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Toxicological basic data for the derivation of EU-LCI values for five substances

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Abstract: Toxicological basic data for the derivation of EU-LCI values for five substances

The subject of this report is the preparation of substance reports for the derivation of EU-LCI values for five substances found in construction products emissions. EU-LCI values are health-based reference concentrations for inhalation exposure of the general population. For their derivation, the toxicological data basis for the substances is researched, compiled and evaluated, and EU-LCI values are derived based on the guidance given in the ECA report No. 29 (EC, 2013). Already existing evaluations and values and the quintessential data for the derivation of the EU-LCI values for the substances are also presented according to the guidance of the ECA report in "fact sheets" and "data collection sheets".

The LCI values derived within the scope of this project are proposals. The final EU-LCI values will be determined by the EU-LCI Working Group, a group of experts from ten European countries. This Working Group is developing a harmonised European list of substances and their corresponding emission limits (EU-LCI values) for building products. The procedure of the EU-LCI Working Group in the derivation of these European reference values for building product emissions in indoor air has been harmonised with all stakeholders and published in the ECA report No. 29 (EC, 2013). All interested parties may keep themselves informed about the ongoing progress in the derivation of EU-LCI values on the website of the Working Group (https://ec.europa.eu/growth/sectors/construction/eu-lci/values_en). The German Environment Agency has continuously worked that the harmonisation initiative will be put forward by the European Commission. In November 2015, the Commission mandated the EU-LCI Working Group to finalise the EU-LCI list. The substance dossiers prepared within the scope of this project will add in and accelerate this process.

This report is part of a series of evaluations for a number of other substances performed on behalf of the German Environment Agency (Umweltbundesamt) by the same authors in previous projects (e.g., Voss et al., 2024).

References

EC (2013) Harmonisation framework for health-based evaluation of indoor emissions from construction products in the European Union using the EU-LCI concept. Report No 29. EUR 26168 EN. Joint Research Centre, Institute for Health and Consumer Protection, Chemical Assessment and Testing Unit. Online: https://op.europa.eu/en/publication-detail/-/publication/d3d78842-bc95-4984-a2fe-2317731324bd

Voss, JU; Bierwisch, A; Kaiser, E (2024). Toxicological basic data for the derivation of EU-LCI values for ß-pinene, other terpenes, pentanols, 5-chloro-2-methyl-4-isothiazolin-3-one (CIT) and 2-methyl-4-isothiazolin-3-one (MIT). Agency, GE. Berlin, Germany. https://www.umweltbundesamt.de/sites/default/files/medien/11850/publikationen/54_2024_toxicological_basic_data.pdf

Kurzbeschreibung: Toxikologische Basisdaten für die Ableitung von EU-LCI-Werten für fünf Stoffe

Gegenstand des Berichts ist die Erstellung von Stoffberichten für die Ableitung von EU-LCI-Werten für fünf Stoffe, die aus Bauprodukten emittieren. EU-LCI-Werte sind gesundheitsbasierte Referenzkonzentrationen für die inhalative Exposition der Allgemeinbevölkerung. Zur Ableitung wurden die toxikologischen Basisdaten für diese Stoffe recherchiert, zusammengestellt und bewertet und auf Basis der Vorgaben des ECA-Berichts Nr. 29 (EC, 2013) EU-LCI-Werte abgeleitet. Bereits bestehende Bewertungen und Richtwerte für diese Stoffe wurden gemäß den Vorgaben des ECA-Berichts in "data collection sheets" und die für die Ableitung der EU-LCI-Werte wesentlichen Daten in "fact sheets" zusammengestellt.

Bei den im Rahmen dieses Vorhabens abgeleiteten LCI-Werten handelt es sich um Vorschläge. Die endgültigen EU-LCI Werte werden von der EU-LCI Arbeitsgruppe, einer Expertengruppe mit Fachleuten aus zehn europäischen Ländern, festgelegt. Diese Arbeitsgruppe erarbeitet aus den verschiedenen Bewertungsstofflisten von Emissionen aus Bauprodukten eine harmonisierte europäische Liste mit Stoffen und den dazugehörigen Emissionsgrenzen (EU-LCI Werte). Die Vorgehensweise der EU-LCI-Arbeitsgruppe bei der Ableitung dieser europäischen Referenzwerten für Bauproduktemissionen in die Innenraumluft ist mit allen Stakeholdern abgestimmt und im ECA-Bericht Nr. 29 publiziert (EC, 2013). Über den aktuellen Fortschritt bei der Ableitung der EU-LCI-Werte können sich alle Interessierten auf der Website der EU-LCI Arbeitsgruppe informieren (https://ec.europa.eu/growth/sectors/construction/eu-lci/values_en). Das Umweltbundesamt hat in den letzten Jahren darauf hingearbeitet, dass die Europäische Kommission diese Harmonisierungsinitiative weiter voranbringt. Im November 2015 hat die Europäische Kommission das Mandat zur Fertigstellung der EU-LCI Liste an die EU-LCI-Arbeitsgruppe erteilt. Die im Rahmen dieses Forschungsvorhabens ausgearbeiteten Stoffdossiers unterstützen und beschleunigen diesen Prozess.

Dieser Bericht ist Teil einer Reihe von Bewertungen für eine Anzahl weiterer Stoffe, die von denselben Autoren im Auftrag des Umweltbundesamtes in früheren Projekten durchgeführt wurden (siehe etwa Voss et al., 2024).

Quellen

EC (2013) Harmonisation framework for health-based evaluation of indoor emissions from construction products in the European Union using the EU-LCI concept. Report No 29. EUR 26168 EN. Joint Research Centre, Institute for Health and Consumer Protection, Chemical Assessment and Testing Unit. Online: https://op.europa.eu/en/publication-detail/-/publication/d3d78842-bc95-4984-a2fe-2317731324bd

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List of abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
AgBB	Ausschuss zur gesundheitlichen Bewertung von Bauprodukten (Committee for Health-related Evaluation of Building Products)
ANSES	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (French Agency for Food, Environmental and Occupational Health and Safety)
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxytoluene
CAS	Chemical abstract service
CLH	Harmonised Classification and Labelling
CLP	Classification, labelling and packaging
CNS	Central nervous system
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation)
DNEL	Derived no effect level
DPGME	Dipropylene glycol mono methyl ether
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EFSA ANS	EFSA Panel on Food Additives and Nutrient Sources added to Food
EU	European Union
F	Female(s)
GD	Gestation day
GLP	Good laboratory practice
GSD	Geometric standard deviation
IUPAC	International union of pure and applied chemistry
IOEL	Indicative Occupational exposure limit
LCI	Lowest concentration of interest
LO(A)EC/L	Lowest observed (adverse) effect concentration
LoD	Limit of detection
Log Pow	Logarithm of octanol/water partition coefficient
M	Male(s)
MAK	Maximale Arbeitsplatzkonzentration (Maximum workplace concentration)
MMAD	Mass median aerodynamic diameter
MW	Molecular weight/mass
NIK	Niedrigste Interessierende Konzentration (Lowest concentration of interest)
NLM	National Library of Medicine
NO(A)EC/L	No observed (adverse) effect concentration/level
OECD	Organization for economic cooperation and development
OEL	Occupational exposure limit

PGME	Propylene glycol monomethyl ether
PND	Postnatal day
POD	Point of departure
REACH	Registration, evaluation, authorization, and restriction of chemicals
SCCS	Scientific Committee on Consumer Safety
SCOEL	Scientific Committee on Occupational Exposure Limits
TBHQ	Tertiary butylhydroquinone
VKM	Vitenskapskomiteen for mat og miljø (Norwegian Scientific Committee for Food and Environment)

Summary

Substance profile and proposed EU-LCI-value for 2,6-di-tert-butyl-4-methylphenol (3,5-di-tert-butyl-p-cresol)

At room temperature, 3,5-di-tert-butyl-p-cresol (2,6-di-tert-butyl-4-methylphenol, 3,5-di-tert-butyl-4-hydroxytoluene, BHT) is an odourless, slightly yellowish solid with a very low vapour pressure. The substance is primarily used as an antioxidant. BHT is contended in a wide range of products, including plastics, rubber, mineral oil products, cosmetics, packaging materials, paints, and adhesives. BHT is also used as a food additive.

BHT may be released into indoor air through paints and adhesives used on large surfaces. However, the database regarding measured concentrations of BHT in indoor air is very limited with reported detection frequencies < 10 % and maximum concentrations < 10 µg/m^3.

Regarding oral uptake from food, conservative estimates concluded that the exposure of adults to BHT is unlikely to exceed the ADI of 0,25 mg/(kg bw x d). For exposure of children to BHT from its use as food additive, it is also unlikely that the ADI for BHT is exceeded at the mean, but may be exceeded for some European countries at the 95th percentile.

No quantitative data is available on the uptake of BHT through the respiratory tract. Toxicokinetic data for humans indicate that at least 75 % of an orally applied dose is absorbed, and data from rat studies indicate near complete absorption (90 %) after oral intake.

No toxicological studies in humans are available which are relevant for the derivation of an EU-LCI value for BHT.

The only inhalation toxicity studies available are studies on sensory irritation in mice (Alarie test). An Alarie test regarded as reliable provided an RD50 of 59.7 ppm (about 546 mg/m^3).

No studies are available with repeated inhalation exposure. A number of animal studies with repeated oral exposure of mice and rats showed that the liver is the main target of BHT effects including histopathological hepatocellular changes.

The majority of evidence indicates a lack of potential for BHT to induce point mutations or chromosomal aberrations, or to interact with or damage DNA. Positive genotoxicity results obtained *in vitro* with BHT and BHT metabolites may be due to pro-oxidative chemistry, such a mechanism of genotoxicity is generally considered to have a threshold. It was concluded that BHT is not of concern with regard to genotoxicity.

A dose-related increase in the numbers of hepatocellular carcinomas was observed in male rats and an increase in the number of hepatocellular adenomas in both males and females fed BHT. In a further study with rats, a higher incidence of foci and in the number of rats with hepatic nodules was observed in the high-dose group but no adenoma or carcinoma. Taking into account the data from the genotoxicity studies, the EFSA-ANS panel (European Food Safety Authority Panel on Food Additives and Nutrient Sources added to Food) concluded that the mode of action of tumour formation by BHT is based on a threshold mechanism.

In a two-generation study, rats were fed BHT in the diet at doses of 0, 25, 100 or 500 mg/(kg bw x d) for 3 weeks prior to mating. The highest dose was reduced to 250 mg/(kg bw x d) in the F1-generation. In the first 5 weeks of BHT administration, a reduction in body weight gain was noted in the high-dose males. At the sacrifice on day 20 of gestation, both absolute and relative liver weights of the dams were increased in a dose-related manner, statistically significant at the high dose. Body weights of the pups from the high-dose group were significantly lower than controls at birth and at days 6 and 21 of lactation. Body weights of the F1 males were lower in the high-dose group throughout the 22-month treatment period. Dose-related increases were

observed in relative, but not absolute liver weights; the differences were statistically significant at the high dose. A dose-related incidence of enlargement and eosinophilia of the centrilobular hepatocytes was also observed. This was indicative of proliferation of the smooth endoplasmic reticulum, consistent with an induction of mixed-function oxidases and of total cytochrome P450 content. Total cytochrome P450 content was increased by 30 - 60 % in the high-dose animals starting at 21 days of age. Dose-related increases were noted in epoxide hydrolase, glutathione-S-transferase and pentoxyresorufin-O-depentylase (PROD) activities, which were statistically significant in the mid- and high-dose groups. The increases in PROD activity were large, 10 – 25fold in the mid-dose, and 20 – 80fold in the high-dose groups.

Based on the NOAEL of 25 mg/(kg bw x d) from two two-generation studies in rats and using an uncertainty factor of 100, the EFSA-ANS Panel derived an ADI of 0.25 mg/(kg bw x d).

The NOAEL of 25 mg/(kg bw x d) obtained in a two-generation study with oral exposure of rats with BHT is also used as POD for the derivation of an EU-LCI value. This NOAEL is based on systemic effects. A route-to-route extrapolation is performed to derive an EU-LCI value for inhalation exposure.

Toxicokinetic data from rat studies indicate near complete absorption (90 %) after oral intake. Absorption after inhalation is, in the absence of experimental data, assumed to be complete by default. It is concluded that BHT is similarly absorbed orally and after inhalation, and no additional assessment factor is applied for differences in absorption.

The following assessment factors are used:

- Route-to-route extrapolation (rats): 1.15 m^3/(kg bw x d)
- Adjustment study length factor: 1
- Allometric scaling: already included in route-to-route extrapolation
- Interspecies extrapolation: 2.5
- Intraspecies extrapolation: 10

Total assessment factor: 25 x 1.15 = 28.75. This leads to a concentration of 25 mg/(kg bw x d) : 28.75 m^3//kg bw x d) = 0.879 mg/m^3 for BHT (rounded to 900 µg/m^3).

An EU-LCI value of 900 µg/m^3 is proposed for BHT.

The LCI-value proposed would fully exploit the ADI of 0.25 mg/(kg bw x d) established by the EFSA. However, exposure to BHT is mainly by oral uptake with food. Taking the oral exposure into account, an allocation for the exposure to BHT by inhalation could be considered. However, no such approach has been discussed, recommended or implemented yet in the harmonisation framework using the EU-LCI concept.

The proposed LCI value is more than 100fold lower than the concentration of 146 mg/m^3 which caused no signs of sensory irritation in mice in an Alarie-test and more than 500fold lower than the RD50 determined in that test.

BHT is reported to be an odourless or nearly odourless compound. No odour threshold for BHT is available.

Substance profile and proposed EU-LCI-value for benzyl alcohol

Benzyl alcohol is a colourless, oily liquid with a faint aromatic and fruity odour. It has a wide range of uses, for example as curing agent in epoxy coatings, as solvent in waterborne coatings or inks, as co-additive for dyeing in the textile industry, in photographic developers, as preservative in cosmetics, pharmaceutical and medicine products, as food additive in flavourings, and as fragrance component in parfums and cosmetics. Naturally benzyl alcohol occurs e.g. in plants, mushrooms, fruits, nuts, spices, and alcoholic beverages. Benzyl alcohol concentrations measured in indoor air were low, with medians of 0.5 µg/m^3 or below the detection limit.

In an oral toxicokinetic study in humans, the substance was rapidly and almost completely absorbed, with 75-85 % of the administered dose being metabolised and excreted in the urine within six hours. In humans, metabolism of benzyl alcohol involves liver oxidation by cytochrome P450 enzymes to benzaldehyde, then to benzoic acid, after conjugation with glycine, is excreted renally as hippuric acid. At high doses, glycine conjugation capacity saturates, leading to unchanged benzoic acid or glucuronic acid conjugate excretion. An *in vivo* dermal absorption study in rhesus monkeys and *in vitro* studies on human skin showed that absorption of benzyl alcohol through the skin is good (up to 80 % of the applied dose) and is expected to contribute in a relevant way to systemic toxicity.

In an acute inhalation study in rats, a 4-h-LC50 of > 4178 mg/m^3 was determined. The acute dermal toxicity of benzyl alcohol is low as shown by a LD50 value of 2000 mg/kg bw in rabbits. Oral LD50 values in animals ranged from 1000-3100 mg/kg bw with symptoms including neurotoxicity (CNS depression, impact on CNS, irritability, and coma). In valid OECD test guideline (TG) studies, benzyl alcohol did not cause skin irritation in rabbits but did cause eye irritation. It showed no skin sensitising potential in a mouse LLNA assay. Human data from case reports, repeated insult patch tests, and patch tests showed positive responses to benzyl alcohol. Compared to the widespread use of benzyl alcohol and the large number of people exposed, the observed positive responses are low. Overall, several expert committees do not consider benzyl alcohol to be a skin sensitiser.

In a subacute inhalation study in rats (according to OECD TG 412, unpublished study report), repeated “nose-only” exposure to benzyl alcohol resulted in a concentration-dependent increase (12.5 % at 290 mg/m^3 and 15.4 % at 1072 mg/m^3) in the relative weight of the epididymis at 290 mg/m^3 and above. This was the only statistically significant effect reported in the registration dossier on the ECHA’s disseminated database and thus a NOAEC of 1072 mg/m^3 was derived. In addition, the MAK commission reported histological findings in the respiratory tract, particularly in the lungs, at 1072 mg/m^3 (only high concentration group and controls were examined histopathologically). Therefore, the MAK commission derived a LOAEC of 1072 mg/m^3 and estimated a NAEC (no adverse effect concentration) of 300 mg/m^3 (based on LOAEC/3).

In valid subchronic oral studies, mice and rats were exposed to up to 800 mg benzyl alcohol/(kg bw x d) by gavage 5 d/w for 13 weeks. Both species showed reduced body weight gain, which resulted in derived NOAELs of 400 mg/(kg bw x d) in rats and 200 mg/(kg bw x d) in mice. These studies have some shortcomings: several animals died due to handling errors during gavage and severe toxicity was observed as evidenced by neurotoxic effects in the highest dose group.

In vitro tests did not provide evidence of genotoxic effects of benzyl alcohol in bacteria. However, *in vitro* studies in mammalian cells were inconclusive. Based on *in vivo* studies in mice, rats and *Drosophila melanogaster* benzyl alcohol was not considered to be genotoxic in somatic or germ cells.

No carcinogenic effects of benzyl alcohol were observed in 2-year carcinogenicity studies in mice and rats.

Studies regarding effects of benzyl alcohol on fertility are not available. Subacute exposure to benzyl alcohol in rats showed a concentration-dependent increase in relative epididymis weight. Benzyl alcohol led to a decrease in foetal body weight at maternally toxic doses in developmental toxicity studies in mice, rats and rabbits (NOEL of 550 mg/(kg bw x d) in mice and 250 mg/(kg bw x d) in rats and rabbits).

The subacute inhalation toxicity study in rats is regarded as valid and suitable for deriving an EU-LCI value.

The following assessment factors are used:

- LOAEC-NOAEC extrapolation: 3
- Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6
- Adjusted study length factor: 6
- Interspecies extrapolation: 2.5 (allometric scaling not performed since route of exposure is inhalation)
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 2520 leading to a value of 1072 mg/m^3 : 2520 = 0.425 mg/m^3 for benzyl alcohol (rounded to 450 µg/m^3).

An EU-LCI value of 450 µg/m^3 is proposed for benzyl alcohol.

The proposed EU-LCI value is below the reported odour threshold of 25 mg/m^3 (5.5 ppm).

Substance profile and proposed EU-LCI value for dipropylene glycol monomethylether

Dipropylene glycol monomethylether (DPGME) is a multi-constituent glycol ether and its commercial product consists of four isomers: 1-(2-methoxy-1-methylethoxy)propan-2-ol, 2-(2-methoxy-1-methylethoxy)propan-1-ol, 1-(2-methoxypropoxy)propan-2-ol, and 2-(2-methoxypropoxy)propan-1-ol. All available data refer to the technical mixture.

DPGME is miscible in water and numerous organic solvents and has a mild, pleasant, ethereal odour. The substance has a widespread use as an ingredient in industrial products and commercial and household cleaning products. DPGME concentrations measured in indoor air were low, with medians of 0.5 µg/m^3 or below the detection limit.

In a toxicokinetic study with oral administration of ^{14}C-DPGME to rats, 60 % of radioactivity was detected in the urine, 27 % in exhaled air and <3 % in faeces within 48 h after dosing. It is metabolised primarily by microsomal O-demethylation, forming metabolites via glucuronic acid and sulphate conjugation, and hydrolysis to dipropylene glycol. Of minor importance is the metabolism pathway by hydrolysis of the dipropylene moiety of DPGME to propylene glycol monomethyl ether (PGME) and propylene glycol. When compared to its degradation products, studies have shown that DPGME is equal to or less toxic than propylene glycol, dipropylene glycol and PGME. An *in vitro* dermal absorption study (according to OECD TG 428) on human skin showed that DPGME can penetrate the skin and its absorption may contribute in a relevant way to the systemic toxicity.

Workers painting with water-based paints containing DPGME at levels of 5 - 7 ppm (30 - 40 mg/m^3) in indoor air reported no symptoms nor signs of irritation, while another study reported that 35 ppm DPGME caused slight irritation to the nose/upper respiratory tract and above 75 ppm irritation of the respiratory tract, eyes and throat. A concentration of 300 ppm DPGME was found to be unpleasant by volunteers.

The acute dermal and oral toxicity of DPGME was low in animals (LD50 values > 5000 mg/kg bw). No mortality was observed in acute inhalation studies in rats exposed to vapour concentrations of DPGME up to the maximum attainable concentration at room temperature of 500 or 552.6 ppm (corresponding to 3100 or 3404.47 mg/m^3) for 7 or 8 h, respectively. The only observed clinical sign was mild narcosis. DPGME was not irritating to the skin but was irritating to the eyes in humans and animals. No skin sensitisation potential of DPGME was observed in patch tests on a total of 250 volunteers.

In a subchronic inhalation study (similar to OECD TG 413) rats and rabbits were exposed to DPGME by whole-body inhalation for 13 weeks (6 h/d, 5 d/week). No toxicologically significant effects were observed up to the highest test concentration of 200 ppm DPGME (NOAEC: 200 ppm).

DPGME was not genotoxic in *in vitro* studies (Ames test, chromosome aberration test, UDS-test). *In vivo* genetic toxicity data for DPGME are not available. For the structurally related glycol, PGME, a negative test result is available from a micronucleus test in mice.

Carcinogenicity studies with DPGME are not available. However, PGME showed no evidence of carcinogenicity in 2-year studies in mice and rats.

No studies are available on the reproductive toxicity of DPGME. Data on PGME were used in a read-across approach. In a two-generation reproductive toxicity study in rats, PGME showed no evidence of specific reproductive toxicity. Observed effects on reproductive parameters or organs in females were associated with systemic toxicity, and neonatal effects were considered to be secondary to maternal toxicity. A no-observed-effect level (NOEL) of 1000 ppm was derived for fertility and reproductive effects.

The NOAEC of 200 ppm (1220 mg/m^3 at 23 °C) obtained in the subchronic inhalation toxicity study in rats is used as POD for the derivation of an EU-LCI value.

The following assessment factors are used:

- Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6
- Adjusted study length factor: 2
- Interspecies extrapolation: 2.5 (allometric scaling not performed since route of exposure is inhalation)
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 280 leading to a value of 1220 mg/m^3: 280 = 4.357 mg/m^3 (rounded to 4400 µg/m^3).

An EU-LCI value of 4400 µg/m^3 is proposed for DPGME.

In the literature, an odour threshold of 35 ppm (210-216 mg/m^3) is reported for DPGME Therefore, it is not to be expected that the odour will be perceived at the proposed EU-LCI value.

Substance profile and proposed EU-LCI value for n-butyl acrylate

At room temperature, n-butyl acrylate (BA) is a colourless liquid with an odour described as "strong fruity" or "pungent, fragrant, acrid, fruity". BHT is only slightly soluble in water but soluble in most organic solvents.

BA is mainly used in the production of polymers and resins for textile and leather finishing, solvent-based coatings, adhesives, paints, binders and emulsifiers. The substance per se is not intended for consumer use, however, end-use consumer products may contain trace amounts of acrylic acid and its esters due to the polymerization process as residuals.

