dam. 1 STOT SE 3 STOT SE 3	H226 H302 H315 H318 H335 H336		

7.6.2. Self-classification

- In the registration(s)*:*

Compared to Annex VI of CLP Regulation the substance has the same classification in the registration.

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory*:*

Acute Tox. 4
STOT SE 3 (respiratory tract)
STOT SE 3 (lung) (oral)
STOT SE 3 (lung) (Inhalation)
STOT SE 3 (stomach)
STOT SE 3 (brain) (Inhalation)
STOT SE 3 (CNS, Respiratory tract)
STOT SE 3 (Dermal)
STOT SE 3 (mouth, pharynx, oesophagus and gastrointestinal tract)
STOT SE 3 (central nervous system) (Inhalation)
Asp. Tox. 1

7.7. Environmental fate properties

Not evaluated.

7.8. Environmental hazard assessment

Not evaluated.

7.9. Human Health hazard assessment

7.9.1. Hypothesis of read-across approach

In addition to the data available directly on butan-1-ol, data from a read-across substance, n-Butyl-acetate (EC no.: 204-658-1; CAS no.: 123-86-4) were also used for human health hazard assessment (repeated dose toxicity and reproductive toxicity).

The target (butan-1-ol) and the source substance (n-Butyl-acetate) are structurally similar and they both degrade into common products, furthermore the source substance is the hydrolysis product of the target substance.

Both substances show similar toxicological effects such as low acute toxicity, and, furthermore, they can enter the central nervous system, and specific target organ toxicity after single exposure could be observed in animal studies, therefore both substances are classified as STOT SE 3.

To further investigate the toxicological profile of the target and the source substance the Registrant used OECD QSAR Toolbox, and concluded that the toxic hazard classification by Cramer for the source and target substance is low (Class I) (Class I substances are simple chemical structures with efficient modes of metabolism suggesting a low order of oral toxicity).

The Registrant gathered enough available experimental data (literature data) to support the similarities of the physical and chemical properties between the target and the source substance. They both are colourless liquids with the comparable boiling, freezing and flash points, density and vapour pressure. Although the water solubility of the target substance (butan-1-ol) is an order of magnitude greater, than of the source compound (n-Butyl-acetate), it is still considered as relatively high water soluble substance.

Both the target and the source substances have linear C4 groups. The source substance (n-Butyl acetate) is the ester of target substance (butan-1-ol) and acetic acid. The hydrolysis of the target substance (butan-1-ol) does accrue reversibly in aqueous solution due to its chemical properties.

In a toxicokinetic study, 25-31 mg/kg bw/d radiolabelled n-Butyl acetate was administered to rats and sampled blood and brain tissue several times after dosing. The main metabolite was butan-1-ol, other metabolites (in smaller degree) were detected in the blood and brain including n-butyric acid and polar metabolites (probably citric acid cycle intermediates, glucuronide and sulphate conjugates). The analysis indicated that n-Butyl acetate is eliminated very rapidly from the blood and brain (t1/2 was 0,41 and 1,9 minutes respectively). The concentration of butan-1-ol reached the maximum level after approximately 2,5 minutes, rapidly eliminated from the blood and brain, and was undetectable after 20 min of dosing (Deisinger PJ et al. 1997).

As a conclusion, based on the similar physico-chemical and toxicokinetic properties of butan-1-ol and n-Butyl acetate, the evaluating Member State considers the read-across approach plausible for repeated dose toxicity and reproductive toxicity endpoints. This is also supported by other assessments (OECD 2001, ECETOC 2003).

7.9.2. Toxicokinetics

The toxicokinetic properties of butan-1-ol were assessed in the ECETOC JACC (2003) document. Several studies were performed on the toxicokinetic properties of butan-1-ol (a gavage study in CD(SD) rats, an inhalation study in Beagle dogs (Di Vincenzo and Hamilton, 1979) and an intravenous administration study in rats). It was concluded that butan-1-ol was readily absorbed through the skin, the intestinal tract and the lungs and distributed almost evenly throughout the whole organism. The substance is rapidly

eliminated by metabolism, primarily by alcohol and aldehyde dehydrogenases and, after oxidisation to butyric acid and further degradation to shorter acids and ketones, the majority of butan-1-ol is excreted in the form of carbon dioxide, while excretion via urine and faeces plays a minor role only. The zero-order kinetics of elimination for butan-1-ol was determined to have a rate of 3.2 +/- 0.4 mmol/kg bw/h in vivo (Plapp 2015).

As already mentioned above, in addition to the data available directly on butan-1-ol, data from a read-across substance, n-Butyl acetate were also used for toxicokinetic assessment. N-Butyl acetate showed a rapid conversion into its metabolite, n-butanol. The rapid decline of n-Butyl acetate in blood and brain was down to the limit of detection within 10 minutes, e.g. elimination after 7.4 minutes from blood and 4 minutes from brain was detected (Deisinger PJ et al. 1997). The half-life of n-Butyl acetate in rat blood in vitro was determined to be 4 min (hydrolytic cleavage of ester to butan-1-ol and acetic acid).

Absorption was also tested in vivo in dogs after 60 minutes dermal exposition of ^{14}C butan-1-ol. The elimination was expressed as a percentage of the administered dose. About 15 % of the dose was eliminated in the breath as $^{14}CO_2$ and 2.7 % was excreted in the urine. There was no unchanged butan-1-ol detected in the breath. The 8-hour elimination of radioactivity in the breath and urine averaged about 17 % of the administered dose.