According to the few data available on measured concentrations in indoor air, BA is detected rarely (less than 5 % of performed measurements) and at low concentrations (maximum: 12 µg/m^3) in indoor air.

No quantitative data is available on the uptake of BA through the respiratory tract. Studies in rats show that following oral administration BA is rapidly absorbed, mainly hydrolysed by carboxyl esterase to acrylic acid and butanol and ultimately eliminated as CO_2. A minor portion (ca. 10 %) is conjugated to glutathione and excreted in urine.

No data regarding sensory irritation of BA are available from controlled human studies. However, no evidence of sensory irritation was observed in a study in which volunteers were exposed with 2.5 ppm ethyl acrylate for four hours with a peak of up to 5 ppm. An RD50 (concentration leading to decrease in breathing rate by 50 % as sign of respiratory irritation) of 340 ppm (1800 mg/m^3) for BA was determined in mice. This RD50 value is very similar to that of 315 ppm determined for ethyl acrylate.

Clinical findings, patch tests, and some clinical epidemiological studies showed that BA is a contact allergen. BA also showed a skin sensitising effect in animal studies.

No data are available regarding sensitising effects of BA on the respiratory tract.

No human data are available relevant for the derivation of an EU LCI-value.

In a subchronic inhalation toxicity study, rats were exposed against 0, 21, 108, 211, or 546 ppm BA (0, 111, 572, 1118, 2894 mg/m^3) 6 h/d, 5 d/week for 13 weeks. At the highest concentration, most animals died. Reported effects were bloody eye and nasal secretions, irritation of the nasal mucosa, metaplastic changes in the trachea and bronchi, and pulmonary hyperaemia and pneumonia. At 211 ppm irritant effects on the eyes and nasal mucosa, reduced body weight gain and increased relative liver weights were observed. The NOAEC of the study was considered to be 108 ppm (572 mg/m^3). At this concentration only minor effects, such as increased liver weights in female animals without histological correlate were observed.

In a chronic inhalation study, rats were exposed whole body against concentrations of 0, 5, 15 and 45 ppm BA (0, 27, 80, 240 mg/m^3) during the first 13 weeks and thereafter against concentrations of 0, 15, 45, or 135 ppm (0, 80, 240, 720 mg/m^3) for up to two years. The severity of nasal mucosa effects increased with concentration and the effects were seen at all doses in males and females. A NOAEC for local effects in the respiratory tract could not be determined. There were no indications of systemic toxicity, except for a slight decrease in food consumption and slightly lower relative heart, kidney, liver, and thyroid weights at the highest dose. The LOAEC in this study was 5 ppm, based on effects in the nasal epithelia.

In vitro genotoxicity studies in bacteria and in mammalian cells were negative or, at most, questionably positive at high cytotoxic concentrations. *In vivo*, no chromosomal aberrations were observed in the bone marrow of Chinese hamsters and rats after inhalation exposure, but chromosomal aberrations were observed in the bone marrow of rats after intraperitoneal

injection of BA. Overall, the available data for alkyl acrylates indicate that acrylate monomers are not genotoxic *in vivo*, and that positive findings *in vitro* are typically observed at cytotoxic concentrations. Based on a WoE (weight of evidence) analysis of the currently available data which took into account data from genotoxicity tests with methyl and ethyl acrylates, it was concluded that there is no concern for mutagenicity of BA.

No evidence of an increase in the incidence of tumours was observed in the chronic inhalation toxicity study with rats (see above), and no treatment-related tumours were observed in mice after skin applications of BA for lifetime.

In an extended one-generation reproductive toxicity study with oral exposure of rats, no evidence of reproductive toxicity was observed up to the highest dosage level of 150 mg BA/(kg bw x d). In an inhalation developmental toxicity study with rats, respiratory tract irritation and reduced body weight gain were noted in dams at 135 and 250 ppm. These concentrations also led to increased embryo lethality, but no teratogenic effect could be observed at any dose. The NOAEC for maternal toxicity and developmental toxicity was 25 ppm (135 mg/m^3). In a further developmental inhalation toxicity study with pregnant rats, the lowest test concentration of 100 ppm (530 mg/m^3) represented a NOAEC for developmental toxicity and a LOAEC for maternal toxicity. An oral developmental toxicity study with mice provided a NOAEL for maternal and developmental toxicity of 1000 mg/(kg bw x d). In rabbits, maternal toxicity was observed at 400 mg/(kg bw x d) but no embryotoxicity or teratogenicity.

The chronic inhalation toxicity study with rats is taken as the basis for the derivation of the EU-LCI. This study provided a LOAEC of 15 ppm BA (79.5 mg/m^3) but no NOAEC since adverse effects were observed down to the lowest applied concentration. A benchmark calculation was performed for the incidence of reserve cell hyperplasia with loss of olfactory or ciliated cells in the nasal olfactory epithelium of male or female rats, respectively. No satisfactory calculation was possible for the incidence in female rats, but the $BMDL_{05}$ of 4.86 ppm BA calculated for male rats is nearly identical with the value of 5 ppm BA obtained using the standard factor of three to extrapolate from a LOAEC to a NOAEC.

The following assessment factors are used:

- LOAEC to NOAEC: 3
- Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6
- Adjusted study length factor: 1
- Interspecies extrapolation: 2.5 (allometric scaling not performed since route of exposure is inhalation)
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 420 leading to a value of 79.5 mg/m^3: 420 = 0.189 mg/m^3 (rounded to 200 µg/m^3).

An EU-LCI value of 200 µg/m^3 is proposed for n-butyl acrylate (BA).

BA has a very low odour threshold 2.9 µg/m^3. It is therefore to be expected that the odour will be perceived at the proposed EU-LCI value.

Substance profile and proposed EU-LCI value for 2-ethylhexyl acrylate

At room temperature, 2-ethylhexyl acrylate (EHA) is a colourless liquid which is only slightly soluble in water but soluble in most organic solvents.

EHA is used as a plasticising co-monomer in the production of resins for pressure-sensitive adhesives, latex paints, reactive diluents and/or cross-linking agents, textile and leather finishes, and coatings for paper.

Few data are available on measured concentrations of EHA in indoor air. EHA could be detected in about 15 % out of 157 measurements but at low concentrations which did not exceed a maximum of 3 µg/m^3. In a larger number of measurement data, the 95th percentile was reported to be below 1.0 µg/m^3. Measurements of EHA residual monomers after painting with paints containing 940 ppm and 2,000 ppm a room with restricted ventilation revealed room air peak concentrations of 2.5 ppm (19 mg/m^3) and 8 ppm (60.8 mg/m^3). EHA was not detectable 25 hours after painting.

No quantitative data is available on the uptake of EHA through the respiratory tract. After oral dosing of rats with EHA about 90 % was eliminated during the first 24 hours, mostly as CO_2 via the expired air and a slightly lesser amount via metabolites with the urine.

Individual case reports were published on the allergenic effect of EHA on human skin. However, no sensitisation could be detected in occupational medical examinations. Thus, the sensitising effect in humans cannot be clearly assessed and the positive reactions described may be partly an expression of an immunological cross-reaction. A weak dermal sensitisation potential was observed in a local Lymph node assay (LLNA) in mice, and various former tests with guinea pigs also provided evidence that EHA is a skin sensitiser.

No data are available regarding sensitising effects of EHA on the respiratory tract.

No data regarding sensory irritation of EHA are available from controlled human studies. However, no evidence of sensory irritation was observed in a study in which volunteers were exposed with 2.5 ppm ethyl acrylate for four hours with a peak of up to 5 ppm. Animal studies with inhalation exposure demonstrate an irritating potential of the test substance, however, quantitative data (RD50 values) are not available.

Relevant repeated dose toxicity studies with EHA in humans are not available.

In a subchronic inhalation toxicity study, rats were exposed “whole body” to 0, 10, 30, and 100 ppm EHA vapour (0, 76, 230, 760 mg/m^3) 6 h/d, 5 d/week for 13 weeks. Local effects in the nasal epithelia were reported. These included degeneration of the olfactory nasal epithelium in animals of both sexes above 30 ppm. No treatment-related lesions of the nasal cavity or otherwise were diagnosed at 10 ppm. A NOAEC for local effects of 10 ppm (76 mg/m^3) and a NOAEC for systemic toxic effects of 30 ppm (230 mg/m^3) could be identified in the study.

Regarding genotoxicity, no such effects of EHA were observed *in vitro* in studies with bacteria. Studies with mammalian cells *in vitro* provided variable results, indicating a weak genotoxic potential, i. e. a clastogenic effect. However, the results were negative at concentrations with no or only weak cytotoxicity. *In vivo,* no genotoxic potential of EHA could be demonstrated. Overall, the available data for EHA and other related alkyl (methyl, ethyl, butyl) acrylates indicate that acrylate monomers are not genotoxic *in vivo,* and that positive findings *in vitro* are typically observed at cytotoxic concentrations.

Carcinogenicity studies with inhalation or oral exposure against EHA are not available. Other alkyl acrylates were not carcinogenic in inhalation studies with chronic exposure of rats (methyl and butyl acrylate) or rats and mice (ethyl acrylate). EHA induced skin tumours in mice at

concentrations which were highly irritative; at lower concentrations, only transient irritation but no tumour response of the skin could be observed. Taking into account the negative results from *in vivo* genotoxicity studies, the induction of sin tumours by EHA is likely via non-genotoxic mechanisms, and tumour growth is associated with the highly irritative properties of EHA.

An extended one-generation reproduction toxicity study with rats exposed to EHA via food provided a NOAEL of 5000 ppm (males: 357 mg/(kg bw x d), females: 453 mg/(kg bw x d)) for general toxicity. The NOAEL for fertility, reproductive performance and developmental toxicity was 12500 ppm (males: 998 mg/(kg bw x d), females: 1136 mg/(kg bw x d)), the highest concentration in food tested.

The subchronic inhalation toxicity study with rats is taken as the basis for the derivation of the EU-LCI. In that study, local effects were observed in the nasal epithelia in animals of both sexes at ≥ 30 ppm. The NOAEC for local effects on the respiratory tract was 10 ppm (76 mg/m^3).

The following assessment factors are used:

- Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6
- Adjusted study length factor (subchronic study): 2
- Interspecies extrapolation: 2.5 (allometric scaling not performed since route of exposure is inhalation)
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 280 leading to a value of 76 mg/m^3: 280 = 0.271 mg/m^3 (rounded to 250 µg/m^3).

An EU-LCI value of 250 µg/m^3 is proposed for 2-ethylhexyl acrylate (EHA).

No reliable odour threshold value could be identified for EHA. In view of the low odour thresholds for other alkyl acrylates, it should be expected that the odour of 2-ethylhexyl acrylate will be perceived at the proposed EU-LCI value.

Zusammenfassung

Stoffprofil und EU-LCI-Wert-Vorschlag für 2,6-Di-tert-butyl-4-methylphenol (3,5-Di-tert-butyl-p-kresol)

3,5-Di-tert-butyl-p-kresol (2,6-Di-tert-butyl-4-methylphenol, 3,5-Di-tert-butyl-4-hydroxytoluol, BHT) ist bei Raumtemperatur ein geruchloser, leicht gelblicher Feststoff mit einem sehr niedrigen Dampfdruck. Die Substanz wird in erster Linie als Antioxidationsmittel verwendet. BHT ist in einer Vielzahl von Produkten enthalten, darunter Kunststoffe, Gummi, Mineralölprodukte, Kosmetika, Verpackungsmaterialien, Farben und Klebstoffe. BHT wird auch als Lebensmittelzusatzstoff eingesetzt.

BHT kann durch Farben und Klebstoffe, die auf großen Oberflächen verwendet werden, in die Innenraumluft gelangen. Die Datenbasis für gemessene Konzentrationen von BHT in der Innenraumluft ist jedoch sehr begrenzt mit Nachweishäufigkeiten < 10 % und Höchstkonzentrationen < 10 µg/m^3.

Hinsichtlich der oralen Aufnahme über die Nahrung ist konservativen Schätzungen zufolge bei Erwachsenen nicht von einer Überschreitung des ADI-Wert von 0,25 mg BHT/(kg KG x d) auszugehen. Bei der Exposition von Kindern gegenüber BHT aus der Verwendung als Lebensmittelzusatzstoff ist es ebenfalls unwahrscheinlich, dass der ADI-Wert für BHT im Mittelwert überschritten wird, in einigen europäischen Ländern kann er jedoch im 95. Perzentil überschritten werden.

Es liegen keine quantitativen Daten über die Aufnahme von BHT über die Atemwege vor. Toxikokinetische Daten für den Menschen deuten darauf hin, dass mindestens 75 % einer oral verabreichten Dosis absorbiert werden, und Daten aus Rattenstudien deuten auf eine nahezu vollständige Absorption (90 %) nach oraler Aufnahme hin.

Es liegen keine toxikologischen Studien am Menschen vor, die für die Ableitung eines EU-LCI-Wertes für BHT relevant sind.

Die einzigen verfügbaren Studien zur Inhalationstoxizität sind Studien zur sensorischen Reizung bei Mäusen (Alarie-Test). Ein als zuverlässig angesehener Alarie-Test ergab einen RD50-Wert von 59,7 ppm (etwa 546 mg/m^3).

Es liegen keine Studien mit wiederholter inhalativer Exposition vor. Eine Reihe von Tierstudien mit wiederholter oraler Exposition von Mäusen und Ratten zeigte, dass die Leber das Hauptziel von BHT-Wirkungen ist, einschließlich histopathologischer hepatozellulärer Veränderungen.

Die meisten Belege deuten darauf hin, dass BHT kein Potenzial hat, Punktmutationen oder Chromosomenaberrationen auszulösen oder mit der DNA zu interagieren oder diese zu schädigen. Positive Befunde zur Genotoxizität, die *in vitro* mit BHT oder BHT-Metaboliten erzielt wurden, könnten auf pro-oxidative Reaktion zurückzuführen sein; eine solche Wirkungsweise der Genotoxizität wird im Allgemeinen als Wirkung mit Schwellenwert angesehen. Dementsprechend wurde der Schluss gezogen, dass im Hinblick auf Genotoxizität für BHT keine Bedenken bestehen.

Bei männlichen Ratten wurde eine dosisabhängig zunehmende Zahl von Leberzellkarzinomen festgestellt und sowohl bei männlichen als auch bei weiblichen Tieren, die mit BHT gefüttert wurden, ein Anstieg der Zahl der Leberzelladenome. In einer weiteren Studie mit Ratten wurde in der Hochdosisgruppe eine höhere Inzidenz von Leberzellfoci und eine höhere Anzahl von Ratten mit Leberknoten, jedoch kein Adenom oder Karzinom beobachtet. Unter Berücksichtigung der Datenlage aus den Genotoxizitätsstudien kam das EFSA-ANS-Gremium (Gremium für Lebensmittelzusatzstoffe und Lebensmitteln zugesetzte Nährstoffquellen der

Europäischen Behörde für Lebensmittelsicherheit) zu dem Schluss, dass die Wirkungsweise der Tumorbildung durch BHT auf einem Schwellenwertmechanismus beruht.

In einer Zwei-Generationen-Studie wurde Ratten vor der Paarung drei Wochen lang BHT in einer Dosierung von 0, 25, 100 oder 500 mg/(kg Körpergewicht x Tag) verabreicht. Die höchste Dosis wurde in der F1-Generation auf 250 mg/(kg Körpergewicht x Tag) reduziert. In den ersten 5 Wochen der BHT-Verabreichung wurde bei den hochdosierten Männchen eine verminderte Körpergewichtszunahme festgestellt. Am 20. Trächtigkeitstag waren sowohl die absoluten als auch die relativen Lebergewichte der Muttertiere dosisabhängig erhöht, bei der hohen Dosis statistisch signifikant. Das Körpergewicht der Jungtiere aus der hochdosierten Gruppe war bei der Geburt und an den Tagen 6 und 21 der Laktation signifikant niedriger als das der Kontrollgruppe. Das Körpergewicht der F1-Männchen war in der hochdosierten Gruppe während des gesamten 22-monatigen Behandlungszeitraums niedriger. Eine dosisabhängige Zunahme des relativen, aber nicht des absoluten Lebergewichts wurde ebenfalls beobachtet; die Unterschiede waren bei der hohen Dosis statistisch signifikant. Außerdem wurde ein dosisabhängiges Auftreten von Hypertrophie und Eosinophilie der zentrilobulären Hepatozyten beobachtet. Dies deutete auf eine Proliferation des glatten endoplasmatischen Retikulums hin, was mit einer Induktion von Oxidasen mit gemischter Funktion und des Gesamtgehalts an Cytochrom P450 übereinstimmte. Der Gesamtgehalt an Cytochrom P450 war bei den hochdosierten Tieren ab einem Alter von 21 Tagen um 30 - 60 % erhöht. Dosisabhängige Anstiege wurden bei den Aktivitäten der Epoxidhydrolase, der Glutathion-S-Transferase und der Pentoxyresorufin-O-Depentylase (PROD) festgestellt, die in den Gruppen mit mittlerer und hoher Dosis statistisch signifikant waren. Die Zunahme der PROD-Aktivität war ausgeprägt: 10- bis 25-fach bei mittlerer und 20- bis 80-fach bei hoher Dosis.

Auf der Grundlage des NOAEL von 25 mg/(kg KG x d) aus zwei Zwei-Generationen-Studien an Ratten und unter Verwendung eines Unsicherheitsfaktors von 100 leitete das EFSA-ANS-Gremium eine ADI von 0,25 mg/(kg KG x d) ab.

Der NOAEL von 25 mg/(kg KG x d), der in einer Zwei-Generationen-Studie mit oraler Exposition von Ratten mit BHT ermittelt wurde, wird ebenfalls als POD für die Ableitung eines EU-LCI-Wertes verwendet. Dieser NOAEL-Wert basiert auf systemischen Wirkungen. Zur Ableitung eines EU-LCI-Wertes für die inhalative Exposition erfolgt eine Pfad-zu-Pfad-Extrapolation.

Toxikokinetische Daten aus Rattenstudien deuten auf eine nahezu vollständige Absorption (90 %) nach oraler Aufnahme hin. Die Absorption nach Inhalation wird in Ermangelung experimenteller Daten standardgemäß als vollständig angenommen. Es wird somit davon ausgegangen, dass BHT nach oraler Aufnahme und nach Inhalation in vergleichbarer Höhe absorbiert wird, und es wird kein zusätzlicher Bewertungsfaktor für Unterschiede in der Absorption angewendet.

Die folgenden Extrapolationsfaktoren werden herangezogen:

- Pfad-zu-Pfad-Extrapolation (Ratten): 1,15 m^3/(kg KG x d)
- Faktor für die Studiendauer: 1
- Allometrische Skalierung: bereits in der Pfad-zu-Pfad-Extrapolation berücksichtigt
- Interspezies-Extrapolation: 2,5
- Intraspezies-Extrapolation: 10

Gesamtextrapolationsfaktor: 25 x 1,15 = 28,75. Daraus ergibt sich eine Konzentration von 25 mg/(kg KG x d) : 28,75 m^3/(kg KG x d) = 0,879 mg/m^3 für BHT (gerundet auf 900 µg/m^3).

Für BHT wird ein EU-LCI-Wert von 900 µg/m^3 vorgeschlagen.

Mit dem vorgeschlagenen LCI-Wert würde der von der EFSA festgelegte ADI-Wert von 0,25 mg/(kg KG x d) voll ausgeschöpft. Die Exposition gegenüber BHT erfolgt jedoch hauptsächlich durch orale Aufnahme mit der Nahrung. Unter Berücksichtigung der oralen Exposition könnte eine Allokation für die inhalative Exposition gegenüber BHT in Betracht gezogen werden. Ein solcher Ansatz wurde jedoch im Harmonisierungsrahmen unter Verwendung des EU-Konzepts für LCI noch nicht diskutiert, empfohlen oder umgesetzt.

Der vorgeschlagene LCI-Wert ist mehr als 100-mal niedriger als die Konzentration von 146 mg/m^3, die in einem Alarie-Test bei Mäusen keine Anzeichen einer sensorischen Reizung hervorrief, und mehr als 500-mal niedriger als der in diesem Test ermittelte RD50-Wert.

BHT ist Berichten zufolge eine geruchlose oder nahezu geruchlose Verbindung. Ein Geruchsschwellenwert für BHT ist nicht verfügbar.

Stoffprofil und EU-LCI-Wert-Vorschlag für Benzylalkohol

Benzylalkohol ist eine farblose, ölige Flüssigkeit mit einem schwachen aromatischen und fruchtigen Geruch. Es hat eine breite Verwendungsmöglichkeit, z. B. als Aushärtungsmittel in Epoxidbeschichtungen, als Lösungsmittel in wässrigen Beschichtungsmitteln oder Tinten, als Hilfsstoff zum Färben in der Textilindustrie, in fotografischen Entwicklern, als Konservierungsmittel in Kosmetika, pharmazeutischen und medizinischen Produkten, als Lebensmittelzusatz in Aromen und als Duftkomponente in Parfums und Kosmetika. Natürlich kommt Benzylalkohol z. B. in Pflanzen, Pilzen, Früchten, Nüssen, Gewürzen, und alkoholischen Getränken vor. Die in der Innenraumluft gemessenen Benzylalkoholkonzentrationen waren niedrig und lagen im Median bei 0,5 µg/m^3 oder unterhalb der Nachweisgrenze.

In einer oralen Toxikokinetikstudie am Menschen wurde die Substanz schnell und fast vollständig resorbiert, wobei 75-85 % der verabreichten Dosis innerhalb von sechs Stunden metabolisiert und mit dem Urin ausgeschieden wurden. Beim Menschen wird Benzylalkohol in der Leber durch Cytochrom-P450-Enzyme zu Benzaldehyd und anschließend zu Benzoesäure oxidiert, die nach Konjugation mit Glycin renal als Hippursäure ausgeschieden wird. Bei hohen Dosen ist die Konjugationskapazität von Glycin gesättigt, was zu einer unveränderten Ausscheidung von Benzoesäure oder Glucuronsäurekonjugaten führt. Eine *In-vivo*-Studie zur dermalen Absorption bei Rhesusaffen und *In-vitro*-Studien an der menschlichen Haut haben gezeigt, dass Benzylalkohol gut durch die Haut resorbiert wird (bis zu 80 % der applizierten Dosis) und wahrscheinlich in relevanter Weise zur systemischen Toxizität beiträgt.

In einer akuten Inhalationsstudie an Ratten wurde eine 4-h-LC50 von > 4178 mg/m^3 ermittelt. Die akute dermale Toxizität von Benzylalkohol ist gering, wie ein LD50-Wert von 2000 mg/kg KG bei Kaninchen zeigt. Die oralen LD50-Werte bei Tieren reichten von 1000-3100 mg/kg KG mit Symptomen wie Neurotoxizität (ZNS-Depression, Auswirkungen auf das ZNS, Reizbarkeit und Koma). In validen Studien nach OECD-Richtlinien verursachte Benzylalkohol bei Kaninchen keine Hautreizung, wohl aber eine Augenreizung. In einem LLNA-Test an Mäusen zeigte es kein hautsensibilisierendes Potenzial. Daten von Menschen aus Fallberichten, wiederholten Insult-Patch-Tests und Patch-Tests zeigten positive Reaktionen auf Benzylalkohol. Verglichen mit der weit verbreiteten Verwendung von Benzylalkohol und der großen Zahl der exponierten Personen, sind die beobachteten positiven Reaktionen jedoch gering. Insgesamt betrachten mehrere Expertengremien Benzylalkohol nicht als hautsensibilisierend.

In einer subakuten Inhalationsstudie an Ratten (gemäß OECD-Richtlinie 412, unveröffentlichter Studienbericht) führte eine wiederholte Exposition ("Nur-Nase") gegenüber Benzylalkohol zu einem konzentrationsabhängigen Anstieg (12,5 % bei 290 mg/m^3 und 15,4 % bei 1072 mg/m^3) des relativen Gewichts der Nebenhoden bei 290 mg/m^3 und darüber. Dies war die einzige statistisch signifikante Veränderung, die im Registrierungsdossier in der von der ECHA bereitgestellten Datenbank gemeldet wurde, und so wurde dort eine NOAEC von 1072 mg/m^3 abgeleitet. Darüber hinaus berichtet die MAK-Kommission über histologische Befunde in den Atemwegen, insbesondere in der Lunge, bei 1072 mg/m^3 (nur die Gruppe mit der höchsten Konzentration und die Kontrollen wurden histopathologisch untersucht). Daher leitet die MAK-Kommission eine LOAEC von 1072 mg/m^3 ab und schätzt eine NAEC (no adverse effect concentration) von 300 mg/m^3 (basierend auf LOAEC/3).

In validen subchronischen oralen Studien wurden Mäuse und Ratten 13 Wochen lang (6 h/d, 5 d/w) über eine Schlundsonde gegenüber bis zu 800 mg Benzylalkohol/(kg KG x d) exponiert. Beide Spezies zeigten eine reduzierte Körpergewichtszunahme, die zu abgeleiteten NOAEL-Werten von 400 mg/(kg KG x d) bei Ratten und 200 mg/(kg KG x d) bei Mäusen führten. Diese Studien weisen einige Mängel auf: Mehrere Tiere starben aufgrund von Handhabungsfehlern während der Verabreichung und es wurde eine hohe Toxizität beobachtet, die durch neurotoxische Wirkungen in der höchsten Dosisgruppe belegt wurde.

In-vitro-Tests erbrachten keine Hinweise auf gentoxische Wirkungen von Benzylalkohol in Bakterien. *In-vitro*-Studien an Säugetierzellen waren jedoch nicht eindeutig. Auf der Grundlage von *In-vivo*-Studien an Mäusen, Ratten und *Drosophila melanogaster* wurde Benzylalkohol als nicht gentoxisch in somatischen oder Keimzellen eingestuft.

In 2-Jahres-Kanzerogenitätsstudien an Mäusen und Ratten wurden keine krebserzeugenden Wirkungen von Benzylalkohol beobachtet.

Studien zu den Auswirkungen von Benzylalkohol auf die Fruchtbarkeit sind nicht verfügbar. Subakute Exposition gegenüber Benzylalkohol zeigte bei Ratten eine konzentrationsabhängige Zunahme des relativen Nebenhodengewichts. Benzylalkohol führte in Studien zur Entwicklungstoxizität bei Mäusen, Ratten und Kaninchen zu einer Abnahme des fötalen Körpergewichts bei maternal toxischen Dosen (NOEL von 550 mg/(kg KG x d) bei Mäusen und 250 mg/(kg KG x d) bei Ratten und Kaninchen).

Die Studie zur subakuten Inhalationstoxizität bei Ratten wird als valide und geeignet für die Ableitung eines EU-LCI-Wertes angesehen.

Die folgenden Extrapolationsfaktoren werden herangezogen:

- LOAEC-NOAEC-Extrapolation: 3
- Anpassung für kontinuierliche Exposition (6 h/d, 5 d/w): 5,6
- Faktor für die Studiendauer: 6
- Interspeziesextrapolation: 2,5 (allometrische Skalierung nicht durchgeführt, da eine inhalative Exposition vorliegt)
- Intraspeziesextrapolation (interindividuelle Variabilität, Allgemeinbevölkerung): 10

Gesamtextrapolationsfaktor: 2520. Daraus ergibt sich eine Konzentration von 1072 mg/m^3 : 2520 = 0,425 mg/m^3 für Benzylalkohol (gerundet auf 450 µg/m^3).

Für Benzylalkohol wird ein EU-LCI-Wert von (gerundet) 450 µg/m^3 vorgeschlagen.

Der vorgeschlagene EU-LCI-Wert liegt unter dem angegebenen Geruchsschwellenwert von 25 mg/m^3 (5,5 ppm).

Stoffprofil und EU-LCI-Wert-Vorschlag für Dipropylenglykolmethylether

Dipropylenglykolmonomethylether (DPGME) ist ein mehrkomponentiger Glykolether. Das kommerzielle Produkt besteht aus vier Isomeren: 1-(2-Methoxy-1-methylethoxy)propan-2-ol, 2-(2-Methoxy-1-methylethoxy)propan-1-ol, 1-(2-Methoxypropoxy)propan-2-ol und 2-(2-Methoxypropoxy)propan-1-ol. Alle verfügbaren Daten beziehen sich auf das technische Gemisch.

DPGME ist mit Wasser und zahlreichen organischen Lösungsmitteln mischbar und hat einen milden, angenehmen, ätherischen Geruch. Die Substanz findet sich häufig als Inhaltsstoff in Industrieprodukten sowie gewerblichen und Haushaltsreinigungsmitteln. Die in der Innenraumluft gemessenen DPGME-Konzentrationen waren gering und lagen im Median bei 0,5 µg/m^3 oder unterhalb der Nachweisgrenze.

In einer Toxikokinetikstudie mit oraler Verabreichung von ^{14}C-DPGME an Ratten wurden innerhalb von 48 Stunden nach Verabreichung 60 % der Radioaktivität im Urin, 27 % in der Ausatemluft und <3 % in den Fäzes nachgewiesen. DPGME wird hauptsächlich durch mikrosomale O-Demethylierung verstoffwechselt, wobei sich Metaboliten über Glucuronsäure- und Sulfatkonjugation sowie Hydrolyse zu Dipropylenglykol bilden. Von geringerer Bedeutung ist der Stoffwechselweg durch Hydrolyse des Dipropylenteils von DPGME zu Propylenglykolmonomethylether (PGME) und Propylenglykol. Studien haben gezeigt, dass DPGME im Vergleich zu seinen Abbauprodukten gleich oder weniger toxisch ist als Propylenglykol, Dipropylenglykol und PGME. Eine *In-vitro*-Studie zur dermalen Absorption (gemäß OECD-Richtlinie 428) an menschlicher Haut zeigte, dass DPGME die Haut durchdringen kann und seine Absorption in relevanter Weise zur systemischen Toxizität beitragen kann.

Arbeiter, die mit DPGME-haltigen Farben auf Wasserbasis in einer Konzentration von 5 - 7 ppm DPGME (30 - 40 mg/m^3) in der Innenraumluft arbeiteten, berichteten keine Symptome oder Anzeichen einer Reizung, während eine andere Studie berichtete, dass 35 ppm DPGME eine leichte Reizung der Nase/oberen Atemwege und über 75 ppm eine Reizung der Atemwege, der Augen und des Rachens verursachte. Eine Konzentration von 300 ppm DPGME wurde von Probanden als unangenehm empfunden.

Die akute dermale und orale Toxizität von DPGME war bei Tieren gering (LD50-Werte > 5000 mg/kg KG). In akuten Inhalationsstudien an Ratten, die 7 bzw. 8 Stunden lang Dampfkonzentrationen von DPGME bis zur maximal erreichbaren Konzentration bei Raumtemperatur von 500 bzw. 552,6 ppm (entsprechend 3100 bzw. 3404,47 mg/m^3) exponiert waren, wurde keine Mortalität beobachtet. Das einzige beobachtete klinische Anzeichen war eine leichte Narkose. DPGME war nicht hautreizend, reizte aber die Augen von Menschen und Tieren. In Patch-Tests an insgesamt 250 Freiwilligen wurde kein Hautsensibilisierungspotenzial von DPGME festgestellt.

In einer subchronischen Inhalationsstudie (ähnlich der OECD-Richtlinie 413) wurden Ratten und Kaninchen 13 Wochen lang (6 h/d, 5 d/w) durch Ganzkörperinhalation mit DPGME exponiert. Bis zur höchsten Testkonzentration von 200 ppm DPGME wurden keine toxikologisch signifikanten Effekte beobachtet (NOAEC: 200 ppm).

DPGME war in *In-vitro*-Studien (Ames-Test, Chromosomenaberrationstest, UDS-Test) nicht gentoxisch. *In-vivo*-Daten zur genetischen Toxizität von DPGME sind nicht verfügbar. Für das strukturell verwandte Glykol, PGME, liegt ein negatives Testergebnis aus einem Mikronukleustest an Mäusen vor.

Kanzerogenitätsstudien mit DPGME sind nicht verfügbar. PGME zeigte hingegen in 2-Jahres-Studien an Mäusen und Ratten keine Hinweise auf Kanzerogenität.

Studien zur Reproduktionstoxizität von DPGME liegen nicht vor. Daten zu PGME wurden in einem Read-Across-Ansatz verwendet. In einer Zwei-Generationen-Studie zur Reproduktionstoxizität an Ratten zeigte PGME keine Hinweise auf eine spezifische Reproduktionstoxizität. Die beobachteten Effekte auf die Reproduktionsparameter oder -organe bei weiblichen Tieren wurden mit der systemischen Toxizität in Verbindung gebracht, und die Auswirkungen auf die Neugeborenen wurden als sekundär zur maternalen Toxizität betrachtet. Für die Auswirkungen auf die Fruchtbarkeit und die Reproduktionsfähigkeit wurde ein NOEL (no-observed-effect level) von 1000 ppm abgeleitet.

Der NOAEC-Wert von 200 ppm (1220 mg/m³ bei 23 °C), der in der Studie zur subchronischen Inhalationstoxizität bei Ratten ermittelt wurde, wird als POD für die Ableitung eines EU-LCI-Wertes verwendet.

Die folgenden Extrapolationsfaktoren werden herangezogen:

- Anpassung für kontinuierliche Exposition (6 h/d, 5 d/w): 5,6
- Faktor für die Studiendauer: 2
- Interspeziesextrapolation: 2,5 (allometrische Skalierung nicht durchgeführt, da der Expositionsweg die Inhalation ist)
- Intraspeziesextrapolation (interindividuelle Variabilität, Allgemeinbevölkerung): 10

Gesamtextrapolationsfaktor: 280. Daraus ergibt sich eine Konzentration von 1220 mg/m³: 280 = 4,357 mg/m³ (gerundet auf 4400 µg/m³).

Für DPGME wird ein EU-LCI-Wert von 4400 µg/m³ vorgeschlagen.

In der Literatur wird für DPGME eine Geruchsschwelle von 35 ppm (210-216 mg/m³) angegeben. Es ist daher nicht zu erwarten, dass der Geruch bei dem vorgeschlagenen EU-LCI-Wert wahrgenommen wird.

Stoffprofil und EU-LCI-Wert-Vorschlag für n-Butylacrylat

Bei Raumtemperatur ist n-Butylacrylat (BA) eine farblose Flüssigkeit mit einem Geruch, der als "stark fruchtig" oder "stechend, wohlriechend, beißend, fruchtig" beschrieben wird. BA ist in Wasser nur schwer, aber in den meisten organischen Lösungsmitteln gut löslich.

BA wird hauptsächlich bei der Herstellung von Polymeren und Harzen für die Textil- und Lederveredelung, Beschichtungen, Klebstoffen, Farben, Bindemitteln und Emulgatoren verwendet. Der Stoff selbst ist nicht für den Einsatz in Verbraucherprodukten bestimmt, jedoch können Produkte für Endverbraucher aufgrund des Polymerisationsprozesses Spuren von Acrylsäure und ihren Estern als Rückstände enthalten.

Den wenigen verfügbaren Daten über gemessene Konzentrationen in der Innenraumluft zufolge wird BA nur selten (in weniger als 5 % der durchgeführten Messungen) und in geringen Konzentrationen (maximal 12 µg/m³) in der Innenraumluft nachgewiesen.

Es liegen keine quantitativen Daten über die Aufnahme von BA über die Atemwege vor. Untersuchungen an Ratten zeigen, dass BA nach oraler Verabreichung rasch resorbiert, hauptsächlich durch Carboxylesterase zu Acrylsäure und Butanol hydrolysiert und schließlich

als CO_2 ausgeschieden wird. Ein geringer Anteil (ca. 10 %) wird an Glutathion konjugiert und mit dem Urin ausgeschieden.

Aus kontrollierten Humanstudien liegen keine Daten zur sensorischen Reizung durch BA vor. In einer Studie, in der freiwillige Versuchspersonen vier Stunden lang mit 2,5 ppm Ethylacrylat mit Spitzenwerten von bis zu 5 ppm exponiert wurden, wurden jedoch keine Anzeichen einer sensorischen Reizung beobachtet. Bei Mäusen wurde ein RD50-Wert (Konzentration, die zu einer Verringerung der Atemfrequenz um 50 % als Zeichen einer Reizung der Atemwege führt) von 340 ppm (1800 mg/m^3) für BA ermittelt. Dieser RD50-Wert ist dem für Ethylacrylat ermittelten Wert von 315 ppm sehr ähnlich.

Klinische Befunde, Patch-Tests und einige klinisch-epidemiologische Studien zeigten, dass BA ein Kontaktallergen ist. Auch in Tierversuchen zeigte BA eine hautsensibilisierende Wirkung. Angaben über sensibilisierende Wirkungen von BA auf die Atemwege liegen nicht vor.

Es liegen keine Humandaten vor, die für die Ableitung eines EU-LCI-Wertes relevant wären.

In einer subchronischen Inhalationstoxizitätsstudie wurden Ratten 13 Wochen lang 6 h/d, 5 d/Woche gegenüber 0, 21, 108, 211 oder 546 ppm (0, 111, 572, 1118, 2894 mg/m^3) exponiert. Bei der höchsten Konzentration starben die meisten Tiere. Als Wirkungen wurden blutige Augen- und Nasensekrete, Reizungen der Nasenschleimhaut, metaplastische Veränderungen der Luftröhre und der Bronchien sowie Lungenhyperämie und Lungenentzündung berichtet. Bei 211 ppm wurden Reizwirkungen an den Augen und der Nasenschleimhaut, eine verringerte Körpergewichtszunahme und erhöhte relative Lebergewichte beobachtet. Die NOAEC der Studie wurde mit 108 ppm (572 mg/m^3) angegeben. Bei dieser Konzentration wurden nur geringfügige Auswirkungen, wie z. B. erhöhte Lebergewichte bei weiblichen Tieren ohne histologisches Korrelat, beobachtet.

In einer chronischen Inhalationsstudie wurden Ratten während der ersten 13 Wochen mit 0, 5, 15 und 45 ppm BA (0, 27, 80, 240 mg/m^3) exponiert und danach bis zu zwei Jahre lang mit 0, 15, 45 oder 135 ppm (0, 80, 240, 720 mg/m^3). Der Schweregrad der Auswirkungen auf die Nasenschleimhaut nahm mit der Konzentration zu; die Effekte traten bei allen Dosen und in beiden Geschlechtern auf. Ein NOAEC-Wert für lokale Wirkungen in den Atemwegen konnte nicht ermittelt werden. Es gab keine Hinweise auf eine systemische Toxizität, abgesehen von einem leichten Rückgang der Nahrungsaufnahme und einem leicht verringerten relativen Gewicht von Herz, Niere, Leber und Schilddrüse bei der höchsten Dosis. Die LOAEC in dieser Studie betrug 5 ppm, basierend auf den Auswirkungen auf die Nasenepithelien.

In-vitro-Gentoxizitätsstudien an Bakterien und Säugetierzellen waren negativ oder bei hohen zytotoxischen Konzentrationen allenfalls fragwürdig positiv. *In vivo* wurden im Knochenmark von chinesischen Hamstern und Ratten nach inhalativer Exposition keine Chromosomenaberrationen beobachtet, jedoch wurden im Knochenmark von Ratten nach intraperitonealer Injektion von n-Butylacrylat Chromosomenaberrationen festgestellt. Insgesamt deuten die verfügbaren Daten für Alkylacrylate im Allgemeinen darauf hin, dass Acrylatmonomere *in vivo* nicht genotoxisch sind und dass positive Befunde *in vitro* typischerweise bei zytotoxischen Konzentrationen beobachtet werden. Auf der Grundlage einer WoE-Analyse (Weight of Evidence) der derzeit verfügbaren Daten, bei der auch Daten aus Gentoxizitätstests mit Methyl- und Ethylacrylaten berücksichtigt wurden, wurde der Schluss gezogen, dass nicht von einer gentoxischen Wirkung von BA auszugehen ist.

In der Studie zur chronischen Inhalationstoxizität mit Ratten (siehe oben) wurden keine Hinweise auf eine Zunahme der Tumorinzidenz festgestellt, und bei Mäusen wurden nach lebenslanger Hautapplikation von BA keine behandlungsbedingten Tumore beobachtet.

In einer erweiterten Ein-Generationen-Studie zur Reproduktionstoxizität mit oraler Exposition von Ratten wurden bis zur höchsten Dosierung von 150 mg BA/(kg KG x d) keine Hinweise auf Reproduktionstoxizität beobachtet. In einer Inhalationsstudie zur Entwicklungstoxizität bei Ratten wurden bei 135 und 250 ppm maternal Reizungen der Atemwege und eine verringerte Körpergewichtszunahme festgestellt. Diese Konzentrationen führten auch zu einer erhöhten Embryoletalität, jedoch konnte bei keiner Dosis ein teratogener Effekt beobachtet werden. Die NOAEC für maternale Toxizität und Entwicklungstoxizität betrug 25 ppm (135 mg/m^3). In einer weiteren Studie zur inhalativen Entwicklungstoxizität mit trächtigen Ratten stellte die niedrigste Testkonzentration von 100 ppm (530 mg/m^3) eine NOAEC für die Entwicklungstoxizität und eine LOAEC für die maternale Toxizität dar. Eine orale Studie zur Entwicklungstoxizität mit Mäusen ergab einen NOAEL für die maternale und die Entwicklungstoxizität von 1000 mg/(kg KG x d). Bei Kaninchen wurde bei 400 mg/(kg KG x d) maternale Toxizität beobachtet, aber keine Embryotoxizität oder Teratogenität.

Die Studie zur chronischen Inhalationstoxizität an Ratten wird als Grundlage für die Ableitung des EU-LCI herangezogen. Diese Studie ergab eine LOAEC von 15 ppm (79,5 mg/m^3), aber keine NOAEC, da schädliche Wirkungen bis zur niedrigsten eingesetzten Konzentration beobachtet wurden. Eine Benchmark-Berechnung wurde für die Inzidenz von Reservezellhyperplasie mit Verlust von Riech- oder Flimmerzellen im nasalen Riechepithel von männlichen bzw. weiblichen Ratten durchgeführt. Für die Inzidenz bei weiblichen Ratten war keine zufriedenstellende Berechnung möglich, die für männliche Ratten berechnete $BMDL_{05}$ von 4,86 ppm BA ist nahezu identisch mit dem Wert von 5 ppm BA, der sich unter Verwendung eines Standardfaktors von drei zur Extrapolation von einer LOAEC zu einer NOAEC ergibt.

Die folgenden Extrapolationsfaktoren werden herangezogen:

- LOAEC zu NOAEC: 3
- Anpassung für kontinuierliche Exposition (6 h/d, 5 d/Woche): 5,6
- Angepasster Faktor für die Studiendauer: 1
- Interspezies-Extrapolation: 2,5 (allometrische Skalierung nicht durchgeführt, da der Expositionsweg die Inhalation ist)
- Intraspezies-Extrapolation (interindividuelle Variabilität, allgemeine Bevölkerung): 10

Gesamtextrapolationsfaktor: 420. Daraus ergibt sich ein Wert von 79,5 mg/m^3: 420 = 0,189 mg/m^3 (gerundet auf 200 µg/m^3).

Für n-Butylacrylat (BA) wird ein EU-LCI-Wert von (gerundet) 200 µg/m^3 vorgeschlagen.

BA hat eine sehr niedrige Geruchsschwelle von 2,9 µg/m^3. Es ist daher zu erwarten, dass der Geruch bei dem vorgeschlagenen EU-LCI-Wert wahrgenommen wird.

Stoffprofil und EU-LCI-Wert-Vorschlag für 2-Ethylhexylacrylat

2-Ethylhexylacrylat (EHA) ist bei Raumtemperatur eine farblose Flüssigkeit, die sich nur wenig in Wasser löst, aber in den meisten organischen Lösungsmitteln löslich ist. EHA wird als weichmachendes Co-Monomer bei der Herstellung von Harzen für druckempfindliche Klebstoffe, Latexfarben, reaktiven Verdünnungsmitteln und/oder Vernetzungsmitteln, Textil- und Lederausrüstungen und Beschichtungen für Papier verwendet.

Es liegen nur wenige Daten über gemessene Konzentrationen von EHA in der Innenraumluft vor. EHA konnte in etwa 15 % von 157 Messungen nachgewiesen werden, allerdings in geringen Konzentrationen, die einen Höchstwert von 3 µg/m^3 nicht überschritten. Bei einer größeren Anzahl von Messdaten wurde das 95. Perzentil als unter 1,0 µg/m^3 liegend angegeben. Messungen von EHA-Restmonomeren nach dem Streichen mit Farben mit einem Gehalt von 940 ppm und 2.000 ppm EHA in einem Raum mit eingeschränkter Belüftung ergaben Spitzenkonzentrationen der Raumluft von 2,5 ppm (19 mg/m^3) und 8 ppm (60,8 mg/m^3). EHA war 25 Stunden nach dem Anstrich nicht mehr nachweisbar.

Es liegen keine quantitativen Daten über die Aufnahme von EHA über die Atemwege vor. Nach oraler Verabreichung von EHA an Ratten wurden etwa 90 % innerhalb der ersten 24 Stunden ausgeschieden, größtenteils als CO_2 über die Ausatmungsluft und eine etwas geringere Menge über Metaboliten mit dem Urin.

Über die allergene Wirkung von EHA auf die menschliche Haut wurden einzelne Fallberichte veröffentlicht. Bei arbeitsmedizinischen Untersuchungen konnte jedoch keine Sensibilisierung festgestellt werden. Somit ist die sensibilisierende Wirkung beim Menschen nicht eindeutig zu beurteilen und die beschriebenen positiven Reaktionen können teilweise Ausdruck einer immunologischen Kreuzreaktion sein. Ein schwaches dermales Sensibilisierungspotenzial wurde in einem lokalen Lymphknoten-Assay (LLNA) bei Mäusen beobachtet, und verschiedene frühere Tests mit Meerschweinchen erbrachten ebenfalls Hinweise darauf, dass EHA ein Hautsensibilisator ist.

Angaben über sensibilisierende Wirkungen von EHA auf die Atemwege liegen nicht vor.