The absorption rate of butan-1-ol across isolated human epidermis was 0.048 mg/cm²/h compared to 0.57 mg/cm²/h for ethanol and the in vitro absorption rate was determined to be 2.30 ± 0.52 mg/cm²/h and permeability constant of 2.84 ± 0.65 x 10 -3 cm/h for pure butan-1-ol through normal split-thickness human thigh skin.

The evaluating Member State accepts that the following values are used in toxicological assessments: oral absorption rate of butan-1-ol is 100%. Dermal absorption rate is 50%, inhalation absorption rate is 60%.

On the basis of the available information butan-1-ol did not show bioaccumulation potential.

7.9.3. Acute toxicity and Corrosion/Irritation

-Oral:

The acute oral toxicity of butan-1-ol was investigated in rats, mice, rabbits, hamsters and dogs.

In a study comparable to OECD TG 401 the acute LD50 value was reported to be 2.83 mL/kg bw in female rats, corresponding to 2290 mg/kg bw (calculated with a density of 0.81 g/mL). A comparable LD50 level was observed in a study following the standard acute method with acceptable restrictions (Jenner et al. 1967). In this study the LD50 was 2510 mg/kg bw in rats. Mortality occurred within 4-18 hours after dosing, and depression and coma were reported as clinical signs. The acute oral LD50 was reported to be 4360 mg/kg bw for female rats (Union Carbide Corporation 1951). For other common test species the following oral LD50 values were reported with limited details: 2680 mg/kg bw for mice (Rumyanstev et al., 1979), 3500 mg/kg bw for rabbits (Munch, 1972; Munch and Schwarze, 1925, Val. 4), 1200 mg/kg bw for Golden hamsters (Dubina and Maksimov, 1976, Val. 4), and a minimum lethal dose of 1782 mg/kg bw for dogs (Von Oettingen, 1943, Val. 4). The ECETOC JACC (2003) document refers also to one publication with an oral LD50 in rats below 2000 mg/kg (790 mg/kg).

The evaluating Member State agreed to the application of the acute oral toxicity (LD50) value of 2290mg/kg bw for human health assessment.

The substance is already listed in Annex VI to the CLP Regulation and has harmonised classification as Acut tox. 4 (H302:" Harmful if swallowed"), and on the basis of the available data, there is no need for stricter classification for acute toxicity.

-Dermal:

The acute dermal toxicity of butan-1-ol was tested in a study comparable to OECD TG 402 (Union Carbide Corporation 1951). Four doses of 1.26 to 10 mL/kg bw were applied to groups of four male rabbits and an LD50 value of 4.24 mL/kg bw (corresponding to ca. 3434 mg/kg bw; calculated with a density of 0.81 g/mL) was determined after an observation period of 14 days. Death occurred on the day of the treatment, three rabbits died out of four in the 5 mL/kg bw and all rabbits died of the 10 mL/kg bw group. In the ECETOC JACC (2003) document further dermal LD50 values in rabbits in the doses of 7600, 5300 and 4200 mg/kg were reported.

The evaluating Member State agreed to the application of the acute dermal toxicity (LD50) value of 3434 mg/kg bw for human health assessment. Based on this, the evaluating Member State concludes that butan-1-ol does not need to be classified for acute dermal toxicity according to the CLP Regulation.

-Inhalation:

The acute inhalation toxicity of butan-1-ol was investigated in three studies in rats. In a study similar to OECD TG 403, 10 Sprague-Dawley rats per sex per dose were whole-body exposed to vapour atmospheres of butan-1-ol for 4 hours and were observed for 14 days. The study resulted an LC0 value of >17.76 mg/L and no mortality or clinical signs but only slightly reduced body weight gain were observed at 17.76 mg/L . The LC50 value can be estimated as above 20 mg/L. In another study, Sprague-Dawley rats of both sexes were exposed to a vapour saturated butan-1-ol atmosphere for 7 hours. None of the animals died. Additionally, in a further study comparable to OECD TG 403 no mortalities were observed after exposure to a substantially saturated vapour for 8 hours in male rats and after exposure to 8000 ppm (ca. 24 mg/L) for 4 hours in female rats, respectively. Poor coordination or prostration was observed in both trials (Union Carbide Corporation 1951).

Due to the very low acute inhalation toxicity of butan-1-ol (rat 4h LC0 vapour >=17.76 mg/L), the substance does not need to be classified for acute inhalation toxicity under Regulation (EC) No. 1272/2008 (CLP). Due to the observed local irritant effects on the respiratory system in an inhalation hazard test and in humans and transient effects on the CNS (drowsiness and dizziness) the current harmonised classification of the substance as STOT Single Exposure Cat. 3 (H335: “May causes respiratory irritation”/H336 “May cause drowsiness or dizziness”) is appropriate according to the requirements of the CLP Regulation.

-Skin irritation:

Various experimental data were available for the skin irritation potential of butan-1-ol. Four studies were performed in rabbits with different exposure conditions such as the duration of treatment, amount of applied test item, occlusive or semi-occlusive conditions. In two studies the test substance was taken directly from the production process (before purification).

The evaluating Member State considers the current harmonised classification as skin irritant (Cat. 2, H315: “Causes skin irritation”) under CLP Regulation appropriate.