Aus kontrollierten Humanstudien liegen keine Daten zur sensorischen Reizung von EHA vor. In einer Studie, in der freiwillige Versuchspersonen vier Stunden lang mit 2,5 ppm Ethylacrylat exponiert wurden, mit Spitzenwerten von bis zu 5 ppm, wurden jedoch keine Anzeichen für sensorische Reizungen beobachtet. Tierstudien mit inhalativer Exposition zeigen ein Reizpotenzial der Prüfsubstanz, quantitative Daten (RD50-Werte) sind jedoch nicht verfügbar.

Relevante Studien zur Toxizität bei wiederholter Verabreichung von EHA an Menschen sind nicht verfügbar.

In einer subchronischen Inhalationstoxizitätsstudie wurden Ratten gegenüber 0, 10, 30 und 100 ppm EHA-Dampf (0, 76, 230, 760 mg/m^3) 6 h/d, 5 d/Woche über 13 Wochen exponiert. Es wurde über lokale Auswirkungen auf die Nasenepithelien berichtet. Konzentrationen oberhalb von 30 ppm führten bei Tieren beiderlei Geschlechts zur Degeneration des olfaktorischen Nasenepithels. Bei 10 ppm wurden keine behandlungsbedingten Läsionen der Nasenhöhle oder anderer Art diagnostiziert. In der Studie konnte eine NOAEC für lokale Effekte von 10 ppm (76 mg/m^3) und eine NOAEC für systemische toxische Effekte von 30 ppm (230 mg/m^3) ermittelt werden.

Was die Genotoxizität betrifft, so wurden *in vitro* in Studien mit Bakterien keine derartigen Wirkungen von EHA beobachtet. Untersuchungen mit Säugetierzellen *in vitro* ergaben unterschiedliche Ergebnisse, die auf ein schwaches genotoxisches Potenzial, d. h. eine klastogene Wirkung, hinweisen. Bei Konzentrationen, die keine oder nur eine geringe Zytotoxizität aufweisen, waren die Ergebnisse jedoch negativ. *In vivo* konnte kein genotoxisches Potenzial von EHA nachgewiesen werden. Insgesamt deuten die verfügbaren Daten für EHA und andere verwandte Alkylacrylate (Methyl-, Ethyl-, Butylacrylate) darauf hin, dass Acrylatmonomere *in vivo* nicht genotoxisch sind und dass positive Befunde *in vitro* typischerweise bei zytotoxischen Konzentrationen beobachtet werden.

Karzinogenitätsstudien mit inhalativer oder oraler Exposition gegenüber EHA sind nicht verfügbar. Andere Alkylacrylate waren in Inhalationsstudien bei chronischer Exposition von Ratten (Methyl- und Butylacrylat) bzw. Ratten und Mäusen (Ethylacrylat) nicht krebserregend. EHA induzierte bei Mäusen Hauttumore bei Konzentrationen, die stark reizend waren; bei niedrigeren Konzentrationen konnte nur eine vorübergehende Reizung, aber keine Tumorreaktion der Haut beobachtet werden. In Anbetracht der negativen Ergebnisse von *In-vivo*-Genotoxizitätsstudien ist die Induktion von Hauttumoren durch EHA wahrscheinlich auf nicht-genotoxische Mechanismen zurückzuführen, und das Tumorwachstum steht in Zusammenhang mit den stark reizenden Eigenschaften von EHA.

Eine erweiterte Reproduktionstoxizitätsstudie über eine Generation mit Ratten, die EHA über die Nahrung ausgesetzt waren, ergab einen NOAEL von 5000 ppm (Männchen: 357 mg/(kg KG x d), Weibchen: 453 mg/(kg KG x d)) für die allgemeine Toxizität. Der NOAEL für Fruchtbarkeit, Reproduktionsleistung und Entwicklungstoxizität betrug 12500 ppm (Männer: 998 mg/(kg KG x d), Frauen: 1136 mg/(kg KG x d)), die höchste getestete Konzentration in Lebensmitteln.

Die subchronische Inhalationstoxizitätsstudie mit Ratten wird als Grundlage für die Ableitung des EU-LCI herangezogen. In dieser Studie wurden bei Tieren beiderlei Geschlechts bei ≥ 30 ppm lokale Effekte in den Nasenepithelien beobachtet. Die NOAEC für lokale Wirkungen auf die Atemwege betrug 10 ppm (76 mg/m^3).

Die folgenden Extrapolationsfaktoren werden verwendet:

- Anpassung für kontinuierliche Exposition (6 h/d, 5 d/Woche): 5,6
- Angepasster Faktor für die Studiendauer (subchronische Studie): 2
- Interspezies-Extrapolation: 2,5 (allometrische Skalierung nicht durchgeführt, da der Expositionsweg die Inhalation ist)
- Intraspezies-Extrapolation (interindividuelle Variabilität, allgemeine Bevölkerung): 10

Gesamtextrapolationsfaktor: 280. Daraus ergibt sich ein Wert von 76 mg/m^3 : 280 = 0,271 mg/m^3 (gerundet auf 250 µg/m^3).

Für 2-Ethylhexylacrylat (EHA) wird ein EU-LCI-Wert von 250 µg/m^3 vorgeschlagen.

Für EHA konnte kein verlässlicher Geruchsschwellenwert ermittelt werden. Angesichts der niedrigen Geruchsschwellenwerte für andere Alkylacrylate ist zu erwarten, dass der Geruch von 2-Ethylhexylacrylat bei dem vorgeschlagenen EU-LCI-Wert wahrgenommen wird.

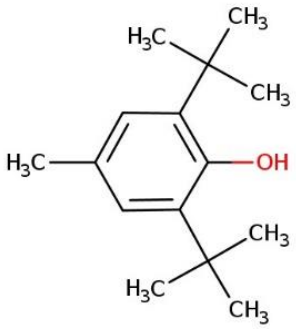
1 Toxicological evaluation of 2,6-di-tert-butyl-4-methylphenol as basis for the derivation of an EU-LCI value

1.1 Substance identification

2,6-Di-tert-butyl-4-methylphenol (3,5-di-tert-butyl-p-cresol, BHT) belongs to the group of alkyl phenols. The substance identification of BHT is shown in Table 1.

The toxicological data basis for BHT is quite comprehensive and has been summarised and evaluated in a number reviews, e. g. (e. g., ANSES, 2016; CIR Expert Panel, 2019; DFG, 1986, 2004, 2007, 2012; ECHA Dissemination, 2023; EFSA-ANS, 2012; HBM-Kommission, 2022; JECFA, 1996; Lanigan & Yamarik, 2002; Leng et al., 2023; Nielsen et al., 1998; OECD SIDS, 2002; SCCS, 2021; U.S.EPA, 2013; VKM et al., 2019).

Table 1: Substance identification of BHT (ECHA Dissemination, 2023)

Cas-No. EU-No. CLP-Index-No.	Systematic name, common name	Sum formula	Structural formula
128-37-0 204-881-4 -	2,6-di-tert-butyl-4-methylphenol, 3,5-di-tert-butyl-4-hydroxytoluene (BHT), 4-methyl-2,6-di-tert-butylphenol, 2,6-di-tert-butyl-p-cresol	$C_{15}H_{24}O$	

1.2 Substance properties and uses

The physicochemical properties of BHT are shown in Table 2. At room temperature, BHT is an odourless and slightly yellowish solid with a very low vapour pressure. BHT is nearly insoluble in water but soluble in most organic solvents (SCCS, 2021).

BHT is a compound from the group of phenol derivatives. It is primarily used as an antioxidant to prevent product alteration due to the ingress of atmospheric oxygen (EFSA-ANS, 2012; Salthammer et al., 2023). After being patented in 1947, BHT was initially used as a stabilising agent in the petroleum and adhesives industries. Due to its antioxidant properties, the field of application was already extended in the 1950s to the stabilisation of food and cosmetics (Leng et al., 2023). BHT is contained in a wide range of products, including plastics, rubber, mineral oil products, cosmetics, packaging materials, paints, and adhesives. BHT is also used as a food additive (E321) in foodstuffs (EFSA-ANS, 2012; Salthammer et al., 2023). In the food sector BHT is, e. g., added to baking mixes, nuts, dried soups, chewing gum, fats and oils (Leng et al., 2023). In the European Union, BHT is authorised as food additive (E321) with a maximum level of 100 mg/kg fat (only fats and oils for the professional manufacture of heat-treated foods; frying oil and frying fat (excluding olive and pomace oil) and lard, fish oil, beef, poultry, and sheep fat). Food supplements supplied in a solid form (excluding food supplements for infants and young

children) and chewing gum may contain BHT, alone or together with propyl gallate, tertiary butylhydroquinone (TBHQ), and butylated hydroxyanisole (BHA), up to 400 mg/kg, and seasonings and condiments up to 200 mg/kg (sum of all four compounds) (EC, 2024).

Several microorganisms present in phytoplankton are capable of producing BHT as a natural product. BHT was also identified in the pericarp of the lychee fruit and in fungi living in olives (Bakthavachalam & Wu, 2008; Gharbi et al., 2017; Jiang et al., 2013). However, for the uses described above, including the use as food additive, BHT is exclusively added as a synthetic compound. It is a large-scale industrial product (tonnage band in the EU: ≥ 10 000 to < 100 000 tonnes/year) (ECHA Dissemination, 2023).

Table 2: Physicochemical properties of BHT (DFG, 2012; ECHA Dissemination, 2023)

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Dissociation constant Pka	Vapour pressure (Pa)	Conversion 1 ppm = x mg/m³ (23 °C)	log pow	Solubility in water (mg/L) at 25 °C
220.35	83 at 1013.25 hPa	265 at 1013.25 hPa	12.2 at 20 °C	0.39 at 20 °C	9.07	5.2 at 37 °C	0.6

1.3 Exposure

1.3.1 Indoor air

BHT is mainly released into indoor air through paints and adhesives used on large surfaces. As many products contain small amounts of BHT, it is stated that the substance can often be detected in air samples, but usually in very low concentrations. However, no representative data are available (Salthammer et al., 2023). No data on the presence of BHT in indoor air were identified in a recent Norwegian risk assessment report (VKM et al., 2019).

Table 3: Data on the occurrence of BHT in indoor air

Indoor	N	LoD (µg/m³)	N > LoD	Median (µg/m³)	P95 (µg/m³)	Maximum (µg/m³)	Source
Offices, homes, (pre)-schools, Germany	834	1.0	51 (6.1 %)	0.5	1.0	9	Hofmann and Plieninger (2008)
Indoor air (not further specified), Germany, 2006-2012	2641	not reported	not reported	<1	< 1.0 *	not reported	AGÖF (2013)
Classrooms, Porto, Portugal	71	not reported	10 (14 %)	0.89	not reported	Range: 0 – 5.12	Paciência et al. (2019)

*: 90th percentile

Accordingly, the database regarding measured concentrations of BHT in indoor air is very limited (Table 3). Hofmann and Plieninger (2008) could detect BHT in less than 10 % out of 834 measurements, with a maximum of 9 µg/m^3. In a recent study in classrooms in Porto, Portugal,

the maximum concentration during a one-week measurement period reached 5.12 µg/m^3 (Paciência et al., 2019).

1.3.2 Other sources

The EFSA Panel on Food Additives and Nutrient Sources added to Food (ANS) estimated the chronic exposure to BHT from its use as food additive combined with national consumption data for different age groups with the general population (Table 4). Since the food categories where BHT is authorised are not directly covered in the underlying database, the EFSA Panel assumed that the food category for which BHT is authorised can be found in fine bakery wares, in snacks (dry, savoury potato, cereal or starch-based snack products, extruded or expanded savoury snack products, other savoury snack products and savoury peanuts, nuts or hazelnuts), and in liquid and solid food supplements. It was also assumed that the fat content of these food categories would be 25 % and that this amount of fat would contain BHT added at the maximum reported use level. The Panel noted that its estimates should be considered as being conservative.

Table 4: Estimated exposure to BHT from its use as food additive*

Estimated exposure	Children, 3 – 9 a mg/(kg bw x d)	Adolescents, 10 – 17 a mg/(kg bw x d)	Adults, 18 – 64 mg/(kg bw x d)
Mean	0.007 – 0.087	0.005 – 0.043	0.003 – 0.022
95th percentile	0.04 – 0.296	0.029 – 0.125	0.017 – 0.161

*: using maximum reported use levels for four population groups (EFSA-ANS, 2012).

The Panel concluded that exposure of adults to BHT is unlikely to exceed the ADI of 0,25 mg/(kg bw x d) at the mean and at the 95th percentile. For exposure of children to BHT from its use as food additive, the Panel noted that it is also unlikely that the ADI for BHT is exceeded at the mean, but is exceeded for some European countries (Finland, The Netherlands) at the 95th percentile (EFSA-ANS, 2012).

A risk assessment performed by the Norwegian VKM (VKM et al., 2019) concluded that the main exposure to BHT is by oral intake via food, but dermal exposure from personal care products (PCP) contributed to the total internal exposure. Due to lack of concentration data, BHT exposure from indoor air was not estimated (VKM et al., 2019).

Depending on the exposure scenarios, the total internal exposure for adults from all routes was estimated in the "realistic" total internal exposure to be within 1.4 – 9.6 µg BHT/(kg bw x d) for females and 0.8 – 9.7 µg BHT/(kg bw x d) for males. The median was estimated to be within 3.5 – 4.2 and 2.2 – 2.8 µg BHT/(kg bw x d) for females and males, respectively. The "high" total internal exposure from all routes was estimated to be within 23 – 281 µg BHT/(kg bw x d) for females and 9 – 319 µg BHT/(kg bw x d) for males. The median of the "high" total exposure was estimated to be within 85 – 111 and 46 – 61 µg BHT/(kg bw x d) for females and males, respectively. VKM concluded that the estimated "realistic" BHT exposure is below the ADI for both women and men. The median (50th percentile) of the estimated "high" exposure for both men and women is also below the ADI, whereas the 95 percentile is above the ADI of 250 µg/(kg bw x d) (VKM et al., 2019).

1.4 Toxicokinetics

According to the EFSA-ANS (2012), toxicokinetics has been studied in mice, rats, rabbits, chickens, monkeys and humans.

No quantitative data is available on the uptake of BHT through the respiratory tract.

BHT is rapidly absorbed in the gastrointestinal tract after oral exposure. Following oral intake, absorption was at least 75 % of the dose in studies with humans, 80 – 90 % in rats, 85 % in guinea pigs, and close to 100 % in mice (HCN, 2004). Complete (100 %) absorption in the gastrointestinal tract was assumed in the recent risk assessment of the Norwegian VKM (VKM et al., 2019).

The BHT metabolism is complex, and important species differences are likely, considering the differences reported in the literature. More than 40 metabolites have been identified. Oxidation of one or both of the tert-butyl groups of BHT, with a following glucuronidation, is seen as one of the main metabolic pathways in humans. It is not known whether the BHT quinone methides, a compound likely to be responsible for lung toxicity in mice, are formed in humans (VKM et al., 2019).

The half-life of excretion in humans was studied in two men who were given a single oral dose of 40 mg ^{14}C-BHT/kg bw. In the first 24 hours, 50 % was excreted, followed by a slower excretion that occurred for the next 10 days. In total, 63 – 67 % of the dose was excreted with the urine (VKM et al., 2019).

BHT is mainly excreted via urine and faeces, but while excretion in faeces is the dominant pathway for rats and mice, including enterohepatic circulation, the main excretion route in humans is via the urine. This is likely due to the size of the metabolites, and different cut-off in rats and humans regarding the molecular size that can be excreted in the urine (VKM et al., 2019).

1.5 Health effects

1.5.1 Acute toxicity, sensory irritation, and local effects

Acute toxicity

No data on the toxicity of BHT following inhalation are available except for studies on sensory irritation (see below).

The acute oral and dermal toxicity of BHT is low. The oral LD50 obtained in a study conducted with male and female rats according to the OECD guideline 401 is greater than 6000 mg/kg bw. In a study conducted according to OECD guideline 402, the acute dermal LD50 in the Sprague-Dawley rat was greater than 2000 mg/kg-bw (ECHA Dissemination, 2023).

Irritation

BHT is slightly irritating based on studies on skin and eyes of rabbits (SCCS, 2021).

In a study for sensory irritation (Alarie-test), Swiss Webster mice (6 M/group) were exposed to BHT concentrations of 4.54, 16, 32, 42.9, 66.6 and 82.6 ppm (head-only) for 30 minutes. The RD50 was calculated to be 59.7 ppm (about 546 mg/m^3). No indications of sensory irritation were observed at 4.54 and 16 ppm (about 41 and 146 mg/m^3, respectively). This result does not support an RD50 of 3.6 ppm (32.7 mg/m^3) reported earlier (Stadler & Lavoie, 1997); the discrepancy was explained by problems in the analysis (recovery) in the earlier study (DFG, 2007; US CPSC, 1996, 1998).

Sensitisation

The SCCS concluded that although the evidence on skin sensitisation in animals is limited, there is no evidence from a range of human experience to suggest that BHT is a significant human skin

sensitiser or contact allergen. A few positive patch-test reactions were considered to reflect cross-reactivity with tert-butylhydroquinone (SCCS, 2021).

No data are available regarding respiratory sensitisation.

1.5.2 Repeated dose toxicity

The following overview is based on the summaries presented by SCCS (2021) and (VKM et al., 2019). Both, in turn, mostly referred to data presented by EFSA-ANS (2012) and ANSES (2016).

Human data

No relevant data is available.

Animal data

Short-term or subchronic exposure to BHT affects the liver of mice, rats and chicken, including histopathological hepatocellular changes. BHT also increased the relative thyroid and adrenal weight in rats. Oral treatment of male rats for 7 consecutive days with 75 or 450 mg BHT/(kg bw x d) induced hepatocellular proliferation, increased hepatocyte apoptosis, elevated immunoreactivity for transforming growth factor (TGF)-β1 in the liver during the treatment, and resulted in hepatocellular inhibition of mitosis following withdrawal (SCCS, 2021).

The results of two two-generation studies regarding non-reproductive effects are described in chapter 1.5.4.

1.5.3 Genotoxicity and carcinogenicity

Genotoxicity

According to EFSA-ANS (2012) and summarised by SCCS (2021), the majority of evidence indicates a lack of potential for BHT to induce point mutations or chromosomal aberrations, or to interact with or damage DNA. Positive genotoxicity results obtained *in vitro* with BHT and BHT metabolites may be due to pro-oxidative chemistry, giving rise to formation of quinones and reactive oxygen species. Such mechanism of genotoxicity is generally considered to have a threshold (SCCS, 2021).

It was concluded that BHT is not of concern with regard to genotoxicity (EFSA-ANS, 2012; SCCS, 2021; VKM et al., 2019).

Carcinogenicity

In a two-generation study described in chapter 1.5.4, histopathological examinations indicated dose-related increases in the numbers of hepatocellular carcinomas in male rats and an increase in hepatocellular adenomas in both male and female rats. Tumours were also found in other organs of some of the treated rats, including thyroid, pancreas, ovary, uterus, thymus, reticulo-endothelial system, and mammary gland, but their incidence was not statistically significantly different from that in controls (Olsen et al., 1986; SCCS, 2021).

In a further two-generation study with rats (McFarlane et al., 1997; Price, 1994), a higher incidence of eosinophilic and basophilic foci and in the number of rats with hepatic nodules was observed in the high-dose group but no adenoma or carcinoma (SCCS, 2021) (see chapter 1.5.4).

The EFSA-ANS (2012) considered that the effects of BHT on tumour formation reported in the study of Olsen et al. (1986) are subject to a threshold since the genotoxicity studies generally indicate a lack of potential for BHT to induce point mutations, chromosomal aberrations, or to interact with or damage DNA. The BMD analysis performed by EFSA-ANS (2012) on the

incidence of hepatocellular carcinoma in male rats induced by BHT as reported by Olsen et al. (1986) gave a BMDL10 of 247 mg/(kg bw x d).

In an unpublished study (Brooks et al., 1976) submitted to JECFA (1996) CFI mice (48 /group) were maintained on diets containing 1000 mg BHT/kg feed. At week 4, one group was then fed a diet containing 2500 mg BHT/kg feed, and at week 8, another group was fed a diet containing 5000 mg BHT/kg feed. These dose levels of 1000, 2500 and 5000 mg/kg feed correspond to approximately 0, 100, 250 and 500 mg/(kg bw x d). The mice were maintained on these diets until 100 weeks of age. There was an increased incidence of lung neoplasia in treated mice (control: 47 %, with increasing dose: 53, 74, and 75 %). There were no morphological features to distinguish the lung tumours in treated mice from those in controls (EFSA-ANS, 2012).

BMD analyses of the data reported by Brooks et al. (1976) on the incidence of lung neoplasia in mice induced by BHT revealed a BMDL10 of 38 mg/(kg bw x d) (EFSA-ANS, 2012). However, EFSA-ANS (2012) also noted that when a larger number of animals were used by the same investigators in a further study (Clapp et al., 1978), the findings from the study of Brooks et al. (1976) were not confirmed.

1.5.4 Toxicity to reproduction

SCCS (2021) summarised the studies as follows:

In the two-generation study by Olsen et al. (1986), F0-groups of Wistar rats (60, 40, 40, or 60 of each sex) were fed BHT at intake doses of 0, 25, 108, or 276 mg/(kg bw x d) for male and of 0, 26, 106 and 287 mg/(kg bw x d) for female rats, respectively. The F0 rats were mated after 13 weeks of treatment. The F1 groups consisted of 100, 80, 80, and 100 F1 rats, respectively, of each sex from the offspring from each group. Because of an adverse effect on the kidney in the parents, the concentration of BHT in the highest dose group was lowered to 250 mg/(kg bw x d) in the F1 generation. The study was terminated when rats in the F1 generation were 144 weeks of age.

The number of litters of ten or more pups at birth decreased with increasing BHT dose with the number of pups/litter amounting to 10.9, 9.6, 10.3 and 9.1 at increasing dose levels. At weaning, treated F1 rats showed a dose dependent reduction in body weight compared to the controls. In the low, mid, and high-dose groups, the reductions in body weight were for males/females 7 %/5 %, 11 %/10 %, and 21 %/16 %. Food intake was comparable for all groups (Olsen et al., 1986; SCCS, 2021).

In the two-generation study by Price (McFarlane et al., 1997; Price, 1994), groups of 6 male and 48 female Wistar rats, aged 13 weeks and 9 weeks, respectively, were fed BHT in the diet at doses of 0, 25, 100 or 500 mg/(kg bw x d) for 3 weeks prior to mating. The litters were either culled or augmented to comprise 8 pups and were fed BHT concentrations corresponding to the diets fed to their parents, with the exception that the highest dose was reduced to 250 mg/(kg bw x d). The study was terminated 22 months after the F1 male rats were placed on test diets (SCCS, 2021).

In the first 5 weeks of BHT administration, a reduction in body weight gain was noted in the high-dose males. Body weight gain in all other treatment groups was similar to that in controls. At the sacrifice on day 20 of gestation, both absolute and relative liver weights of the dams were increased in a dose-related manner, statistically significant at the high dose. The body weights of the females, both including and excluding their litters, were similar in all groups (SCCS, 2021).