-Eye irritation:

Both vertebrate study data from four rabbit studies and human data are available on the eye irritation potential of butan-1-ol. In a GLP compliant study performed according to OECD guideline 405 with three rabbits exposed to 0.1 mL butan-1-ol for 24 hours, corneal opacity, iritis, conjunctivae redness and chemosis were observed, which were not fully reversible within 7 days, indicating a serious risk for eye damage, but the observation period applied was not sufficient to detect irreversibility as the recommended length for

this period is 21 days. Comparable conditions were used in another GLP guideline study by ECETOC (1998), where corneal opacity, iritis, conjunctivae redness and chemosis were observed, which were fully reversible within at least 21 days. Results of further tests indicate irritative to severe irritative effects on rabbit eyes. In another rabbit study (Union Carbide Corporation 1951) the rabbit's eye was severely injured by the undiluted compound (0.5 ml), moderately damaged by a 15% dilution of the substance in propylene glycol and only slightly affected by a 5% dilution applied in excess.

Due to irreversible and severe effects on corneal opacity, iritis, conjunctivae redness and chemosis within 7 days, the evaluating Member State considers the current harmonised classification according to the CLP Regulation as Cat. 1, H318: "Causes serious eye irritation" appropriate.

7.9.4. Sensitisation

The skin sensitisation properties of butan-1-ol was tested in a battery of in-vitro tests and an in-vivo LLNA test in mice. These reliable studies (among them GLP compliant and guideline studies with reliability factor 1) showed that butan-1-ol has no sensitising effects, hence there is no concern regarding the potential skin sensitising properties of this substance.

No animal study is available for respiratory sensitisation, and no human data observed to warrant the classification of butan-1-ol as respiratory sensitizer.

The evaluating Member State concludes that no classification is necessary for skin and respiratory sensitisation.

7.9.5. Repeated dose toxicity

-Oral:

Two studies are available for investigating the repeated dose oral toxicity properties of butan-1-ol. In a 90-day study with butan-1-ol (US EPA, 1986) four groups of male and female Sprague-Dawley rats (30/sex/group) were dosed orally once daily with 0, 30, 125, or 500 mg/kg bw/day. In this study the only unequivocal effects generated by butan-1-ol were ataxia and hypoactivity at the 500 mg/kg bw/d dose level. Ataxia and hypoactivity were not seen as treatment-related signs until the final six weeks of the study with maximum weekly incidences of 32% and 29% respectively. Onset of ataxia and hypoactivity was about 2-3 minutes after dosing and duration was less than one hour. Other treatment related observations included slight decrease (5% compared to controls) in the red blood cell count, packed cell volume, and hemoglobin concentration were noted only in the 500 mg/kg/day dose group females at the interim evaluation.

In another study butan-1-ol was administered via gavage to 20 male rats at concentrations of 0.04, 0.2, 1.0 and 5.0 mg/kg bw/d for 30 days. No details on clinical observations and other endpoints were provided. The only observations described were increased activation of alcoholdehydrogenase and katalase in serum, membrane lesions of hepatocytes and lysosomas and a decrease of adrenal weight in animals treated with 0.2 mg/kg bw/d and above (Sinitsyna 2002 and 2003).

The evaluating Member State agreed in application of no-observed-effect level (NOEL) for repeated dose toxicity of 125 mg/kg bw/d (nominal) for male and female rats based on butan-1-ol, as no effects were observed in a 90-day repeated dose study at this dose level. The lowest-observed-effect level (LOEL) of 500 mg/kg bw/d can be set based on transient clinical signs of central nervous system (CNS) depression (ataxia and hypoactivity).

-Inhalation:

Valid experimental data to assess systemic toxicity after repeated exposure were available only for the oral pathway.

The inhalation exposure of butan-1-ol was tested in rats for 3 months (5 d/week, 5 h/d, vapour). Observed effect concentration was 320 mg/m^3, but no NOAEC/LOAEC could be established in this study (Jajte et al. 2003).

Therefore, for the inhalative route, reliable data were taken from the read-across substance, n-Butyl acetate (CAS-No. 123-86-4). A definitive subchronic toxicity study was performed according to EPA guideline OTS 798.2450 (Bernard, 1996). In this study exposure to n-Butyl acetate vapors resulted acute, transient signs of reduced activity levels during exposure to 1500 and 3000 ppm. Decreased body weight and feed consumption were noted for the 1500 and 3000 ppm groups, but there was no sign of systemic, organ-specific toxicity. Signs of upper respiratory tract irritation were seen in the nasal passages of exposed animals at 1500 and 3000 ppm. The NOEC for this study is considered to be 500 ppm = 2.35 mg/L.

-Dermal:

The repeated dose dermal toxicity of butan-1-ol was tested in rabbits. No guideline was followed when butan-1-ol was applied to rabbit skin at 100% concentration under occlusive conditions for 12 times for 5 h duration within 21 days (McOmie et al. 1949). Drying of the skin was reported and on continuous exposure cracking, furrowing and exfoliation of the epidermis was recorded. The observed effects were reversible. No systemic effects were described by the authors.

The CNS effects observed in the repeated dose studies were not focused on a specific organ but considered as general impairments of neurological and behavioural functions (drowsiness and dizziness). The evaluating Member State supports the harmonised classification of butan-1-ol as STOT SE 3, H336. Those observations typically occur for alcohols and there is no need for classification of butan-1-ol for repeated dose systemic toxicity.