There was a slight decrease in the numbers of pups/litter in the low and high-dose groups, but a dose-related trend was not observed. Body weights of the pups from the high-dose group were

significantly lower than controls at birth (10 %), and at days 6 (12 %) and 21 (21 %) of lactation. Mortality of the pups between culling and day 21 of lactation was 2 %, 8 %, 12 % and 15 %, in order of the increasing dose. Body weights of the F1 males were lower in the high-dose group, compared with controls, throughout the 22-month treatment period. At the scheduled sacrifices, dose-related increases were observed in relative, but not absolute liver weights; the differences were statistically significant at the high dose (SCCS, 2021).

A dose-related incidence of enlargement and eosinophilia of the centrilobular hepatocytes was observed at the scheduled sacrifices, starting at 6 months. This was indicative of proliferation of the smooth endoplasmic reticulum, consistent with an induction of mixed-function oxidases. Immunohistochemical staining of liver sections from control and high-dose rats revealed a marked increase in hepatocellular content and distribution of cytochrome P450 2B with BHT treatment which persisted throughout the study. Histochemical staining revealed a marked induction of gamma-glutamyl transpeptidase (GGT) activity in the periportal hepatocytes of nearly all of the high-dose rats, starting at 11 months of treatment. At 22 months, there was a higher incidence of eosinophilic and basophilic foci in the high-dose group. Histochemical staining of liver sections revealed a small number of high-dose animals with glucose-6-phosphatase-deficient AHF (altered hepatocellular foci) which was statistically significant. At 22 months, there was also a significant increase in the number of rats with hepatic nodules in the high-dose group (6/19 animals compared with none in the other groups) (SCCS, 2021).

Total cytochrome P450 content was increased by 30 - 60 % in the high-dose animals starting at 21 days of age. Dose-related increases were noted in epoxide hydrolase, glutathione-S-transferase and pentoxyresorufin-O-depentylase (PROD) activities, starting at 21 days of age, which were statistically significant in the mid- and high-dose groups. The increases in PROD activity were large, 10 – 25fold in the mid-dose, and 20 – 80 fold in the high-dose groups (SCCS, 2021).

No effects on the adrenal were noted. Histopathology of the adrenal was conducted starting at 11 months post-weaning. Evidence of thyroid hyper-activity, characterised by reduction of follicular size, absence or reduction of colloid, irregularities in the follicular outline, hyperaemia and an increase in the number of follicular cells was noted starting at 11 months in both the mid-dose group (mild changes affecting 75 - 82 % of the rats) and the high-dose group (marked changes affecting 100 % of the rats). Serum thyroxin levels in treated rats did not differ from controls (SCCS, 2021).

1.5.5 Other effects

The SCCS evaluated the data from studies on endocrine disrupting (ED) potential of BHT.

Although there are converging pieces of evidence suggesting that BHT might act on thyroid homeostasis through increased thyroid hormone hepatic catabolism, currently there is no direct proof that this mechanism holds true (SCCS, 2021). ANSES (2016) also concluded that the amount of information available is limited and evaluations are based on old studies, not always available, of poor reliability, with limited reports and not statistically powerful.

The SCCS concluded that neither the *in silico* nor *in vitro* data give indication of ED properties of BHT. *In vivo* studies provide evidence that the liver is the primary target for BHT via the oral route of exposure, with increased liver weight and an increased activity of some phase 1 and phase 2 liver enzymes at oral doses exceeding 25 mg BHT/(kg bw x d). The thyroid effects observed are likely a consequence of hepatic enzyme induction (SCCS, 2021).

1.5.6 Odour perception

No odour threshold for BHT is available. However, BHT is reported to be an odourless compound implying that the saturated vapour concentration is lower than the odour threshold. It is known that odour thresholds are generally below the sensory irritation threshold. Thus, it is concluded that the sensory irritation of BHT vapours is negligible in relation to indoor air impurities (Nielsen et al., 1998).

1.6 Evaluation

1.6.1 Existing regulations and classifications

There is no harmonised classification for BHT (ECHA C&L Inventory, 2023). There is no current proposal for classification nor any intention indicated in the Registry of intentions (ANSES, 2023).

The IARC evaluated BHT in 1986 and classified the substance in group 3, since no evaluation of the carcinogenicity of BHT in humans could be made, and there was limited evidence for the carcinogenicity in experimental animals (IARC, 1986). The MAK Commission has classified BHT in carcinogenicity category 4 ("substances with carcinogenic potential for which a non-genotoxic mode of action is of prime importance; no significant contribution to human cancer risk is expected at exposures at MAK and BAT values") (DFG, 2023).

As summarised by the SCCS (2021), BHT was previously evaluated by JECFA at several meetings. At the 37th meeting, the temporary ADI of 0 - 0.125 mg/kg bw, established at an earlier meeting, was extended, pending the results of a study designed to elucidate the role of hepatic changes in the development of hepatic carcinomas observed in Wistar rats following in utero and lifetime exposure to BHT (JECFA, 1996). In view of the probable involvement of hepatic enzyme induction in the development of the hepatocellular damage associated with exposure to repeated doses of BHT, JECFA (1996) stated that a well-defined threshold was demonstrated at 100 mg/(kg bw x d) in the long-term study reviewed for the first time at this meeting, giving a NOAEL of 25 mg/(kg bw x d). Effects observed in the reproduction segments of in utero/lifetime exposure studies were also taken into account in the derivation of this NOAEL. The Committee used an uncertainty factor of 100 to allocate an ADI of 0-0.3 mg/(kg bw x d) for BHT. The evaluation was mainly based on the studies of Olsen et al. (1986) and Price (1994, unpublished) (the Price study was later published by McFarlane et al., 1997). In addition, new data were taken into account relating to the previously noted effects of BHT on the lung, liver, kidney, clotting mechanisms and promotion/inhibition of carcinogenesis, new long-term and reproductive toxicity studies, genotoxicity assays and human observations (JECFA, 1996).

The OECD evaluation (OECD SIDS, 2002) concluded that upon chronic oral exposure of rats, liver and thyroid are the main targets and that 25 mg/(kg bw x d) can be considered as NOAEL for chronic exposure. This report also stated that the haemorrhagic effects of high repeated doses of BHT seen in certain strains of mice and rats, but not in other species, may be related to its ability to interact with prothrombin and vitamin K. It was also concluded that BHT is not a genotoxic carcinogen, but that it cannot be excluded that high and chronic doses of BHT may result in persistent cell proliferation, which is known as a possible mechanism of non-genotoxic carcinogens. It was stated that for the possible carcinogenic and tumour promoting effect of BHT, a threshold level of 100 mg/(kg bw x d) can be assumed. The NOAEL for effects on reproduction, resulting in lower numbers of litters of ten or more pups at birth was 25 mg/(kg bw x d). Thus, the OECD evaluation is in line with that of JECFA (1996).

The same derivation was performed by the EFSA-ANS Panel (2012). Based on the NOAEL of 25 mg/(kg bw x d) from two two-generation studies in rats for dose-related effects on litter size and pup body weight gain during the lactation period and using an uncertainty factor of 100, the Panel derived an ADI of 0.25 mg/(kg bw x d). Since the NOAEL of 25 mg/(kg bw x d) is below the $BMDL_{10}$ of 247 mg/(kg bw x d) derived from the data for the incidence of hepatocellular carcinomas in male rats, the Panel concluded that this NOAEL also covers the hepatocellular carcinomas observed in the long-term studies with BHT (EFSA-ANS, 2012).

The Norwegian VKM (VKM et al., 2019) performed a systematic literature search to identify publications indicating that the ADI established by EFSA-ANS (2012) needed to be revised. No such publications were identified. As a result, the ADI of 0.25 mg/(kg bw x d) established by EFSA-ANS derived from two two-generation studies was used for the risk characterisation of the VKM (VKM et al., 2019).

The SCCS concurred with the conclusion of the EFSA-ANS (2012) and used the NOAEL of 25 mg/(kg bw x d) for their MoS (Margin of Safety) calculations of BHT in cosmetics (SCCS, 2021).

This overview of the existing assessments shows that all committees and authorities consider two reproduction studies in rats and a NOAEL of 25 mg/(kg bw x d) obtained in these studies to be relevant for the assessment. Existing guide values for BHT in air are summarised in Table 5 and Table 6.

Table 5: Guide values for BHT, part I (for explanation, see text)

Guide value Parameter/Organisation	ECHA Dissemination (2023)	AGBB (2021)	Nielsen et al. (1998)
Name	DNEL (chronic, general population)	NIK value	Indoor Air Guideline Level
Value (mg/m³)	0.435	0.100	0.5
Organ/critical effect	Not reported		Liver: enzyme induction
Species	Rat		Rat
Basis	NOAEL: 25 mg/(kg bw x d)		NOAEL: 25 mg/(kg bw x d), ADI: 0 – 0.3 mg/(kg bw x d)
Adjusted for continuous exposure	-		-
Extrapolation factors Time LOAEC to NAEC Interspecies Intraspecies Route-to-route Total	 1 - 2.5 10 2, 1.15 50 x 1.15 = 57.5		Allocation
Remarks	Route-to-route extrapolation	Adopted ascribed EU-LCI-value	Maximum indoor air concentration corresponding to 0.15 mg/(kg bw x d) „accepted“, 70 kg bw, 20 m³/d

The DNEL for the general population presented in the registration dossier (ECHA Dissemination, 2023) is based on a route-to-route extrapolation using the ADI of 25 mg/(kg bw x d) as POD. Standard assessment factors were used, including a default factor for differences between oral

absorption (assumed to be 50 %) and absorption by inhalation (assumed to be 100 %). The same POD was used for the derivation of a DNEL for workers. The oral NOAEL was converted to a NOAEC of 22.04 mg/m^3 with a factor of (1/0.38 m^3/kg bw x d) x 0.67 and the default factor for differences between oral and inhalation absorption as above (ECHA Dissemination, 2023).

Nielsen et al. (1998) accepted the JECFA assessment with an ADI of 0 – 0.3 mg/(kg bw x d) based on the NOAEL of 25 mg/(kg bw x d). However, because BHT may be found both in food and air, Nielsen et al. (1998) assumed that an airborne exposure corresponding to 0.15 mg/(kg bw x d) (50 % of the reported ADI) should not be exceeded. Assuming a lung ventilation rate of 20 m^3/d, a body weight of 70 kg, and an absorption fraction of one in the lungs, this corresponds to an airborne concentration of 0.5 mg/m^3 (Nielsen et al., 1998).

The German MAK-commission (DFG, 2004) stated that the systemic effect on the liver is the most important factor in deriving a threshold limit value (TLV) and that it can be expected that concentrations of BHT that do not cause a measurable induction of xenobiotic-inducing enzymes in the liver do not cause tumour promotion. Therefore, the induction of these enzymes was considered to be the lead effect of tumour promotion. According to the commission, the NOAEL for effects on the liver for chronic exposure is 25 mg/(kg bw x d). The commission refers to the study of (Price, 1994). However, as minor adaptive effects were still observed in young animals at this dose, the estimated NEL (no effect level) was assumed to be around 10 mg/(kg bw x d) (DFG, 2004). The commission stated that the values were not elevated at all examination times and the findings were assessed as adaptive. Although enzyme induction per se was not considered adverse, it can influence the metabolisation of endogenous substrates such as hormones. At 10 mg/(kg bw x d), such effects are no longer to be expected (DFG, 2012).

In their recent evaluation of BHT, the German Human Biomonitoring (HBM) Commission reported that enzyme activities of two liver (xenobiotic metabolising) enzymes were increased in the study of Price (1994) by a factor of about 1.5 on day 21 after birth compared to the control group. Due to the relatively small increase and the adaptivity of the effects, the HBM Commission decided not to follow the approach of the MAK-commission (HBM-Kommission, 2022).

Table 6: Guide values for BHT, part II (for explanation, see text)

Guide value Parameter/ Organisation	ECHA Dissemination (2023)	DFG (2012)	HCN (2004)	ACGIH, 2018
Name	DNEL (chronic, workers)	MAK value (workplace)	HBROEL[#] (workplace)	TWA (workplace)
Value (mg/m³)	1.76	10	5	2
Organ/critical effect	Not reported	Liver: enzyme induction and increased organ weight	Reduced weight gain of the offspring and induction of liver enzymes	Sensory irritation
Species	Rat	Rat	Rat	Mouse
Basis	NOAEL: 25 mg/(kg bw x d)	NOAEC: 25 mg/(kg bw x d)	NOAEC: 25 mg/(kg bw x d)	RD50: 32.4 mg/m³
Adjusted for continuous exposure	-	-		

Guide value Parameter/ Organisation	ECHA Dissemination (2023)	DFG (2012)	HCN (2004)	ACGIH, 2018
Extrapolation factors Time NOAEL to NEL Interspecies Intraspecies Route-to-route Total	 1 - 2.5 5 2 25 x 0.567 = 14.2	 2.5 4	 4 (allometric) 18 (inter- and intraspecies)	
Remarks	Route-to-route extrapolation	Further factors: oral absorption 0.9, work shift 5 d exposure/ 7 d exposure, 70 kg bw, 10 m³/shift, resulting concentration of 22 mg/m³, "preferred value approach" rounding to 10 mg/m³	Work shift 5 d exposure/ 7 d exposure, 70 kg bw, 10 m³/shift, resulting concentration of 22 mg/m³, "preferred value approach" rounding to 5 mg/m³	Results of the base study considered unreliable by other evaluations (DFG, 2007; SWA, 2019; US CPSC, 1998)

#: HBROEL: Health-based recommended occupational exposure limit

The Dutch Committee on Updating of Occupational Exposure Limits also concluded that decreases in body weight in BHT-treated offspring and hepatic enzyme induction are the most sensitive toxic effects in animal studies and took the NOAEL of 25 mg/(kg bw x d) as a starting point in establishing a health-based recommended occupational exposure limit (HBROEL). The NOAEL was adjusted to account for an exposure on 5 working days/week by multiplying with a factor of 7/5 resulting in a value of 35 mg/(kg bw x d). For the extrapolation to a HBROEL, a factor of 4 for allometric scaling from rats to humans, and an overall factor of 18, covering inter- and intraspecies variation and the differences between experimental conditions and the exposure pattern of the workers, are applied, resulting in a NAEL for humans of 0.5 mg/(kg bw x d). Assuming a 70-kg worker inhales 10 m^3 of air during an 8-hour working day and a retention of 100 %, and applying the preferred value approach, a HBROEL of 5 mg/m^3 was recommended for BHT (HCN, 2004).

The US-American ACGIH used an RD50 of 32.4 mg/m^3 (3.6 ppm) (ACGIH, 2018; Stadler & Lavoie, 1997) for sensory irritation in mice to derive a TWA at the workplace of 2 mg/m^3. However, the results of the base study were considered unreliable by other evaluations because of problems in the analysis (recovery) of the test substance (DFG, 2007; SWA, 2019; US CPSC, 1998).

1.6.2 Derivation of an EU-LCI value

No toxicological studies in humans are available which are relevant for the derivation of an EU-LCI value for BHT.

The only inhalation toxicity studies available are studies on sensory irritation in mice (Alarie test). One of these studies reported an RD50 of 3.6 ppm (32.7 mg/m^3) but was rated as unreliable. Another study provided a markedly higher RD50 of 59.7 ppm (about 546 mg/m^3) (DFG, 2007; US CPSC, 1998).

No studies are available with repeated inhalation exposure.

The NOAEL of 25 mg/(kg bw x d) obtained in two-generation studies with oral exposure of rats with BHT is used as POD for the derivation of an EU-LCI value. This NOAEL is based on systemic effects. A route-to-route extrapolation is performed to derive an EU-LCI value for inhalation exposure.

Toxicokinetic data for humans indicate that at least 75 % of an orally applied dose is absorbed, and data from rat studies indicate near complete absorption (90 %) after oral intake. Absorption after inhalation is, in the absence of experimental data, assumed to be complete by default. It is concluded that BHT is similarly absorbed orally and after inhalation, and no additional assessment factor is applied for differences in absorption.

The following assessment factors are used:

- Route-to-route extrapolation (rats): 1.15 m^3/(kg bw x d)
- Adjustment study length factor: 1
- Allometric scaling: already included in route-to-route extrapolation
- Interspecies extrapolation: 2.5
- Intraspecies extrapolation: 10

Total assessment factor: 25 x 1.15 = 28.75. This leads to a concentration of 25 mg/(kg bw x d) : 28.75 m^3//kg bw x d) = 0.879 mg/m^3 for BHT (rounded to 900 µg/m^3).

An EU-LCI value of 900 µg/m^3 is proposed for BHT.

The LCI-value proposed above would fully exploit the ADI of 0.25 mg/(kg bw x d) established by EFSA-ANS (2012). However, exposure to BHT is mainly by oral uptake with food. Estimates performed by the EFSA-ANS Panel (see Table 4) indicate that – based on mean values – the calculated exposure via food in adults, adolescents, and children may amount up to 34.8 % of the ADI, but under high-exposure conditions, the calculated 95th percentile in children could exceed the ADI by about 20 % (EFSA-ANS, 2012). A similar conclusion regarding the calculated exposure of adults was reached in a recent risk assessment performed by the Norwegian VKM (see chapter 1.3.2) which additionally took into account dermal and oral exposure from personal care products (VKM et al., 2019).

Taking the oral exposure into account, an allocation for the exposure to BHT by inhalation could be considered. However, no such approach has been discussed, recommended or implemented yet in the harmonisation framework using the EU-LCI concept (EC, 2013).

The proposed LCI value is more than 100fold lower than the concentration of 146 mg/m^3 which caused no signs of sensory irritation in mice in an Alarie-test and more than 500fold lower than the RD50 determined in that test (see chapter 1.5.1).

No odour threshold for BHT is available. BHT is reported to be an odourless or nearly odourless compound. Since it is known that odour thresholds are generally below the sensory irritation threshold, it was concluded that any sensory irritation of BHT vapours is negligible in relation to indoor air impurities (Nielsen et al., 1998). No sensory irritation in humans is to be expected at the proposed LCI value.

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The links listed in the bibliography were last checked and confirmed on 2. May 2024.

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A Appendix

A.1 Data collection and fact sheet for 2,6-di-tert-butyl-4-methylphenol (2,6-di-tert-butyl-p-cresol, butylated hydroxytoluene, BHT)

Table 7: Data collection sheet for 2,6-di-tert-butyl-p-cresol (BHT), part I

Compound	**BHT**	**Data collection sheet**	
N° CAS: 128-37-0 1 ppm = 9.1 mg/m³ at 23 °C	**EU-Classification:** no **CLP, harmonised classification:** -		
Organisation name	**REACH registrant**	**AgBB**	**Nielsen et al.**
Risk value name	DNEL	NIK ('Lowest Concentration of Interest')	Indoor air guideline level
Risk value (mg/m³)	0.435	0.100	0.5
Reference period	Chronic (general population)		Chronic (general population)
Risk value (mg/m³) Short term (15 min)	Not derived		-
Year	2023	2021	1998
Key study	Not explicitly reported	See below	Derived ADI (see remarks)
Study type	Two-generation oral toxicity study		
Species	Rat, Wistar (n = 6 M + 48 F/dose)		
Duration of exposure in key study	7 d/week, 22 months		
Critical effect	Not explicitly reported		
Critical dose value	NOAEL: 25 mg/(kg bw x d)		
Adjusted critical dose	25 : 1.15 = 21.7 mg/m³ : 2 = 10.87 mg/m³		
Single assessment factors	UF_A 2.5, UF_H 10, ABS_{inh}/ABS_{oral} 2; total = 50		
Other effects			

Compound	BHT	Data collection sheet	
Remarks	Route-to-route-extra-polation, adjustment for differences in oral/ inhalation bioavailability	Adopted ascribed EU-LCI-value	ADI: 0 – 0.3 mg/(kg bw x d), based on NOAEL of 25 mg/(kg bw x d), allocation 50 % for inhalation route, 20 m³/d, 70 kg bw

AgBB = Committee for Health-related Evaluation of Building Products

UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_{SA} Used subacute study; UF_D data deficiencies.

Table 8: Data collection sheet for 2,6-di-tert-butyl-p-cresol (BHT), part II

Compound	BHT	Data collection sheet		
N° CAS: 128-37-0 1 ppm = 9.1 mg/m³ at 23 °C	**EU-Classification:** no **CLP, harmonised classification:** -			
Organisation name	**REACH registrant**	**DFG**	**HCN**	**ACGIH**
Risk value name	DNEL (workers)	MAK value (workplace)	HBROEL (workplace)	TWA (workplace)
Risk value (mg/m³)	1.76	10	5	2
Reference period	Chronic	Chronic	Chronic	Chronic
Risk value (mg/m³) Short term (15 min)	Not derived	20	-	-
Year	2023	2012	2004	2018
Key study	Not explicitly reported	Price, 1994	McFarlane et al., 1997; Price, 1994	Stadler and Lavoie, 1997
Study type	Two-generation oral toxicity study	Two-generation oral toxicity study	Two-generation oral toxicity study with rats	Sensory irritation study with mice
Species	Rat, Wistar (n = 6 M + 48 F/dose)	Rat	Rat	Mouse
Duration of exposure in key study	7 d/week, 22 months	7 d/week, 22 months	7 d/week, 22 months	30 min
Critical effect	Not explicitly reported	Hepatic enzyme induction	Decreased body weight, hepatic enzyme induction	Sensory irritation
Critical dose value	NOAEL: 25 mg/(kg bw x d)	NOEL: 10 mg/(kg bw x d)	NOAEL: 25 mg/(kg bw x d)	RD50: 32.4 mg/m³
Adjusted critical dose	25 : 0.38 x 0.67: 2 = 22.04 mg/m³		25 x 7/5 = 35 mg/(kg bw x d)	

Compound	BHT	Data collection sheet		
Single assessment factors	UF_A 2.5, UF_H 5, ABS_{inh}/ABS_{oral} 2; total = 25		UF_A 4, total: 18, 10 m^3/8-h shift, 100 % retention	
Other effects				
Remarks	Route-to-route-extrapolation, adjustment for differences in oral/inhalation bioavailability			Results of the base study considered unreliable by other evaluations (DFG, 2007; SWA, 2019; US CPSC, 1998)

AgBB = Committee for Health-related Evaluation of Building Products

UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_{SA} Used subacute study; UF_D data deficiencies.

Table 9: Fact sheet for 2,6-di-tert-butyl-p-cresol (BHT)

Compound	2,6-Di-tert-butyl-p-cresol (BHT) C15H24O		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	900
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2024
General information			
CLP-Index No.	4	INDEX	-
EC-No.	5	EINECS	204-881-4
CAS-No.	6	Chemical Abstract Service number	128-37-0
Harmonised CLP classification	7	Human health risk related classification	-
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	220.35 1 ppm = 9.1 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	Two-generation oral toxicity study with rats (McFarlane et al., 1997; Price, 1994)
Read across compound	10	Where applicable	-
Species	11	Rat, human, etc.	Rat, Wistar
Route / type of study	12	Inhalation, oral feed, etc.	Oral feed
Study length	13	Days, subchronic, chronic, etc.	Chronic (two-generation study)
Exposure duration	14	h/d, d/w	7 d/week
Critical endpoint	15	Effect (s), site of	Decreased body weight, hepatic enzyme induction
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEL
POD value	17	[mg/m³] or ppm or [mg/kg_{BW}×d]	25 mg/(kg bw x d)
Assessment factors (AF)			
Adjustment for exposure duration	19	Study exposure h/d, d/w	1
Study length	20	sa→sc→c	1
Route-to-route extrapolation factor	21	-	1.15 m³/(kg bw x d)

Compound	2,6-Di-tert-butyl-p-cresol (BHT) C15H24O		Fact sheet
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	1
	22b	Severity of effect (R8 6d)	1
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	1
	23b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		
Other adjustment factors Quality of database	26	Quality of database	1
Results			
Summary of assessment factors	27	Total Assessment Factor	1.15 x 25
POD/TAF	28	Calculated value [µg/m³ and ppb]	879 µg/m³ (97 ppb)
Molar adjustment factor	29		
Rounded value	30	[µg/m³]	900
Additional comments	31		
Rationale selection	32		

Rationale for critical effects

The acute oral and dermal toxicity of 2,6-di-tert-butyl-p-cresol (BHT) is low (oral LD50 in rats > 6000 mg/kg bw, dermal LD50 in rats > 2000 mg/kg-bw) (ECHA Dissemination, 2023). No data on the toxicity of BHT following inhalation is available except for studies on sensory irritation.