7.9.6. Mutagenicity

-In vitro:

Gene mutation potential of butan-1-ol has been tested in bacteria S. typhimurium TA 1535, TA 1537, TA 98 and TA 100 strains, with and without metabolic activation. In another study S. typhimurium TA 102 strain was tested, with and without metabolic activation (Jung et al. 1992).

Gene mutation potential of butan-1-ol was also tested in mammalian V79 cells, HPRT Test, with and without metabolic activation (GLP, OECD 476). Furthermore is was also tested in L5178 cells in a mouse lymphoma assay, with and without metabolic activation.

Genotoxicity of butan-1-ol was tested in mammalian CHL V79 cells, in an in vitro micronucleus test, without metabolic activation (Lasne et al. 1984), and in CHO cells, SCE assay, without metabolic activation (Obe et al. 1977).

Butan-1-ol has also been tested in S. thyphimurium TA 1535/pSK1 002 strain, in umu test (Nakamura et al. 1987).

All of the abovementioned tests gave negative results.

No adverse mutagenic effects were observed in a battery of in vitro genetic toxicity tests.

-In vivo:

Genotoxic potential of butan-1-ol in mammals has been tested in a mouse micronucleus test (OECD 474; BASF 1998). The result of this in vivo test was negative, butan-1-ol did not have any chromosome-damaging (clastogenic) effect, and there were no indications of any impairment of chromosome distribution in the course of mitosis.

Based on the available information, no concern for the mutagenic potential of butan-1-ol has been raised.

7.9.7. Carcinogenicity

There were no experimental data available on the carcinogenic potential of butan-1-ol, so the Evaluating Member State checked the available information and used a weight of evidence approach.

Considering the lack of mutagenic activity, a carcinogenic potential of butan-1-ol based on genotoxic mode of action is not expected.

In order to investigate whether there is any concern for carcinogenicity based on a non-genotoxic mode of action, a (Q)SAR analysis has been performed. No structural fragments were found in a structure-activity-relationship model (CASE) indicating a carcinogenic alert.

According to the informations from the repeated dose toxicity studies with butan-1-ol and n-Butyl acetate, there is no indication that butan-1-ol is able to induce hyperplasia or pre-neoplastic lesions (US EPA, 1986).

In an occupational health study workers were exposed to butan-1-ol and several other solvents while employed as dockyard painters (Chen et al.,1999) and mortality rates due to cancer were examined; however, neither proportional mortality nor standardized mortality ratios due to cancer were increased in the group of the painters relative to controls.

U.S. EPA has also evaluated the carcinogenic potential of butan-1-ol and classified the substance in Classification-D; not classifiable as to human carcinogenicity, based on no human and no animal cancer data. (U.S. EPA, 2000)

Based on the available data - the lack of genotoxic potential of butan-1-ol, the lack of "specific repeat-dose target organ" toxicity, the lack of pre-neoplastic lesions in the repeated dose toxicity studies as well as absence of (Q)SAR alerts for non-genotoxic mode of action, and considering that no human cancer data available in the scientific literate - no concern for a carcinogenic potential of butan-1-ol has been raised.

7.9.8. Toxicity to reproduction (effects on fertility and developmental toxicity)

The major concern raised in this substance evaluation comes from a teratogenicity study performed with butan-1-ol (Nelson et al. 1989a), as skeletal malformations (mainly rudimentary cervical ribs) were observed at the highest tested concentration of 8000 ppm.

The authors of the study concluded that the results suggest a possible selective developmental effect that maternal toxicity per se was not responsible for, although they did not consider this as a strongly selective effect. Occasional visceral malformations and variations (e.g. enlarged brain ventricles) were also observed, although these effects did not reach statistical significance.

A study by Ema et al. (2005) gave negative results, however, in another study by Sitarek et al. (1994) developmental anomalies were observed, including central nervous system

and rib defects, at doses with no maternal toxicity. The authors of this study concluded that even maintaining workplace concentrations below maternally acceptable levels may prove insufficient in protecting the progeny.

-Fertility:

A two-generation reproductive toxicity study on a read-across substance Butyl acetate in rats via inhalation has been considered as a key study in the evaluation of the fertility effect of butan-1-ol. The study was well documented and conducted according to OECD test guideline 416. In this study no test article-related mortalities were observed in the adult animals of the F0, F1 and F2 generations; there were no clinical or macroscopic signs of toxicity for the test article-exposed animals. No indications of toxicity on reproductive function were reported at any exposure level. In each generation the reproductive performance, parturition, the mean numbers of implantation sites at weaning and spermatogenic endpoints in the test article-exposed groups were similar to the respective control group.

Effects on fertility have been examined in three further, supporting studies with butan-1-ol as test substance:

Oral administration of butan-1-ol was performed in an explorative study on female fertility and prenatal development on rats (Sitarek 1994). In this study no effects were noted for general toxicity in the form of impaired general appearance, food consumption, body weight/weight gain, absolute and relative organ weight, haemoglobin concentration, haematocrit values. Fertility and developmental parameters in the form of number and length of oestrous cycles, corpora lutea, total implants, intra-uterine mortality, foetal body weights and placental weight were not affected by butan-1-ol exposure. The NOAEL for maternal toxicity including fertility was determined to be 5000 mg/kg bw/d.

Information on the possible effects of butan-1-ol on the reproductive organs administered by oral route is also available in a 90-day repeated dose toxicity study in rats (US EPA 1986). No dose-related differences were observed between treatment or control rats with regards to reproductive organs up to the highest dose (500 mg/kg bw/d). Thus, the NOEL for reproductive organ toxicity was 500 mg/kg bw/d.