BHT is slightly irritating based on studies on skin and eyes of rabbits (SCCS, 2021).

In a study for sensory irritation (Alarie-test), Swiss Webster mice showed no signs of respiratory irritation at 4.54 and 16 ppm (about 41 and 146 mg/m^3, respectively) after 30 min exposure; the RD50 was calculated to be 59.7 ppm (about 546 mg/m^3). This result does not support a previously reported RD50 of 3.6 ppm (32.7 mg/m^3) (Stadler und Lavoie, 1997); the discrepancy was explained by problems in the analysis (recovery) in that earlier study (DFG, 2007; US CPSC, 1996; US CPSC, 1998).

The evidence on skin sensitisation in animals is limited, there is no evidence from a range of human experience to suggest that BHT is a significant human skin sensitiser or contact allergen (SCCS, 2021). No data are available regarding respiratory sensitisation.

A considerable number of animal studies was conducted with repeated oral exposure to BHT. Reviews and summaries were presented by SCCS (2021) and (VKM et al., 2019). Both, in turn, mostly referred to data presented by EFSA-ANS (2012) and ANSES (2016).

Short-term or subchronic exposure to BHT affects the liver of mice, rats and chicken, including histopathological hepatocellular changes. BHT also increased the relative thyroid and adrenal weight in rats. Oral treatment of male rats for 7 consecutive days with 75 or 450 mg BHT/(kg bw x d) induced hepatocellular proliferation, increased hepatocyte apoptosis, elevated immunoreactivity for transforming growth factor (TGF)-β1 in the liver during the treatment, and resulted in hepatocellular inhibition of mitosis following withdrawal (SCCS, 2021).

The majority of evidence indicates a lack of potential for BHT to induce point mutations or chromosomal aberrations, or to interact with or damage DNA. Positive genotoxicity results obtained *in vitro* with BHT and BHT metabolites may be due to pro-oxidative chemistry, giving rise to formation of quinones and reactive oxygen species. Such a mechanism of genotoxicity is generally considered to have a threshold (SCCS, 2021). It was concluded that BHT is not of concern with regard to genotoxicity (EFSA-ANS, 2012; SCCS, 2021; VKM et al., 2019).

In a two-generation study (see below) histopathological examinations indicated dose-related increases in the numbers of hepatocellular carcinomas in male rats and an increase in hepatocellular adenomas in both male and female rats. Tumours were also found in other organs of some of the treated rats, including thyroid, pancreas, ovary, uterus, thymus, reticulo-endothelial system, and mammary gland, but their incidence was not statistically significantly different from that in controls (Olsen et al., 1986; SCCS, 2021). In a further two-generation study with rats (McFarlane et al., 1997; Price, 1994), a higher incidence of eosinophilic and basophilic foci and in the number of rats with hepatic nodules was observed in the high-dose group but no adenoma or carcinoma (SCCS, 2021).

The EFSA-ANS (2012) considered that the effects of BHT on tumour formation reported in the study of Olsen et al. (1986) are subject to a threshold since the genotoxicity studies generally indicate a lack of potential for BHT to induce point mutations, chromosomal aberrations, or to interact with or damage DNA. The BMD analysis performed by EFSA-ANS (2012) on the incidence of hepatocellular carcinoma in male rats induced by BHT as reported by Olsen et al. (1986) gave a BMDL10 of 247 mg/(kg bw x d).

The IARC classified the substance in group 3, since no evaluation of the carcinogenicity of BHT in humans could be made, and there was limited evidence for the carcinogenicity in experimental animals (IARC, 1986).

In an unpublished study (Brooks et al., 1976) submitted to JECFA (1996) CFI mice were maintained on diets containing 1000 mg BHT/kg feed. At week 4, one group was then fed a diet containing 2500 mg BHT/kg feed, and at week 8, another group was fed a diet containing 5000 mg BHT/kg feed. These dose levels of 1000, 2500 and 5000 mg/kg feed correspond to approximately 0, 100, 250 and 500 mg/(kg bw x d). The mice were maintained on these diets until 100 weeks of age. There was an increased incidence of lung neoplasia in treated mice. Benchmark analyses of the incidence of lung neoplasia revealed a BMDL10 of 38 mg/(kg bw x d) (EFSA-ANS, 2012). However, EFSA-ANS (2012) also noted that when a larger number of animals were used by the same investigators in a further study (Clapp et al., 1978), the findings from the study of Brooks et al. (1976) could not be not confirmed.

In a two-generation study by Price (McFarlane et al., 1997; Price, 1994), male and female Wistar rats were fed BHT in the diet at doses of 0, 25, 100 or 500 mg/(kg bw x d) for 3 weeks prior to mating. The highest dose was reduced to 250 mg/(kg bw x d) in the F1-generation. The study was terminated 22 months after the F1 male rats were placed on test diets. In the first 5 weeks of BHT administration, a reduction in body weight gain was noted in the high-dose males. Body weight gain in all other treatment groups was similar to that in controls. At the sacrifice on day 20 of gestation, both absolute and relative liver weights of the dams were increased in a dose-

related manner, statistically significant at the high dose. The body weights of the females, both including and excluding their litters, were similar in all groups (SCCS, 2021).

There was a slight decrease in the numbers of pups/litter in the low and high-dose groups, but a dose-related trend was not observed. Body weights of the pups from the high-dose group were significantly lower than controls at birth (10 %), and at days 6 (12 %) and 21 (21 %) of lactation. Mortality of the pups between culling and day 21 of lactation was 2 %, 8 %, 12 % and 15 %, in order of increasing dose. Body weights of the F1 males were lower in the high-dose group, compared with controls, throughout the 22-month treatment period. At the scheduled sacrifices, dose-related increases were observed in relative, but not absolute liver weights; the differences were statistically significant at the high dose (SCCS, 2021).

A dose-related incidence of enlargement and eosinophilia of the centrilobular hepatocytes was observed at the scheduled sacrifices, starting at 6 months. This was indicative of proliferation of the smooth endoplasmic reticulum, consistent with an induction of mixed-function oxidases. Immunohistochemical staining of liver sections from control and high-dose rats revealed a marked increase in hepatocellular content and distribution of cytochrome P450 2B with BHT treatment which persisted throughout the study. Histochemical staining revealed a marked induction of gamma-glutamyl transpeptidase (GGT) activity in the periportal hepatocytes of nearly all of the high-dose rats, starting at 11 months of treatment. At 22 months, there was a higher incidence of eosinophilic and basophilic foci in the high-dose group. Histochemical staining of liver sections revealed a small number of high-dose animals with glucose-6-phosphatase-deficient AHF (altered hepatocellular foci) which was statistically significant. At 22 months, there was also a significant increase in the number of rats with hepatic nodules in the high-dose group (6/19 animals compared with none in the other groups) (SCCS, 2021).

Total cytochrome P450 content was increased by 30 – 60 % in the high-dose animals starting at 21 days of age. Dose-related increases were noted in epoxide hydrolase, glutathione-S-transferase and pentoxyresorufin-O-depentylase (PROD) activities, starting at 21 days of age, which were statistically significant in the mid- and high-dose groups. The increases in PROD activity were large, 10 – 25fold in the mid-dose, and 20 – 80 fold in the high-dose groups (SCCS, 2021).

No effects on the adrenal were noted. Histopathology of the adrenal was conducted starting at 11 months post-weaning. Evidence of thyroid hyper-activity, characterised by reduction of follicular size, absence or reduction of colloid, irregularities in the follicular outline, hyperaemia and an increase in the number of follicular cells was noted starting at 11 months in both the mid-dose group (mild changes affecting 75 - 82 % of the rats) and the high-dose group (marked changes affecting 100 % of the rats). Serum thyroxin levels in treated rats did not differ from controls (SCCS, 2021).

The SCCS also evaluated the data from studies on endocrine disrupting (ED) potential of BHT. The SCCS concluded that neither the *in silico* nor *in vitro* data give indication of ED properties of BHT. *In vivo* studies provide evidence that the liver is the primary target for BHT via the oral route of exposure, with increased liver weight and an increased activity of some phase 1 and phase 2 liver enzymes at oral doses exceeding 25 mg BHT/(kg bw x d). The thyroid effects observed are likely a consequence of hepatic enzyme induction (SCCS, 2021).

Rationale for starting point

Based on the NOAEL of 25 mg/(kg bw x d) from two two-generation studies in rats for dose-related effects on litter size and pup body weight gain during the lactation period and using an uncertainty factor of 100, the EFSA-ANS Panel derived an ADI of 0.25 mg/(kg bw x d). Since the

NOAEL of 25 mg/(kg bw x d) is below the BMDL10 of 247 mg/(kg bw x d) derived from the data for the incidence of hepatocellular carcinomas in male rats, the Panel concluded that this NOAEL also covers the hepatocellular carcinomas observed in the long-term studies with BHT (EFSA-ANS, 2012). Recently, the SCCS concurred with the conclusion of the EFSA-ANS (2012) and used the NOAEL of 25 mg/(kg bw x d) for their MoS (Margin of Safety) calculations of BHT in cosmetics (SCCS, 2021).

The Norwegian VKM (VKM et al., 2019) performed a systematic literature search to identify publications indicating that the ADI established by EFSA-ANS (2012) needed to be revised. No such publications were identified. As a result, the ADI of 0.25 mg/(kg bw x d) established by EFSA-ANS derived from two two-generation studies was used for the risk characterisation of the VKM (VKM et al., 2019).

The NOAEL of 25 mg/(kg bw x d) obtained in two-generation studies with oral exposure of rats with BHT is used as POD for the derivation of an EU-LCI value. This NOAEL is based on systemic effects. A route-to-route extrapolation is performed to derive an EU-LCI value for inhalation exposure.

Rationale for assessment factors

Toxicokinetic data for humans indicate that at least 75 % of an orally applied dose is absorbed, and data from rat studies indicate near complete absorption (90 %) after oral intake. Absorption after inhalation is, in the absence of experimental data, assumed to be complete by default. It is concluded that BHT is similarly absorbed orally and after inhalation, and no additional assessment factor is applied for differences in absorption.

The following assessment factors are used:

- Route-to-route extrapolation (rats): 1.15 m^3/(kg bw x d)
- Adjustment study length factor: 1
- Allometric scaling: already included in route-to-route extrapolation
- Interspecies extrapolation: 2.5
- Intraspecies extrapolation: 10

Total assessment factor: 25 x 1.15 = 28.75. This leads to a concentration of 25 mg/(kg bw x d) : 28.75 m^3//kg bw x d) = 0.879 mg/m^3 for BHT (rounded to 900 µg/m^3).

An EU-LCI value of 900 µg/m^3 is proposed for BHT.

The LCI-value proposed above would fully exploit the ADI of 0.25 mg/(kg bw x d) established by EFSA-ANS (2012). However, exposure to BHT is mainly by oral uptake with food. Estimates performed by the EFSA-ANS Panel (2012) indicate that – based on mean values – the calculated exposure via food in adults, adolescents, and children may amount up to 34.8 % of the ADI, but under high-exposure conditions, the calculated 95th percentile in children could exceed the ADI by about 20 % (EFSA-ANS, 2012). A similar conclusion regarding the calculated exposure of adults was reached in a recent risk assessment performed by the Norwegian VKM (2019) which additionally took into account dermal and oral exposure from personal care products.

Taking the oral exposure into account, an allocation for the exposure to BHT by inhalation could be considered. However, no such approach has been discussed, recommended or implemented yet in the harmonisation framework using the EU-LCI concept (EC, 2013).

The proposed LCI value is more than 100fold lower than the concentration of 146 mg/m³ which caused no signs of sensory irritation in mice in an Alarie-test and more than 500fold lower than the RD50 determined in that test (DFG, 2007; US CPSC, 1998).

No odour threshold for BHT is available. BHT is reported to be an odourless or nearly odourless compound. Since it is known that odour thresholds are generally below the sensory irritation threshold, it was concluded that any sensory irritation of BHT vapours is negligible in relation to indoor air impurities (Nielsen et al., 1998). No sensory irritation in humans is to be expected at the proposed LCI value.

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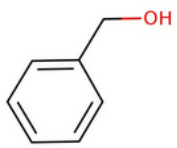
2 Toxicological evaluation of benzyl alcohol as basis for the derivation of an EU-LCI value

2.1 Substance identification

The substance identification of benzyl alcohol is shown in Table 10. Benzyl alcohol is an aromatic alcohol consisting of benzene with a single hydroxymethyl substituent (NLM, 2023).

Table 10: Substance identification of benzyl alcohol (ECHA Dissemination, 2023)

CAS-No. EU-No. CLP-Index-No.	Systematic name, common name	Sum formula	Structural formula
100-51-6 202-859-9 603-057-00-5	benzyl alcohol, phenylmethanol, benzenemethanol, phenylcarbinol	C_7H_8O	

2.2 Substance properties and uses

The physicochemical properties of benzyl alcohol are shown in Table 11. Benzyl alcohol is a colourless, oily liquid, which is (slightly) soluble in water and soluble in organic solvents (e.g., benzene, methanol, ethanol, chloroform, acetone, ether) (EFSA Panel on Food Additives and Flavourings (FAF) et al., 2019a; NLM, 2023; NTP, 1989).

The action of sodium or potassium carbonate on benzyl chloride is used in the commercial production of benzyl alcohol. It is mainly used as a curing agent in epoxy coatings, in which benzyl alcohol is chemically bound and not released (30 % of world production). The use of benzyl alcohol is widespread, e.g., in paint strippers (only as industrial use), as solvent in waterborne coatings or inks, as a co-additive for dyeing in the textile industry, in photographic developers, as a preservative (due to its bacteriostatic properties) in cosmetics, pharmaceutical and medicine products, as food additive in flavourings (E1519) and as a fragrance component in parfums and cosmetics (Ad-hoc-AG, 2010; NLM, 2023; NTP, 1989; OECD, 2001). Further, benzyl alcohol is authorised to be used as a preservative for products during storage (product category 6) (ECHA Dissemination, 2023). It is also used in household products (e.g., fragrance in household detergents) and professional cleaning products (Gerster et al., 2014; Wieck et al., 2018).

Table 11: Physicochemical properties of benzyl alcohol (EC, 2013; ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017)

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa) (at 20 °C)	Conversion 1 ppm = x mg/m³ (23 °C)	log pow (at 20 °C)	Solubility in water (g/L) at 25 °C
108.14	-15.4	205.3	0.07	4.45 *	1.05 at 20 °C	40

* Conversion at 23 °C and 101.3 kPa (EC, 2013)

2.3 Exposure

2.3.1 Indoor air

Few data are available regarding the occurrence of benzyl alcohol in indoor air (see Table 12). Benzyl alcohol was detected in 24 % of all samples (n=746) from offices, homes, and (pre)schools in Germany. The measured concentrations were low as indicated by a median of 0.5 µg/m³ (UBA, 2008). Two further evaluations with a lower number of total measurements (142 and 285) detected benzyl alcohol in less than 5 % of all samples, with a mean lower than the detection limit (Ad-hoc-AG, 2010; Ostendorp et al., 2009). For another evaluation with a large database of 3311 measurements only limited information is given. The reported median is below the detection limit, but the 90th percentile is 4.6 µg/m³, indicating that either a single value or a few values with benzyl alcohol concentrations above the LOD were measured (AGÖF, 2013).

Table 12: Data on the occurrence of benzyl alcohol in indoor air from homes, schools, children day care centres and offices

Indoor	N	LoD (µg/m³)	N > LoD	Median (µg/m³)	P95 (µg/m³)	Maximum (µg/m³)	Source
Indoor air (not further specified), Germany, 2006-2012	3311	not reported	not reported	<1	4.6 *	not reported	(AGÖF, 2013)
Offices, homes, kindergarten, Germany, 2001-2009	142	1	6	<1	<1	544	(Ad-hoc-AG, 2010)
Schools, kindergarten, Germany, 2005-2007	285	2**	11	<2	<2	260	(Ad-hoc-AG, 2010; Ostendorp et al., 2009)
Offices, homes, (pre)-schools, Germany, 2002-2006	746	0.1 - 5.0 (mean: 1.0)	180	0.5	10.0	870	(Ad-hoc-AG, 2010; UBA, 2008)

* given as P90 value

** determined as toluene equivalent

2.3.2 Other sources

Benzyl alcohol naturally occurs in plants (e.g., maize, snap beans), mushrooms, fruits (e.g., grapes, sour cherries, tomatoes, apricots), nuts (e.g., chestnuts, almonds), spices (e.g., clover, cinnamon bark), and alcohol (e.g., wines, cider) and is found in essential oils of plants like jasmine, hyacinth, and ylang-ylang (Api et al., 2015; EFSA Panel on Food Additives and Flavourings (FAF) et al., 2019a; Nair & Cosmetic Ingredient Review Expert, 2001)

2.4 Toxicokinetics

Toxicokinetic information after inhalation exposure is not available (Ad-hoc-AG, 2010; Hartwig & MAK Commission, 2017).

An oral exposure to 1.5 g benzyl alcohol resulted in humans in a fast and almost complete resorption. Within six hours, 75-85 % of the applied dose is metabolised and excreted in the urine (ECHA Dissemination, 2023; MAK Commission, 2006). Rabbits given an oral dose of 400 mg benzyl alcohol/kg bw excreted 65.7 % of the resorbed substance in the urine within six hours after the application (MAK Commission, 2006).

Studies in humans and animals showed that benzyl alcohol is metabolised by oxidation firstly to benzaldehyde and then to benzoic acid, which after conjugation with glycine is excreted renally as hippuric acid. As metabolising enzymes were identified alcohol and aldehyde dehydrogenase in mice and cytochrome (CYP) P450 enzyme (not alcohol dehydrogenase) in human liver microsomes (ECHA Dissemination, 2023; EFSA Panel on Food Additives and Flavourings (FAF) et al., 2019a; Hartwig & MAK Commission, 2017). The oxidation of benzoic acid to hippuric acid is subject to saturation kinetics due to limited capacity of glycine conjugation at high doses (ECHA Dissemination, 2023; EFSA Panel on Food Additives and Flavourings (FAF) et al., 2019a). Depletion of glycine results in excretion of benzoic acid as unchanged or the glucuronic acid conjugate (EFSA Panel on Food Additives and Flavourings (FAF) et al., 2019a). Approximately 80 % of resorbed benzyl alcohol is excreted as hippuric acid and up to 20 % as glucuronic acid conjugate (Hartwig & MAK Commission, 2017).

An *in vivo* dermal absorption study exposed rhesus monkeys to radioactive labelled benzyl alcohol dissolved in acetone under occlusive conditions (in total 4 µg/cm^2) for 24 hours and determined a flux value of 0.1 µg/cm^2 x h. Up to 80 % of the applied dose were absorbed. *In vitro* skin permeation studies performed in human skin in physiological receptor media, resulted in flux values of 29 to 275 µg/cm^2 x h, which corresponds to a total dermal absorption of 58 to 550 mg benzyl alcohol during exposure of both underarms and hands (ca. 2000 cm^2) for one hour (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017). Based on the calculated total dose, dermal absorption is expected to contribute in a relevant way to systemic toxicity (Hartwig & MAK Commission, 2017).

2.5 Health effects

2.5.1 Acute toxicity, sensory irritation, and local effects

Acute toxicity

The database for acute exposure of humans to benzyl alcohol is mainly limited to case reports were co-exposure to other solvents also occurred. For example, Fukuda et al. (2022) reported a case, where a 27-year-old Asian man, who was exposed to a paint stripper containing benzyl alcohol, ethylene glycol, and hydrogen peroxide, had impaired consciousness, metabolic acidosis, and developed a paralytic ileus. After 11 days in hospital the patient was discharged without obvious complications (Fukuda et al., 2022).

For benzyl alcohol the saturation concentration of 567 mg benzyl alcohol/m^3 (126 ppm; based on a saturated vapour pressure of 0.13 hPa at 25 °C) indicates that at an independently generated exposure atmosphere above 500-600 mg/m^3 aerosol and vapour are in equilibrium and at lower concentrations benzyl alcohol is mainly present as a vapour (Hartwig & MAK Commission, 2017).

In an acute inhalation toxicity study (according to OECD TG 403) rats were exposed "nose only" to 3297 or 4178 mg benzyl alcohol/m^3 (aerosol, maximum technically achievable concentration), respectively, for four hours. At 4178 mg/m^3 clinical signs observed were piloerection and slight bradypnea, which were regarded as a sign of sensory irritation by the authors of the study. The NOEC was 3297 mg/m^3 and because no animal died the 4-h-LC50 is > 4178 mg/m^3 (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017; OECD, 2001). Older studies in rats reported an 8-h-LC50 value of 4492 mg benzyl alcohol/m^3 (1000 ppm) and a 6-h-LC50 value of 1059 mg/m^3; effects observed in dead animals were asthenia, hyperthermia, tremor, impaired locomotor function, and hind limb paresis (Hartwig & MAK Commission, 2017).

The dermal toxicity of benzyl alcohol has been investigated in older studies in rabbits and guinea pigs resulting in LD50 values of 2000 mg/kg bw in rabbits and less than 5 ml/kg bw (corresponding to approx. 5200 mg/kg bw) in guinea pigs (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017; OECD, 2001).

Oral LD50 values in the range of 1000 to 3100 mg benzyl alcohol/kg bw were reported in rabbits, rats, guinea pigs, and mice. Symptoms of intoxication included central nervous system (CNS) depression, impacts on CNS (rapid breathing, unusual gait), irritability, and coma (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017; NLM, 2023; OECD, 2001).

Irritation

In an older, open epicutaneous test, seven out of 32 patients developed urticaria after 5 % benzyl alcohol in vaseline was applied to skin. Skin irritation was also evident in 18 of 614 volunteers, who were conclusively exposed to 0.05 % benzyl alcohol in either ethanol or ointment base for 24 or 48 hours. However, it needs to be noted that a clear delimitation between irritating and allergic skin diseases is not always possible. The application of a 1 % benzyl alcohol solution on mucous membranes or skin led to local anaesthetic effects. In eyes, 1 % benzyl alcohol dissolved in physiological saline solution initially leads to pain and within a few minutes to complete anaesthesia (MAK Commission, 2006).