Butan-1-ol has also been tested via inhalation route of administration in a behavioural peri-, postnatal developmental neurotoxicity study in rats (Nelson 1989a). In this study no effects on maternal or paternal general toxicity were observed and no effects on the pregnancy rate after either maternal or paternal exposure were reported up to the 6000 ppm concentration. Thus, 6000 ppm (18.5 mg/L) was the NOAEC for parental toxicity including fertility.

The evaluating Member State considers the overall NOEL of butan-1-ol for fertility for the oral route to be 500 mg/kg bw/d. For the inhalation route the NOAEC used for the evaluation of butan-1-ol for fertility is 6000 ppm (18.5 mg/L).

-Developmental toxicity:

-Oral route:

In a key prenatal developmental toxicity study in rats with butan-1-ol, the NOAEL for maternal and developmental toxicity was determined to be 1454 mg/kg bw/d and no teratogenicity was observed up to the highest dose (5654 mg/kg bw/d) tested (Ema et al., 2005). In this test, maternal body weight gain was significantly decreased in the group exposed to a dose of 5654 mg/kg bw/d and the food consumption similarly decreased in mid- and high-dose dams throughout pregnancy compared to controls. Decreases were also recorded in water consumption throughout gestation in the mid- and high-dose dams. There were no statistically significant differences between exposed and control rats in placental weight or numbers of corpora lutea, implantations, pre- or post-implantation losses, resorptions, or live or dead fetuses. The sex ratio of the offspring did not differ among the groups. Foetal body weight was significantly reduced in both male (8% lower

than controls) and female (10%) offspring of dams exposed to 5654 mg/kg bw/d. Body weights were decreased in the mid- and low-dose foetuses. However, the difference from control was not statistically significant. The crown-rump length of the offspring was not affected. The incidences of external, oral, and visceral malformations were not increased by treatment with butan-1-ol. At the highest dose, a statistically significant increase (20/20 versus 11/20 litters in controls) in the incidence of litters with skeletal variations (primarily short supernumerary ribs) was observed, as well as a decrease in the degree of ossification (number of forepaw proximal phalanges was 0.3 ± 0.4 versus 1.6 ± 1.3 in controls). These effects were considered to be variations and not adversely affecting the survival or health.

The obtained results demonstrated that in this study butan-1-ol exposure caused developmental toxicity only at maternotoxic doses. No evidence for teratogenicity of butan-1-ol was observed. Based on the significant decreases in maternal body weight gain, foetal weight and increased incidence of skeletal variations, the NOAEL for maternal toxicity and developmental toxicity was determined to be 1454 mg/kg bw/d in rats. The limit dose for this study type is 1000 mg/kg bw/d. Thus, the effects,which were observed clearly (2 – 5 fold) above this limit dose should be considered questionable or at least of minor relevance. Furthermore, the highest dose level considerably exceeded the oral LD50 in rats.

-Inhalation route:

The lack of specific developmental toxicity study on butan-1-ol is supported by inhalation studies in rats and rabbits with the read across substance n-Butyl-acetate.

In a prenatal developmental toxicity study in rabbits the NOAEC for maternal and developmental toxicity was 1500 ppm (7.2 mg/L, Hackett 1982a). In this study food consumption was decreased in Group 2 and 3 in the week following initiation of n-Butyl acetate exposure, but it was recorded also in controls. The body weight in Groups 2 and 3 were consistently higher than in controls; organ weights and histopathology appeared normal in the n-Butyl acetate exposed animals. Mating and reproductive performance and intrauterine mortality were unaffected by n-Butyl acetate exposure. Foetal growth parameters (foetal body weights and crown-rump length), placental weights, and sex ratios were not affected by n-Butyl acetate exposures. Foetal effects of n-Butyl acetate exposure included increased incidences of retinal folds, misaligned sternebrae, and morphological variations of the gallbladder in litters or rabbits exposed from gestation day 1 through 19. No major malformations were observed. The authors concluded that rabbit foetuses were unaffected by n-Butyl acetate exposure as none of the effects occurred consistently in both exposure groups.

In a prenatal developmental toxicity study in rats the LOAEC for maternal and developmental toxicity 1500 ppm (7.2 mg/L, Hackett 1982b). The developmental effects were associated with clear maternal toxicity and they were not considered as independent effects. Food consumption, body weight and liver weight was reduced in maternal rats exposed to n-Butyl acetate. Foetal size was reduced in all n-Butyl acetate exposed litters. Increased incidences of foetal rib dysmorphology were observed in rats exposed from gestation day 7 through 16, and more numerous hydroureters in foetuses from rats exposed prior to mating and from gestation day 1 through 16. There was no evidence of teratogenic effects following exposure of rats to 1500 ppm of n-Butyl acetate.

In a supporting behavioural peri-, postnatal developmental neurotoxicity study in rats with butan-1-ol the parental NOAEC including behavioural or teratogenic effects was 6000 ppm (18.5 mg/L, Nelson 1989b). In this test no general toxicity to maternal and paternal animals was reported. No effect on pregnancy rate was found after either maternal or paternal exposure. There were no behavioral changes in the offspring in terms of their performance in ascent test, rotorod performance, open field performance, or operant conditioning. The study authors also indicated that the changes in both the neurobehavioral tests and neurotransmitter concentrations observed in the animals exposed to butan-1-ol were within the range of control data from their laboratory or within normal biological variance.

In a supporting prenatal developmental toxicity study in rats with butan-1-ol the NOAEC for maternal toxicity was 500 ppm (2.4 mg/L), and for developmental toxicity was 2000 ppm (9.6 mg/L). Sprague-Dawley rats (19 -21 pregnant rats/dose group) were exposed from day 6 to 20 of gestation to concentrations of 0, 500, 1000, 2000, 3000 ppm (corresponding to 0, 2.4, 4.8, 9.6 and 14.5 mg/L) for 6 h/d. Under the conditions of this test maternal toxicity was evident at concentrations of 1000 ppm or higher. Significant decrease in body weight gain was reported at 2000 and 3000 ppm; reduced food consumption was observed at and above 1000 ppm. The only effect on prenatal development observed was a significant decrease in foetal weight at 3000 ppm that can be the consequence of the maternal toxicity as the body weight gain and food consumption decreased in this group significantly during the pregnancy.

-Assessment of developmental neurotoxicity:

Recently an overview on butan-1-ol induced developmental neurotoxicity and the potential mechanisms related to these effects was published (Bale AS and Lee JS, 2016), in which several papers were mentioned, among others Sitarek et al. (1994), Ema et al. (2005), Nelson et al. (1989a), Nelson et al. (1989b). Based on their evaluation, the authors stated that notable signs of neurotoxicity and developmental neurotoxicity have been observed in some studies where laboratory animals (rodents) were gestationally exposed, and that mechanistic data supported these observations.

The evaluating Member State followed the assessment of the above mentioned studies and found that the authors' (Bale and Lee) conclusion is not coherent regarding the developmental neurotoxicity effects of butan-1-ol.

In another in vitro study (Hen's Egg Test Chorioallantoic Membrane (HET-CAM)) the observed effects (corneal opacity and nerve damage) can be clearly associated to the local irritation effects of butan-1-ol (Eye Cat. 1, H318).

In the study of Sitarek et al. (1994), the author observed developmental anomalies in the foetus skeleton such as wavy in the 13th rib pair, presence of an extra rib in the 14th pair and central nervous system defects, but the study lacks historical control data. An own-breed species has been used in the study fed with non-standard diet makes the interpretation of observed effects difficult. Most of the reported "congenital defects" are listed as variations or delayed development in commonly used historical databases, and there is a lack of dose response relationship. The NOAEL for maternal and developmental toxicity was 5000 mg/kg bw/day, however the evaluating Member State consider that this data is questionable, given that this value is much higher than the oral LD50 value in rats.

Due to the above-mentoined limitations this study can not be accepted reliable, thus a clear indication for developmental toxicity or developmental neurotoxicity cannot be deduced from this study.

In the studies of Ema et al. (2005) and Nelson et al. (1989a) developmental toxicity of butan-1-ol appeared to be low and did not indicate selective foetal effects as it occurred only in the presence of maternal toxicity. In the study of Nelson et al. (1989b) the authors indicated that the changes in both the neurobehavioral tests and neurotransmitter concentrations observed in the animals exposed to butan-1-ol were within the range of control data from their laboratory or within normal biological variance. Overall there is no indication that butan-1-ol induces developmental neurotoxicity.

Summary of reproductive toxicity assessment

The evaluating Member State concluded that based on the experimental results of the developmental toxicity studies, butan-1-ol did not have an adverse effect on fertility. Results from valid experimental studies showed no indication, that butan-1-ol caused developmental toxicity/developmental neurotoxicity/teratogenicity in doses below maternal toxic doses in rats. The lack of specific developmental toxicity/developmental

neurotoxicity/teratogenicity is confirmed by inhalation studies in rats and rabbits with the read across substance n-Butyl acetate.

Based on the available data after a weight-of-evidence determination the evaluating Member State concluded that butan-1-ol is not a reproductive toxicant and the concern for reproductive toxicity (including developmental neurotoxicity) was removed in this substance evaluation.

7.9.9. Hazard assessment of physico-chemical properties

Not relevant for this evaluation.

7.9.10. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

Based on the available scientific data the evaluating Member State selected the following qualitative/semi-quantitative descriptors for the assessment of butan-1-ol's critical health effects.

Acute toxicity:

-Oral:

In a study comparable to OECD TG 401 the acute LD50 value was determined to be 2.83 mL/kg bw in female rats, corresponding to 2290 mg/kg bw (calculated with a density of 0.81 g/mL). The evaluating Member State selected the acute oral toxicity (LD50) value of 2290 mg/kg bw for human health assessment.

-Dermal:

The acute dermal toxicity of butan-1-ol was tested in a study comparable to OECD TG 402 (Union Carbide Corporation 1951). Four doses of 1.26 to 10 mL/kg bw were applied to groups of four male rabbits and an LD50 value of 4.24 mL/kg bw (corresponding to ca. 3434 mg/kg bw; calculated with a density of 0.81 g/mL) was determined after an observation period of 14 days. The evaluating Member State concluded that the application of the acute dermal toxicity (LD50) value of 3434 mg/kg bw for human health assessment is appropriate.

Inhalation:

The acute inhalation toxicity of butan-1-ol was investigated in three studies in rats. Among them, in a study similar to OECD TG 403, 10 Sprague-Dawley rats per sex per dose were whole-body exposed to vapour atmospheres of butan-1-ol for 4 h and observed for 14 days. The LC0 is >17.76 mg/L; no mortality or clinical signs were observed at 17.76 mg/L; only slightly reduced body weight gain was observed. The LC50 value can be estimated as above 20 mg/L and the evaluating Member State used this value for the assessment.