A study on skin irritation (comparable to OECD TG 404) of benzyl alcohol in rabbits showed slight irritating effects (erythema) in one animal, which were reversible within 72 hours. It was concluded that benzyl alcohol does not fulfil the criteria for classification as a skin irritant (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017; OECD, 2001). Further *in vivo* studies in rabbits and guinea pigs as well as an *in vitro* skin corrosion test with reconstructed human epidermis (according to OECD TG 431) support this conclusion (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017).

Benzyl alcohol is an eye irritant. In two eye irritation studies (according to OECD TG 405), benzyl alcohol (100 µl, no vehicle) installed in rabbits' eye and either washed out 24 hours after instillation or not, caused irritating effects (e.g., irritation of mucous membrane and cornea, moderate chemosis, white coloured discharge), which were reversible within the observation period (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017; OECD, 2001).

No data are available on respiratory sensitisation for benzyl alcohol (Hartwig & MAK Commission, 2017).

Sensitisation

Few case reports of occupational contact allergic reactions induced by benzyl alcohol are available. Several cases are linked to topical application of benzyl alcohol to pre-damaged skin but are of limited value in assessing the significance to evaluate the sensitising potential of benzyl alcohol because the transferability from pre-damaged to intact skin is not suitable.

Positive reactions occurred in 1.6 % and 2.5 % of patients in epicutaneous (patch) tests performed in the 1980s in large groups of 2028 and 4246 patients, respectively, with benzyl alcohol concentrations of 5 % or 10 % (Hartwig & MAK Commission, 2017). In patients, who had skin lesions (652 patients with eczema), higher reaction rates of up to 5 % were observed (Hartwig & MAK Commission, 2017). Lower reaction rates have been observed in more recent epicutaneous tests. For example, in the clinics of the Information Network of Departments of Dermatology (IVDK,) 223 of 65398 (0.3 %) patients who were patch tested with 1 % benzyl alcohol in petrolatum showed positive reactions. Studies with human volunteers, who participated in repeated insult patch tests with benzyl alcohol doses ranging from 3-20 % benzyl alcohol for induction and challenge, observed that increasing benzyl alcohol doses (> 7.5 %) caused an increase in sensitised cases (0-11 %) (ECHA, 2020). It was noted that a few volunteers developed oedemas during the induction period, which may have been in previous contact to benzyl alcohol due to its widespread use and may have been sensitised beforehand (ECHA, 2020).

In a LLNA assay (according to OECD TG 429) in mice, benzyl alcohol (up to 50 % solution dissolved in ethanol:diethyl phthalate (1:3)), showed no skin sensitising potential (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017). Older studies in guinea pigs were inconclusive: positive in an open cutaneous test and a Freund's complete adjuvant test and negative results in a maximisation test and Draize test (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017; OECD, 2001).

Overall, based on the available experimental data, the expert committees and the registrant of the registration dossier in the disseminated database do not consider benzyl alcohol to be a skin sensitiser, although there were a few positive reactions in humans with particularly damaged skin (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017; OECD, 2001).

In 2020 a proposal for Harmonised Classification and Labelling (CLH) was published, in which the classification of benzyl alcohol as a skin sensitiser, subcategory 1B is proposed based on positive reactions observed in humans (ECHA, 2020). In its opinion from 2021, RAC agreed with the proposal made by the member state, Germany (RAC, 2021). Geier et al. (2022) disagree with the proposed classification in Skin Sens. 1B because *"no lower threshold of this category is defined, and hence every substance eliciting a contact allergy reaction in only 1 individual must be categorized as 1B"* and therefore the classification of *"extremely rare allergens"* is counterproductive as the warning effect for users and consumers is lost (Geier et al., 2022).

According to the Cosmetic Products Regulation (EC) No 1223/2009[1], benzyl alcohol can be used as a preservative up to a maximum concentration of 1.0 % in ready for use preparations and must be declared in the list of ingredients, when its concentration exceeds 0.001 % in leave-on products or 0.01 % in rinse-off products due to its sensitising potential.

2.5.2 Repeated dose toxicity

Human data

In a case report from Inada et al. (2022), a 58-year-old man, who has been spraying a paint stripper containing 65-75 % benzyl alcohol for the last five days, had a headache and loss of appetite every evening. Prior to admission to the hospital the patient did not recognise his wife and became violent towards her. In serum samples, 4.7 µg/ml benzyl alcohol and 1120 µg/ml benzoic acid were detected on day 1 and 0.97 g/l hippuric acid was found in a urine sample on

[1] Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products. Available at: https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=celex%3A32009R1223, accessed on 20.12.2023.

day 3, thus a benzyl alcohol intoxication was diagnosed. The patient's symptoms included altered mental status, metabolic acidosis, hypokalemia, hypophosphatemia, and hyperammonemia, which was associated with a renal tubular dysfunction. After ten days in hospital the patient was discharged with improved mental status (Inada et al., 2022).

Two studies investigated the efficiency of a lotion containing 5 % benzyl alcohol, which was dermally applied on the head of 628 children, to eliminate lice. During the study investigation of six months, 2 % of the children reported a local loss of sensitivity or skin irritation, respectively (Ad-hoc-AG, 2010). After repeated dermal exposure of nine female volunteers to 3 % benzyl alcohol subcutaneously by injection for four consecutive days skin irritation was observed at the site of application (Hartwig & MAK Commission, 2017).

In the 1980s, benzyl alcohol was added as a preserving agent to isotonic saline solutions (0.9 % solution), which were used for example for flushing catheters. In this way premature neonates were exposed to doses of benzyl alcohol of about 99 to 234 mg/(kg bw x d) for two to 28 days. A prominent sign of intoxication was gasping (thus also called gasping syndrome) among others such as: *"gradual neurologic deterioration, severe metabolic acidosis, the striking onset of gasping respirations, thrombocytopenia, hepatic and renal failure, hypotension, cardiovascular collapse and death"* (Ad-hoc-AG, 2010; Hartwig & MAK Commission, 2017; OECD, 2001). As these symptoms are not observed in term newborns and adults it is concluded that preterm infants have a reduced metabolic capacity (reduced glycine acyltransferase activity and depletion in glycine) (Hartwig & MAK Commission, 2017).

Animal data

In an inhalation study, rats (4/group) were exposed to 0, 190, 334, 643 or 1119 mg benzyl alcohol/m^3 for 6 h/d on three days with an observation period of 16 days. One animal died after the first exposure and another one was terminated due to moribund signs after the second exposure in the high concentration group. Locomotor coordination was disturbed in both terminated animals. At 334 mg/m^3 and above, the nasal region of all animals was discoloured (Hartwig & MAK Commission, 2017).

Groups of six male rats were exposed whole-body to benzyl concentrations of 971 to 1214 mg/m^3 for 4 h/d for 14 days. No substance-related effects (e.g., body weight, clinical or pathological observations, organ weights) were observed. However, no details on microscopic or histopathological examinations were provided (Hartwig & MAK Commission, 2017).

In a subacute inhalation study (according to OECD TG 412, unpublished study report) Sprague-Dawley rats (10/sex/group) were exposed "nose-only" to benzyl alcohol concentrations of 0, 41, 102, 290 or 1072 mg/m^3 (ca. 0, 9.2, 22.9, 65.2 or 240.9 ppm) as an aerosol (at 1072 mg/m^3 MMAD: 3.3 µm and GSD: 2.39) 6 h/d, 5d/week for a total of at least 20 exposures. No treatment-related effects on body weight, body weight gain, clinical observations, mortality, haematology, and clinical chemistry were reported. At 290 mg/m^3 and above, a concentration-dependent increase in the relative weight of epididymis was observed, which was the only statistically significant effect found (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017). The relative epididymides weight was 0.279 g, 0.307 g, 0.304 g, 0.314 g, and 0.322 g in control and treatment groups, which corresponds to an increase of 10.0 %, 8.9 %, 12.5 %, and 15.4 % in the treatment groups relative to the control (ECHA Dissemination, 2023). In its 2017 assessment, the MAK Commission also reports on histological findings, which were only examined in the highest concentration and the control group. Incidences of minimal mononuclear infiltrates in the lungs (5/10 in M; 1/10 in F) were found in the highest concentration group, but none in the control group. Examination of nasal cavities revealed slight hyperplasia of squamous cells (2/10 in M; 2/10 in F), minimal acute (1/10 in M) and subacute (1/10 in M; 2/10 in F), and minimal

mononuclear infiltrates (2/10 and 1/10, nasal level I and II in F), which were either not found or were with low incidence in the control groups. The examined lymph nodes of the respiratory tract showed minimal hyperplasia in the mandibular region (1/10 in M; 3/10 in F) and haemorrhage (1/10, 2/9, mandibular and mediastinal region in M) compared to none or one animal in the control. According to the disseminated REACH registration dossier, these findings, which were not reported in the registration dossier, were not treatment-related (no further information provided) and thus a NOAEC of 1072 mg/m^3 was established (ECHA Dissemination, 2023). Despite its limitations (e.g., no real-time monitoring of aerosol presence, determination of measurement of particles, no data on method validation, no histopathological examination in low and mid concentration group), the MAK Commission regarded this study as suitable for the derivation of a threshold value. Due to the observed microscopic changes in the respiratory tract at 1072 mg/m^3, a LOAEC of 1072 mg/m^3 was derived and a NAEC (no adverse effect concentration) of 300 mg/m^3 is estimated (based on LOAEC/3) (Hartwig & MAK Commission, 2017).

In a valid subchronic oral study, F344/N rats (10 M +F) were daily exposed to benzyl alcohol by gavage to doses of 0, 50, 100, 200, 400 or 800 mg/(kg bw x d), 5 d/w for 13 weeks. At 800 mg/(kg bw x d) animals of both sexes showed symptoms of intoxication and clear signs of neurotoxicity like staggering, lethargy or laboured breathing (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017; NTP, 1989). Females in the low and mid dose group and males in the high dose group had lower relative body weight gains in comparison to the control group (NTP, 1989). At the highest dose group, the mean body weight was lower compared to the controls (7 % for males and 5 % for females) (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017; NTP, 1989). At 800 mg/(kg bw x d) histopathological changes were observed in the brain necrosis of dental gyrus of hippocampus (9/9 males and 7/7 females), thymus (congestion, haemorrhage and atrophy in 8/10 males), skeletal muscles (necrosis in 5/10 males) and kidneys (nephrosis 6/9 males) (Hartwig & MAK Commission, 2017; NTP, 1989). Mortalities occurred mainly in the highest dose group while 8/10 males and 2/10 females died as well as one female of the mid dose group and one male of the low dose group died. The reason was often the gavage procedure. The effects on the body weight are not considered as adverse thus a NOAEL of 400 mg/(kg bw x d) was established (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017).

The same study with an exposure schedule as described above was also conducted with B6C3F1 mice. The only observed toxicity sign was staggering in the high dose group. Females in the low dose group and above and males in the mid dose group had lower relative body weight gains in comparison to the control group (NTP, 1989). At the mid and high dose group, the mean body weight of females was lower compared to the controls (5 % and 8 %) (ECHA Dissemination, 2023). Mortalities occurred but were mostly caused by the gavage application. A NOAEL of 200 mg/(kg bw x d) was derived (ECHA Dissemination, 2023; MAK Commission, 2006).

In a 2-year carcinogenicity study, benzyl alcohol was daily administered by gavage (vehicle: corn oil) in doses of 0, 200 and 400 mg/(kg bw x d) to F344/N rats and 0, 100 and 200 mg/(kg bw x d) to B6C3F1 mice. No treatment-related effects were observed and thus the derived NOAELs in rats and mice were identical to the high dose groups, respectively (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017).

2.5.3 Genotoxicity and carcinogenicity

Genotoxicity

Many *in vitro* genotoxicity studies on benzyl alcohol are available.

No mutagenicity of benzyl alcohol was observed *in vitro* in the absence or presence of exogenous metabolic activation systems in assays with bacteria (similar to OECD TG 471, Ames test with *Salmonella typhimurium* strains TA92, TA94, TA 98, TA 100, TA 1535, TA 1537, TA 1538 and with *Escherichia coli* WP2 uvrA) (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017). No induction of micronuclei up to the maximum tested concentration of 1081 µg benzyl alcohol/ml was seen in a micronucleus test according to OECD TG 487 (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017). An *in vitro* mammalian chromosome aberration test with Chinese hamster lung cells without metabolic activation benzyl alcohol was negative (AICIS, 2016; ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017). However, benzyl alcohol induced chromosome aberrations in Chinese hamster ovary cells in presence of S9 mix, but not in the absence of S9 mix (AICIS, 2016; ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017). In a sister chromatid exchange assay in mammalian cells benzyl alcohol led to equivocal results (AICIS, 2016; ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017). The positive result of DNA double-strand breaks after alkaline elution in rat hepatocytes at the highest tested benzyl alcohol concentration (1084 mg/ml) was revised after re-evaluation as false positive (Hartwig & MAK Commission, 2017). In a comet assay with human lymphocytes a positive result was observed at higher benzyl alcohol concentrations of 2710 and 5420 µg/ml, which may also be a false positive result due to a lack of dose-response relationship and information on cytotoxicity (Hartwig & MAK Commission, 2017). In conclusion, benzyl alcohol was not genotoxic and clastogenic effects were observed only at high benzyl alcohol concentrations in *in vitro* studies. (Hartwig & MAK Commission, 2017).

In vivo genotoxicity data on benzyl alcohol is available. Benzyl alcohol was negative in a mouse micronucleus assay and in replicative DNA synthesis assays in rats and mice. A positive result of benzyl alcohol was observed in the wing somatic mutation and recombination test (SMART) in *Drosophila melanogaster* at the highest tested concentration (50 nM), however a negative result was obtained in a sex-linked recessive lethal mutations test (SLRL) in *Drosophila melanogaster* at a similar concentration (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017).

Based on the available *in vitro* and *in vivo* database as well as supportive data from analogous substances (e.g., benzoic acid or benzyl acetate) several expert committees concluded that benzyl alcohol is not causing genotoxic effects in somatic or germ cells (EFSA Panel on Food Additives and Flavourings (FAF) et al., 2019a; Hartwig & MAK Commission, 2017; OECD, 2001).

Carcinogenicity

In a 2-year carcinogenicity study, benzyl alcohol was daily administered by gavage (vehicle: corn oil) in doses of 0, 200 and 400 mg/(kg bw x d) to F344/N rats and 0, 100 and 200 mg/(kg bw x d) to B6C3F1 mice (details see above in section on repeated dose toxicity). The survival of control female mice and high-dose female rats was significantly lower and considered as being caused by gavage errors. During gross necropsy and histopathology, no substance-related effects were observed. In male rats of the high-dose group, a not statistically significant increase in epithelial hyperplasia of the forestomach was seen, which is caused by local irritation of the test substance. The incidence of anterior pituitary neoplasms in female rats and Harderian gland adenomas in male mice showed negative dose-related trends. No increases in tumours incidences were noted in rats or mice (ECHA Dissemination, 2023; EFSA Panel on Food Additives and Flavourings (FAF) et al., 2019a; Hartwig & MAK Commission, 2017; OECD, 2001).

2.5.4 Toxicity to reproduction

Fertility

No studies are available on the reproductive toxicity or fertility of benzyl alcohol.

A concentration-dependent increase in the relative weight of epididymis at 290 mg/m³ and above (12.5 % at 290 mg/m³ and 15.4 % at 1072 mg/m³) was the only statistically significant effect observed in rats exposed "nose-only" to benzyl alcohol concentrations up to 1072 mg/m³, 6h/d, 5d/w for 4 weeks (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017).

In the 2-year carcinogenicity studies of benzyl alcohol in rats and mice, no adverse effects on reproductive organs were observed (Hartwig & MAK Commission, 2017).

Developmental toxicity

In a preliminary developmental toxicity test, 50 pregnant CD-1 mice were administered benzyl alcohol by gavage (vehicle: distilled water) at 0 or 750 mg/(kg bw x d) on GD 7-14. Up to 20 mice showed clear signs of toxicity, which included *"hunched posture, tremors, inactivity, prostration, hypothermia, ataxia, dyspnoea, swollen or cyanotic abdomen, and piloerection"* (OECD, 2001). The maternal body weight was significantly reduced on GD 18 and PND 3 and the body weight gain was significantly reduced from GD 7-18. Of the 50 dams treated, 19 died. Gestational parameters were not affected by exposure to benzyl alcohol. Foetal body weight and body weight gain per litter was significantly reduced on PND 1 and 3. Teratogenic effects were not investigated in the study. The derived LOAELs for maternal toxicity and developmental toxicity were 750 mg/(kg bw x d). Due to the observed effects, a NOAEL could not be established (ECHA Dissemination, 2023; MAK Commission, 2006; OECD, 2001).

In a developmental toxicity study (not according to OECD TG), pregnant CD-1 mice (50 F/group) were exposed daily to benzyl alcohol diluted in corn oil by gavage at 0 or 550 mg/(kg bw x d) on GD 6-15. Clinical signs of languid behaviour, laboured breathing, and brittle coat were observed in one dam that died. Apart from this, there was no evidence of maternal toxicity and gestational parameters were not affected by exposure. There were no treatment-related changes in the foetal body weight per litter or survival. An investigation of teratogenicity did not take place. The NOAEL for developmental toxicity was 550 mg/(kg bw x d) (MAK Commission, 2006; OECD, 2001).

In its 2017 assessment, the MAK Commission cited two additional developmental toxicity studies with benzyl alcohol in rats and rabbits that are not available as full study reports. Twenty-five pregnant Sprague-Dawley rats/group were exposed subcutaneously daily to benzyl alcohol in corn oil at doses of 0, 100, 250 or 500 mg/(kg bw x d) from GD 6-17. Maternal toxicity was evident by decreased body weight as well as reduced body weight gain (NOEL: 250 mg/(kg bw x d). In the offspring, a decrease in foetal body weight was observed in comparison to controls. A NOEL for foetal toxicity of 250 mg/(kg bw x d) was derived. No treatment-related changes in the incidence of external, visceral, or skeletal malformations or variations were noted up to 500 mg/(kg bw x d) (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017).

In a similar study, benzyl alcohol was administered subcutaneously to 23 pregnant New Zealand White Rabbits/group in doses of 0, 100, 250 or 400 mg/(kg bw x d) from GD 6-18. At 400 mg/kg bw x d), maternal toxicity was noticed by decreased body weight and body weight gain, presence of clinical signs (e.g., reduced activity, laboured breathing), and mortalities (7 dams died out of 23). At 250 mg/(kg bw x d), reduced body weight gain and two mortalities were seen. The NOEL for maternal toxicity was 100 mg/(kg bw x d). A reduction in foetal body weights was observed and considered to be due to maternal toxicity which is why a NOEL for foetal toxicity of 250 mg/(kg bw x d) was established. Teratogenicity did not occur up to the highest test dose (Hartwig & MAK Commission, 2017).

2.5.5 Odour perception

The odour of benzyl alcohol is described as characteristic, faint aromatic, and fruity (EFSA Panel on Food Additives and Flavourings (FAF) et al., 2019b; NLM, 2023). An odour threshold of 25 mg/m^3 (5.5 ppm) has been reported for benzyl alcohol (Ad-hoc-AG, 2010; NLM, 2023). Results of a pilot study indicate that the threshold of olfaction may be as low as 1.5 mg benzyl alcohol/m^3(Ad-hoc-AG, 2010).

2.6 Evaluation

2.6.1 Existing regulations and classifications

In its harmonised classification benzyl alcohol is classified for acute toxicity category 4 * (H302 and H332, * = minimum classification) (ECHA C&L Inventory, 2023). In 2020, a proposal for Harmonised Classification and Labelling (CLH) according to the CLP criteria was published, which proposes to classify benzyl alcohol as acute toxicity category 4 (H302), eye irritation category 2, and skin sensitisation category 1B (ECHA, 2020; RAC, 2021).

Existing guide values for benzyl alcohol in air are summarised in Table 13.

The German Ad-hoc Working Group on Indoor Guidelines has evaluated the toxicity of benzyl alcohol. The Guidance value II ("Richtwert II") is based on a subchronic oral toxicity study in rats that observed neurotoxicity at 800 mg benzyl alcohol/(kg bw x d). To derive the lowest adverse effect level for chronic exposure a factor of 2 for considering data gaps, a factor of 2 for extrapolation to chronic exposure, a standard factor of 10 for intraspecies extrapolation, and as well a factor of 10 for interspecies extrapolation and route-to-route extrapolation were applied, resulting in 2 mg benzyl alcohol/(kg bw x d). In addition, the breathing rate of 20 m^3/d, body weight for an adult of 70 kg and an additional factor of two for a possibly higher susceptibility/breathing rate of children were considered to derive a guidance value II of approx. 4 mg/m^3 (2*70/20/2=4). One tenth of this concentration (0.4 mg/m^3) was set as guidance value I ("Richtwert I") (Ad-hoc-AG, 2010).

A NIK (Lowest Concentration of Interest) value of 440 µg/m^3 is reported for benzyl alcohol by the Committee for Health-related Evaluation of Building (AGBB, 2021). This value is based on the Workplace Environmental Exposure Level (WEEL) of 44000 mg/m^3 for benzyl alcohol derived by the American Industrial Hygiene Association (AIHA) (EC, 2013).

In the registration dossier for benzyl alcohol, a DNEL of 5.4 mg/m^3 for the protection of the general population via inhalation route has been derived on the basis of a NOAEC of 1072 mg/m^3 obtained in a subacute inhalation toxicity study in rats. Adjusting for continuous exposure (6 h/24 h) lead to a NOAEC of 268 mg/m^3. The standard default factor of 6 for extrapolation from subacute to chronic exposure was not considered as appropriate. Instead, a factor of 2 was applied because toxicity is not dependent on exposure time indicated by similar toxicity (NOAEL values) after subchronic and chronic oral exposure. Furthermore, a factor of 10 for intraspecies differences and a factor of 2.5 for interspecies differences (no factor for allometric scaling necessary) were applied. With a total extrapolation factor of 50, a DNEL of 5.4 mg/m^3 was derived (ECHA Dissemination, 2023).

In 2017 the MAK Commission updated the MAK value and derived a value of 22 mg/m^3 (5 ppm). Due to the local irritation, the peak limitation is according to category I, the exceedance factor is 2. The MAK value was derived based on a subacute inhalation study in rats (LOAEC: 1072 mg/m^3, NAEC: 300 mg/m^3, corresponding to approx. 67 ppm in vapour form) and applying an assessment factor of 6 for the increase in effects with longer exposure and a factor of

2 for differences between humans and animals. Furthermore, the substance is labelled as skin sensitising ("Sh") and categorised in Pregnancy Group C (prenatal toxic effects are unlikely at the MAK- or the BAT value) (Hartwig & MAK Commission, 2017).