-Repeated dose:

-Oral:

The evaluating Member State agreed in application of NOEL for repeated dose toxicity of 125 mg/kg bw/d (nominal) for male and female rats based on test material, as no effects were observed in a 90-day repeated dose study at this dose level. LOEL of 500 mg/kg bw/d can be set based on transient clinical signs of CNS depression (ataxia and hypoactivity).

-Inhalation:

The only available study on butan-1-ol was not suitable for NOAEC/LOAEC determination (Jajte et al. 2003).

Therefore, for the inhalative route, reliable data were taken from the read-across substance, n-Butyl acetate (CAS-No. 123-86-4). A definitive subchronic toxicity study (6 h/day, 5 days/week 65 exposure days) was performed with n-Butyl acetate according to EPA guideline OTS 798.2450 (Bernard, 1996). The no-observed-effect level (NOEL) for this study is considered to be 500 ppm = 2.35 mg/L.

-Toxicity to reproduction:

-Fertility:

Information on the possible effects of butan-1-ol on the reproductive organs administered by oral route is available in a 90-day repeated dose toxicity study in rats (US EPA 1986). No dose-related differences were observed between treatment or control rats with regards to reproductive organs up to the highest dose. Thus, the NOEL for reproductive organ toxicity was 500 mg/kg bw/d.

Furthermore, butan-1-ol has been tested via inhalation in a behavioural peri-, postnatal developmental neurotoxicity study in rats (Nelson 1989a). In this study no effects on maternal or parental general toxicity were observed and no effects on the pregnancy rate after either maternal or paternal exposure were reported up to the highest concentration. Thus, 6000 ppm (18.5 mg/L) was a NOAEC for parental toxicity including fertility.

Therefore, the evaluating Member State agreed to set the overall NOAEL of butan-1-ol for fertility for the oral route as 500 mg/kg bw/day. For the inhalation route the NOAEC of butan-1-ol for fertility is 6000 ppm (18.5 mg/L).

-Developmental toxicity:

In a key study of prenatal developmental toxicity in rats the NOAEL for maternal and developmental toxicity was determined in 1454 mg/kg bw/d, no teratogenicity was observed up to the highest dose (5654 mg/kg bw/d) tested (Ema 2005). The obtained results demonstrated that in this study butan-1-ol exposure caused developmental toxicity only at maternal toxic doses. No evidence for teratogenicity of butan-1-ol was observed. Based on the significant decreases in maternal body weight gain, foetal weight and increased incidence of skeletal variations, the NOAEL for maternal toxicity and developmental toxicity is 1454 mg/kg bw/d in rats.

7.9.11. Conclusions of the human health hazard assessment and related classification and labelling

The assessment of the human health hazard endpoints affirmed the appropriateness of the substance's current harmonised classification (see section 7.6.1.).

7.10. Assessment of endocrine disrupting (ED) properties

Not evaluated.

7.11. PBT and vPvB assessment

Not evaluated.

7.12. Exposure assessment

7.12.1. Human health

Based on the available literature data and physico-chemical properties, the evaluating Member State concluded that there are three possible exposure routes for butan-1-ol: oral, inhalation and dermal. However, the ingestion is probable only in the following cases: in a minor degree - natural sources in foods and drinks; or accidental/misuse poisoning, although no poisoning reports were found. Thus the evaluating Member State considered only the inhalation and dermal uptakes as relevant routes of exposure.

Butan-1-ol has approximately half the vapour pressure of water, thus exposure via inhalation is probable, especially when aerosol formation can occur.

Several studies confirmed that butan-1-ol can absorb through the intact skin, while solvent co-exposures increase and ventilation decreases absorption (Boman and Maibach 2000, DiVincenzo and Hamilton, 1979). The evaluating Member State carried out a computer modelling by the on-line application UPERCUT (Gorman et al. 2016). It indicated 88% probability that the dose from dermal uptake passes the amount that one may get from 8-hour inhalation exposure at the level of an occupational exposure limit (parameters: 480 minutes exposure, both hands and arms exposed to butan-1-ol). Although this is a worst-case scenario and the limit value that the program uses is set for inhalation irritation (not systemic effects), the modelling emphasises the consideration of the dermal route.

Animal studies applied oral, inhalation and intravenous intakes. During inhalation and intravenous administration the first-pass metabolism effect of the liver is not present. However, no study was found to indicate relevant differences in toxicokinetics and toxicodynamics in relation to intake ways.

Butan-1-ol has a low sensory odour limit and irritant properties to the mucous membranes at higher concentrations (Cometto-Muniz & Cain 1998). The evaluating Member State assessed that in reliable human (epidemiological, occupational) studies only acute irritative effects on the mucous membranes, and mild passing acute central nervous depression ("dizziness") could be observed.

There are contradicting reports regarding the limit for respiratory tract irritation in humans, ranging values from 25 ppm (Nelson et al. 1943) in chamber to 4163 ppm applied directly into the nose in a mineral oil solution (Cometto-Muniz & Cain 1998). An overview of studies concluded that regarding the eyes "a concentration of 50 ppm poses some risk of mild irritation in persons who have not adapted to 1-butanol" (James, 1996).

The calculation in a follow up study of the overview above, in which the authors determined limit values in spacecrafts, concluded that up to 80 ppm the human central nervous system can be considered unaffected (James, 2008).

Worker

Exposure and work with 100% butan-1-ol is rare and is limited to manufacture; exposure is usually mixed with other organic solvents in preparations. There is little data available on direct and indirect exposure measurements for butan-1-ol. Exposure levels ranged between 0.02-32.6 ppm in furniture and woodworking factories using lacquers and paints.

In 95% of workers in the acrylate industry the exposure did not exceed 1.62 ppm (Tuček et al. 2002) and it ranged 7.0-16.60 ppm for painting ships in confined spaces (Costa &

Costa 2002). In parquet layers the average value of 21.6 ppm was accompanied with peaks up to 400 ppm (Denkhaus et al. 1986).

Substantial inhalation exposure may occur during aerosol formation however the evaluating Member State could not identify measurement data sources that could specify aerosol exposure. Nor the Registrant could provide datasets concerning this issue.

The evaluating Member State concluded that the dermal uptake route can be significant and would need targeted prevention measures in scenarios where the skin could be in prolonged contact with high concentrations of the substance.

Furthermore, it is probable that inhalation and dermal doses may add together, because the evaluating Member State did not find any publication on different metabolism via the skin versus the lung.

It cannot be excluded that long-term exposure to butan-1-ol and acute ethanol ingestion may impair antioxidant capacity and lipid membranes. This presumption is based on a single animal study (Jajte et al. 2003). Nonetheless, it may require special consideration to be given to affected worker groups.

The lack of measurement data regarding aerosol generating activities is a source of uncertainty. Micro- and small enterprises are unlikely to use automatic spraying booths, and may not have local exhaust ventilation installed.

Consumer

Prolonged substantial exposure is less likely for consumers because butan-1-ol is mainly used in products that are either used rarely (paints) or the preparations contain only a small amount of butan-1-ol (cleaning products).

7.12.2. Environment

Not evaluated.

7.12.3. Combined exposure assessment

Not evaluated.

7.13. Risk characterisation

-Workers:

The current European occupational exposure limit values range in between 15 and 100 ppm. Exposures within the industry published in the last three decades scarcely exceeded 30 ppm. The highest published exposure was peak exposure up to 400 ppm. It could not be verified whether these exposures were built up from vapours or included aerosols as well.

In a study in men exposed to 100-200 ppm (i.e. 300-600 mg/m^3) concentrations during exercise and resting the uptake of butyl alcohol taken up via lungs was below 50% (36-

47%)(Ästrand et al. 1976). In the calculation of the evaluating Member State 60% absorption from the lungs was assumed: if a person stayed for an entire shift (breathing volume: 10 m^3) exposed to 400 ppm butan-1-ol could result a dose no more than of 7.4 grams. It is 106.3 mg/ kg bw for a 70 kg person. This is still 13.7 times lower than the NOAEL observed in the key animal study for (maternal and developmental) toxicity (1454 mg/bwkg/d). Based on this calculation, the evaluating Member State concluded that solely inhalation of butan-1-ol is not a concern in relation to these endpoints.

Furthermore, it cannot be ruled out that dermal uptake may be a substantial route and with a high inhalation exposure the RCR may get close to 1.

As the above mentioned risks can be managed by appropriate measures (local exhaust ventilation, protective clothing and gloves, respiratory protection) and butan-1-ol is typically not used in 100% concentrations in the activities of concern, the evaluating Member State concluded that there is no overall concern for worker exposure, and the risk management measures indicated in the CSR by the Registrant are appropriate.

-Consumers:

The evaluating Member State concludes that consumers may be at risk only during excessive use and poisoning.
Butan-1-ol is readily biodegradable in the environment. Foods may naturally contain low doses of butan-1-ol and is also used in the food industry (OECD 2001). Altogether, the evaluating Member State concludes that indirect exposure of humans via the environment is negligible.

-Human health (combined for all exposure routes):

The evaluating Member State concludes that there is no concern for risks posed by butan-1-ol if appropriate good practice is followed. If in a use scenario the containment of butan-1-ol is not complete, appropriate measures needs to be applied to avoid skin contact (gloves, protective clothing) and inhalation (respiratory protection) especially in cases where aerosol formation is substantial. Consumer risk is only possible during excessive use and poisoning. The above conclusion of the evaluating Member State is reinforced by the fact that despite the high tonnage production, no reliable publication is available on substantial ill-health due to butan-1-ol.

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7.15. Abbreviations

CHO - Chinese hamster ovary

CNS - Central nervous system

CSR – Chemical Safety Report

DMEL - Derived minimal effect level

DNEL - Derived no-effect level

EPA - United States Environmental Protection Agency

GLP – Good Laboratory Practice

HPRT - Hypoxanthine-Guanine Phosphoribosyltransferase

LC0 – No lethal concentration

LD50 – Median lethal dose

LLNA - Local lymph node assay

LOAEC - Lowest observed adverse effect concentration

LOEL - Lowest observed effect level

NOAEC - No observed adverse effect concentration

NOAEL - No observed adverse effect level

NOEL - No observed effect level

OECD - Organisation for Economic Co-operation and Development

PBT – Persistent, bioaccumulative and toxic

(Q)SAR – (Quantitative) Structure-Activity Relationship

RCR – Risk Characterisation Ratio

RMM – Risk Management Measure

SCE - Sister-chromatid exchange

SVHC - Substance of very high concern

U.S. EPA - United States Environmental Protection Agency