Table 13: Guide values for benzyl alcohol (for explanation, see text)

Guide value Parameter/Organisation	(ECHA Dissemination, 2023)	(AGBB, 2021)	(Hartwig & MAK Commission, 2017)	(Ad-hoc-AG, 2010)
Name	DNEL (chronic, general population)	NIK value, ascribed EU-LCI value[2]	MAK value	Guidance value I and II
Value (mg/m³)	5.4	0.440	22 (5 ppm)	Guidance value I: 0.4 Guidance value II: 4
Organ/critical effect	-	-	Microscopic changes in the respiratory tract	Neurotoxicity
Species	rat	rat	rat	rat
Basis	NOAEC: 1072 mg/m³	-	LOAEC: 1072 mg/m³	LOAEL: 800 mg/(kg bw x d)
Adjusted for cont. exposure	0.25	-	-	-
Extrapolation factors Time LOAEC-NOAEC Interspecies Intraspecies	 2 - 10 2.5	 - - - -	 6 3.5 2 -	 2 2 10 10
Remarks	-	-	-	Further, a breathing rate of 20 m³/d, adult body weight of 70 kg and higher susceptibility/breathing rate of children a factor of 2 was added to derive the guidance value II. For the derivation of guidance value I one tenth the guidance value of II was considered.

[2] Agreed EU-LCI values. December 2023. Available at: https://ec.europa.eu/docsroom/documents/56194, accessed on 02.08.2024

2.6.2 Derivation of an EU-LCI value

The data basis for benzyl alcohol is limited. No reliable inhalation study with benzyl alcohol after subchronic or chronic exposure is available. However, a subacute inhalation toxicity study performed according to OECD TG 412 in rats is available, which is regarded as valid and suitable for deriving an EU-LCI value.

In humans and animals, a fast and almost complete absorption of benzyl alcohol was observed after a single oral dose. Details on benzyl alcohol absorption after inhalation are not available (Hartwig & MAK Commission, 2017). *In vitro* studies with human skin and an *in vivo* study in rhesus monkeys showed that benzyl alcohol permeates skin and determined flux values of 0.1 µg/cm^2 x h and 29-275 µg/cm^2 x h (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017). The absorption of benzyl alcohol through the skin may contribute in a relevant way to the systemic toxicity (Hartwig & MAK Commission, 2017).

The metabolism of benzyl alcohol involves oxidation by alcohol/aldehyde dehydrogenase or other CYP P450 enzyme to benzaldehyde and subsequently to benzoic acid, which is conjugated with glycine and excreted renally as hippuric acid. The glycine conjugation has a limited capacity, therefore exposure to high concentration of benzyl alcohol may result in an excretion of benzoic acid unchanged or as the glucuronic acid conjugate (EFSA Panel on Food Additives and Flavourings (FAF) et al., 2019a). Of resorbed benzyl alcohol is approx. 80 % excreted via urine and 20 % as glucuronic acid conjugate (Hartwig & MAK Commission, 2017).

Case reports describe the acute toxic effects of benzyl alcohol on humans. After applying a paint stripper, a man developed impaired consciousness, metabolic acidosis, and paralytic ileus (Fukuda et al., 2022). In an inhalation study according to OECD TG 403 in rats, a 4-h-LC50 of > 4178 mg/m^3 was determined (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017; OECD, 2001). The acute dermal toxicity of benzyl alcohol is low as shown by a dermal LD50 value of 2000 mg/kg bw in rabbits (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017). In animals, LD50 values of 1000 to 3100 mg/kg bw have been reported after oral administration. Observed symptoms included neurotoxicity (CNS depression, impact on CNS), irritability, and coma (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017; OECD, 2001).

In valid OECD TG studies in rabbits, benzyl alcohol was not skin irritating but led to eye irritation (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017; OECD, 2001). In a LLNA assay in mice, benzyl alcohol showed no skin sensitising potential. Human data from case reports, repeated insult patch tests, and patch tests showed positive responses to benzyl alcohol (ECHA, 2020). Compared to benzyl alcohol's widespread use and large number of exposed people, the observed positive responses are low. Overall, several expert committees consider benzyl alcohol to be not skin sensitising (Hartwig & MAK Commission, 2017; OECD, 2001). However, a proposal for harmonised classification of benzyl alcohol as skin sensitiser, subcategory 1B has been made based on the observed human data (ECHA, 2020; RAC, 2021).

In humans, repeated dermal exposure of a lotion containing 5 % benzyl alcohol on childrens' heads or applying 3 % benzyl alcohol subcutaneously by injection in female adults resulted in local loss of sensitivity and skin irritation without further reported signs of toxicity (Ad-hoc-AG, 2010; Hartwig & MAK Commission, 2017).

Rat exposed up to 1119 mg benzyl alcohol/m^3 for 6 h/d on three consecutive days had discoloured nasal regions at 334 mg/m^3. One animal died after the first exposure and another one was terminated due to moribund signs after the second exposure in the high concentration

group. Observed toxicity signs in both dead animals were disturbance of the locomotor coordination (Hartwig & MAK Commission, 2017).

In a subacute inhalation study in rats (according to OECD TG 412), repeated "nose-only" exposure to benzyl alcohol at concentrations of 0, 41, 102, 290 or 1072 mg/m^3 (ca. 0, 9.2, 22.9, 65.2 or 240.9 ppm) for 6 h/d 5 d/w for a total of 20 exposures resulted in a concentration-dependent increase (12.5 % at 290 mg/m^3 and 15.4 % at 1072 mg/m^3) in the relative weight of the epididymis at 290 mg/m^3 and above. This was the only statistically significant effect reported in the registration dossier in the ECHA's disseminated database and thus a NOAEC of 1072 mg/m^3 was derived (ECHA Dissemination, 2023). In addition, the MAK commission reports on histological findings in the respiratory tract particularly in the lungs at 1072 mg/m^3 (only high concentration group and controls were examined histopathologically). Therefore, the MAK commission derived a LOAEC of 1072 mg/m^3 and estimated a NAEC (no adverse effect concentration) of 300 mg/m^3 (based on LOAEC/3) (Hartwig & MAK Commission, 2017).

Repeated dose studies with longer exposure durations to benzyl alcohol are only available for oral application. In valid subchronic oral studies mice and rats were exposed to up to 800 mg benzyl alcohol/(kg bw x d) by gavage 5d/w for 13 weeks (NTP, 1989). In both species the most sensitive observed effect was a reduction in body weight gain, which resulted in derived NOAELs of 400 mg/(kg bw x d) in rats and 200 mg/(kg bw x d) in mice (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017).

Benzyl alcohol was not genotoxic in *in vitro* in assays with bacteria following OECD test guidelines. *In vitro* studies in mammalian cells showed equivocal results. No genotoxicity effects in somatic or germ cells were observed in a mouse micronucleus assay and in replicative DNA synthesis assays in rats and mice. In addition, the sex-linked recessive lethal mutations test (SLRL) in *Drosophila melanogaster* was also negative, whereas the wing somatic mutation and recombination test (SMART) in *Drosophila melanogaster* led to a positive result at the highest tested concentration (50 nM). Overall, benzyl alcohol was regarded as not genotoxic in somatic or germ cells (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017).

In 2-year carcinogenicity studies performed in mice and rats, benzyl alcohol did not lead to increases in tumours incidences. The derived NOAELs are the highest tested dose and thus 400 mg/(kg bw x d) in rats and 200 mg/(kg bw x d) in mice, respectively (ECHA Dissemination, 2023; EFSA Panel on Food Additives and Flavourings (FAF) et al., 2019a; Hartwig & MAK Commission, 2017; OECD, 2001).

Studies regarding effects of benzyl alcohol on fertility are not available. Benzyl alcohol caused a concentration-dependent increase in the relative weight of epididymis in rats at 290 mg/m^3 and above in the subacute inhalation study with rats mentioned above (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017). In developmental toxicity studies in mice, rats, and rabbits, the only effect observed with exposure to benzyl alcohol was a decrease in foetal body weight at maternally toxic doses. Therefore, NOELs of 550 mg/(kg bw x d) in mice after gavage administration, and NOELs of 250 mg/m^3 in rats and rabbits after subcutaneous application were derived (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017; OECD, 2001).

For derivation of guidance values the German Ad-hoc Working Group on Indoor Guidelines regarded the subacute inhalation study in rats (unpublished study report, cited by ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017) as not suitable because the results of the acute and subacute inhalation studies are considered to be contradictory (no further information provided). The authors of this report have reviewed the data and do not see a contradiction. One acute inhalation study reported a 6-h-LC50 value of 1059 mg/m^3, which differs from the others that have relevant higher LC50 values (approx. 4000 mg/m^3). This study

was only secondarily cited by Hartwig and MAK commission (2017) and thus its reliability cannot be assessed. The subchronic oral toxicity study in rats (NTP, 1989) has some shortcomings: several animals died due to handling errors during gavage, severe toxicity was observed as evidenced by neurotoxic effects in the highest dose group and the authors of this assessment regard the highest dose as LOAEL. Using this study and the corresponding LOAEL of 800 mg/(kg bw x d) to derive an EU-LCI value, the LOAEL in rats is converted to a LOAEC in humans (24 h) of 695.65 mg/m^3 and an overall assessment factor of 150 (3 for LOAEL-NOAEL extrapolation, 2 for time duration, 2.5 for interspecies extrapolation and 10 for intraspecies extrapolation) is applied, resulting in approx. 4600 µg/m^3 (695.65 mg/m^3 : 150 = 4.638 mg/m^3).

Due to the shortcomings of the subchronic oral toxicity study (NTP, 1989) and to be the most conservative, the subacute inhalation toxicity study (unpublished study report, cited by ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017) in rats summarised above is considered an appropriate key study for deriving an EU-LCI value for benzyl alcohol. The authors of this assessment agree with the derived LOAEC of 1072 mg/m^3 (240.9 ppm at 23 °C) from this study derived by the MAK commission and used the LOAEC as POD for the calculation. No NOAEC could be derived as only the high concentration group and controls were examined histopathologically.

The following assessment factors are used (EC, 2013; ECHA, 2018):

- LOAEC-NOAEC extrapolation: 3
- Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6
- Adjusted study length factor: 6
- Interspecies extrapolation: 2.5 (allometric scaling not performed since route of exposure is inhalation)
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 2520 leading to a value of 1072 mg/m^3 : 2520 = 0.425 mg/m^3 for benzyl alcohol (rounded to 450 µg/m^3).

An EU-LCI value of 450 µg/m^3 is proposed for benzyl alcohol.

The proposed EU-LCI value is below the reported odour threshold of 25 mg/m^3 (5.5 ppm) (Ad-hoc-AG, 2010; NLM, 2023).

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B Appendix

B.1 Data collection and fact sheet for benzyl alcohol

Table 14: Data collection sheet for benzyl alcohol

Compound	**Benzyl alcohol**	**Data collection sheet**		
Nº CAS (100-51-6) 1 ppm = 4.45 mg/m³ at 23 °C	**EU-Classification:** - **CLP, harmonised classification:** Acute Tox. 4 *(H302, H332, *= minimum classification)			
Organisation name	**REACH registrant**	**AgBB**	**MAK commission**	**German Ad-hoc Working Group on Indoor Guidelines**
Risk value name	DNEL	NIK ('Lowest Concentration of Interest')	MAK value	Guidance value I and II ("Richtwert I und II")
Risk value (mg/m³)	5.4	0.440	22	Guidance value I: 0.4 Guidance value II: 4
Reference period	Chronic (general population)	Chronic (general population)	Chronic (workers)	Chronic (general population)
Risk value (mg/m³) Short term (15 min)	27	-	44	-
Year	2023	2021	2006, 2016	2010
Key study	OECD TG 413 (Subacute Inhalation Toxicity: 28-Day)		OECD TG 413 (Subacute Inhalation Toxicity: 28-Day)	Subchronic oral toxicity study
Study type	28-d inhalation study		28-d inhalation study	Subchronic oral toxicity study
Species	Rat, Sprague-Dawley		Rat, Sprague-Dawley	Rat, F344/N
Duration of exposure in key study	28 days		28 days	90 days
Critical effect	No effect observed		Microscopic changes in the respiratory tract and lungs	Neurotoxicity
Critical dose value	NOAEC: 1072 mg/m³		LOAEC: 1072 mg/m³	LOAEL: 800 mg/(kg bw x d)

Compound	Benzyl alcohol	Data collection sheet		
Adjusted critical dose	Adjustment for continuous exposure (6/24)			
Single assessment factors	UF_{SA} 2, UF_H 10, UF_A 2.5 *"The NOAEL in oral sub-chronic and chronic studies are similar. Consequently, the factor of 2 used in this derivation can be considered conservative."*		UF_L 3, UF_{SA} 6, UF_H 2	UF_D 2, UF_S 2, UF_H 10, UF_A 10, $UF_{children}$ 2 RW II to RW I, additional: 10
Other effects				
Remarks				

AgBB = Committee for Health-related Evaluation of Building Products

UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_{SA} Used subacute study; UF_D data deficiencies.

Table 15: Fact sheet for benzyl alcohol

Compound	Benzyl alcohol C7H8O		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	450
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2024
General information			
CLP-Index No.	4	INDEX	603-057-00-5
EC-No.	5	EINECS	202-859-9
CAS-No.	6	Chemical Abstract Service number	100-51-6
Harmonised CLP classification	7	Human health risk related classification	Acute Tox. 4 *(H302, H332, *= minimum classification)
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	108.14 1 ppm = 4.45 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	OECD TG 413 (Subacute Inhalation Toxicity: 28-Day)
Read across compound	10	Where applicable	-
Species	11	Rat, human, etc.	Rat, Sprague-Dawley
Route / type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic, etc.	Subacute (28 d)
Exposure duration	14	h/d, d/w	6 h/d, 5 d/week
Critical endpoint	15	Effect (s), site of	Microscopic changes in the respiratory tract and lungs
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	LOAEC
POD value	17	[mg/m³] or ppm or [mg/kg_{BW}×d]	1072 mg/m³
Assessment factors (AF)			
Adjustment for exposure duration	19	Study exposure h/d, d/w	5.6
Study length	20	sa→sc→c	6
Route-to-route extrapolation factor	21	-	-

Compound	Benzyl alcohol C7H8O		Fact sheet
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	3
	22b	Severity of effect (R8 6d)	1
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	1
	23b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		
Other adjustment factors Quality of database	26	Quality of database	1
Results			
Summary of assessment factors	27	Total Assessment Factor	2520
POD/TAF	28	Calculated value [µg/m³ and ppb]	425 µg/m³ (96 ppb)
Molar adjustment factor	29		
Rounded value	30	[µg/m³]	450 µg/m³
Additional comments	31		
Rationale selection	32		

Rationale for critical effects

The data basis for benzyl alcohol is limited. No reliable inhalation study with benzyl alcohol after subchronic or chronic exposure is available.

Based on experience in humans and animal studies, the critical effects of benzyl alcohol are irritation of eyes, mucous membranes, and respiratory airways as well as impairment of the central nervous system.

A case report described that a man after applying a paint stripper developed impaired consciousness, metabolic acidosis, and paralytic ileus (Fukuda et al., 2022). A 4-h LC50 of > 4178 mg/m^3 was determined in an inhalation study (according to OECD TG 403) in rats (ECHA Dissemination, 2023; Hartwig and MAK Commission, 2017; OECD, 2001). The acute dermal toxicity of benzyl alcohol is low, as indicated by a dermal LD50 of 2000 mg/kg bw (ECHA Dissemination, 2023; Hartwig and MAK Commission, 2017). In animals, the LD50 values after oral administration are 1000-3100 mg/kg bw. Observed symptoms included neurotoxicity (CNS depression, impact on CNS), irritability, and coma (ECHA Dissemination, 2023; Hartwig and MAK Commission, 2017; OECD, 2001).

Benzyl alcohol is not skin irritating; however, it is eye irritating in rabbits. No skin sensitising potential was observed in mice in a LLNA assay. Human data from case reports, repeated insult patch tests, and patch tests showed positive responses to benzyl alcohol (ECHA, 2020). However,

the observed positive reactions are small in comparison with the widespread use of benzyl alcohol and the large number of people exposed. Overall, several expert committees do not consider benzyl alcohol to be a skin sensitiser (Hartwig and MAK Commission, 2017; OECD, 2001).

In humans, repeated dermal exposure of a lotion containing 5 % benzyl alcohol on the head of children or applying 3 % benzyl alcohol subcutaneously by injection in female adults resulted in local loss of sensitivity and skin irritation with no further reported signs of toxicity (Ad-hoc-AG, 2010; Hartwig and MAK Commission, 2017).

In a subacute inhalation study in rats (according to OECD TG 412, unpublished study report), repeated "nose-only" exposure to benzyl alcohol at concentrations of 0, 41, 102, 290 or 1072 mg/m^3 (ca. 0, 9.2, 22.9, 65.2 or 240.9 ppm) for 6 h/d 5 d/w for a total of 20 exposures resulted in a concentration-dependent increase (12.5 % at 290 mg/m^3 and 15.4 % at 1072 mg/m^3) in the relative weight of the epididymis at 290 mg/m^3 and above. This was the only statistically significant effect reported in the registration dossier on the ECHA's disseminated database and thus a NOAEC of 1072 mg/m^3 was derived. In addition, the MAK commission reported on histological findings in the respiratory tract particularly in the lungs at 1072 mg/m^3 (only high concentration group and controls were examined histopathologically). Therefore, the MAK commission derived a LOAEC of 1072 mg/m^3 and estimated a NAEC (no adverse effect concentration) of 300 mg/m^3 (based on LOAEC/3) (Hartwig and MAK Commission, 2017).

Repeated dose studies with longer exposure durations to benzyl alcohol are only available for oral application. In valid subchronic oral studies mice and rats were exposed to up to 800 mg benzyl alcohol/(kg bw x d) by gavage 5d/w for 13 weeks (NTP, 1989). In both species the most sensitive observed effect was a reduction in body weight gain, which resulted in derived NOAELs of 400 mg/(kg bw x d) in rats and 200 mg/(kg bw x d) in mice (ECHA Dissemination, 2023; Hartwig and MAK Commission, 2017). These studies have some shortcomings: several animals died due to handling errors during gavage and severe toxicity was observed as evidenced by neurotoxic effects in the highest dose group.

Benzyl alcohol was negative in *in vitro* assays with bacteria but showed equivocal results in *in vitro* studies in mammalian cells. Based on *in vivo* studies in mice, rats and *Drosophila melanogaster* benzyl alcohol was not considered to be genotoxic in somatic or germ cells.

In 2-year carcinogenicity studies in mice and rats, benzyl alcohol was not carcinogenic.

Studies regarding effects of benzyl alcohol on fertility are not available. The concentration-dependent increase of relative epididymis weight in rats after subacute exposure is already described above. In developmental toxicity studies in mice, rats and rabbits, benzyl alcohol led to a decrease in foetal body weight at maternally toxic doses (NOEL of 550 mg/(kg bw x d) in mice and 250 mg/(kg bw x d) in rats and rabbits) (ECHA Dissemination, 2023; Hartwig & MAK Commission, 2017; OECD, 2001).

Rationale for starting point

The subacute inhalation toxicity study in rats is regarded as valid and suitable for deriving an EU-LCI value. In this study, a concentration-dependent increase in relative epididymis weight at 290 mg/m^3 and above and histological findings in the respiratory tract particularly in the lungs at 1072 mg/m^3 were observed (LOAEC: 1072 mg/m^3). As during the histopathological examination only the high concentration group and controls were examined, a NOAEC could not be derived. Therefore, the LOAEC of 1072 mg/m^3 was used as POD for the calculation.

Rationale for assessment factors

The following assessment factors are used (EC, 2013; ECHA, 2018):

- LOAEC-NOAEC extrapolation: 3
- Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6
- Adjusted study length factor: 6
- Interspecies extrapolation: 2.5 (allometric scaling not performed since route of exposure is inhalation)
- Intraspecies extrapolation: 10

Total assessment factor: 2520. This leads to a concentration of 1072 mg/m^3 : 2520 = 0.425 mg/m^3 for benzyl alcohol (rounded to 450 µg/m^3).

An EU-LCI value of 450 µg/m^3 is proposed for benzyl alcohol.

An odour threshold of 25 mg/m^3 is available for benzyl alcohol, which is higher than the proposed LCI value (Ad-hoc-AG, 2010; NLM, 2023).

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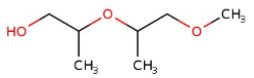
3 Toxicological evaluation of dipropylene glycol monomethylether as basis for the derivation of an EU-LCI value

3.1 Substance identification

Dipropylene glycol monomethylether (DPGME) belongs to the group of glycol ethers. It is a multi-constituent substance because the commercial product of DPGME consists of four isomers: 1-(2-methoxy-1-methylethoxy)propan-2-ol (CAS-No.: 20324-32-7), 2-(2-methoxy-1-methylethoxy)propan-1-ol (CAS-No.: 55956-21-3), 1-(2-methoxypropoxy)propan-2-ol (CAS-No.: 13429-07-7), and 2-(2-methoxypropoxy)propan-1-ol (CAS-No.: 13588-28-8) (ECHA Dissemination, 2023). Of the structural isomers the respective fractions are 40-50 % 1-(2-methoxypropoxy)propan-2-ol, 40 -45 % 1-(2-methoxy-1-methylethoxy)propan-2-ol, 2-5 % 2-(2-methoxypropoxy)propan-1-ol, and 3-5 % 2-(2-methoxy-1-methylethoxy)propan-1-ol (BUA, 1996; OECD, 2001).

All available data refer to the technical mixture. The substance identification of dipropylene glycol monomethylether (DPGME) is shown in Table 16.

Table 16: Substance identification of DPGME (ECHA Dissemination, 2023)

CAS-No. EU-No. CLP-Index-No.	Systematic name, common name	Sum formula	Structural formula
34590-94-8 252-104-2	dipropylene glycol monomethylether, DPGME, 2-[(1-methoxypropan-2-yl)-oxy]propan-1-ol, (2-methoxymethylethoxy)propanol, methyl diproxitol, DOWANOL DPM, Acrosolv DPM	$C_7H_{16}O_3$	 representative structure

3.2 Substance properties and uses

The physicochemical properties of DPGME are shown in Table 17. DPGME is miscible with water and numerous organic solvents (BUA, 1996; SCOEL, 1993). DPGME is used as a solvent for organic compounds, including in manufacturing water-based surface coatings (BUA, 1996; OECD, 2001; SCOEL, 1993). In water-based paints and inks, the substance acts as a coalescing agent (OECD, 2001). In addition, DPGME is also used as hydraulic fluids as well as in substances used in the oil and drilling industry (ACGIH, 2001; OECD, 2001). Due to its widespread use as an ingredient, DPGME can be found in industrial products (e.g., stripper/degrease, solvent in paints, inks, cleaning agents, cosmetic agents, detergents, disinfectants) and commercial and household cleaning products (e.g., cleaners for glass, surface, paintbrush, carpet and all purposes, industrial degreasers, aluminium brighteners, and rust removers)(OECD, 2001). Thus, multiple indoor exposures to DPGME are possible.

Table 17: Physicochemical properties of DPGME (ECHA Dissemination, 2023; SCOEL, 1993)

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa) (at 20 °C)	Conversion 1 ppm = x mg/m³ (23 °C)	log pow	Solubility in water (g/L)
148.2	-83.15	189.6 at 1013.25 hPa	0.371	6.10	0.004 at 25 °C	1 at 25 °C and pH 7

3.3 Exposure

3.3.1 Indoor air

A limited database is available regarding the occurrence of DPGME in indoor air (see Table 18).

An evaluation analysing 2871 measurements provided limited information on the details of the evaluation. The reported median is below the detection limit of 1 µg/m^3, but the 90th percentile is 7.0 µg/m^3, indicating that either a single value or a few values with high DPGME concentrations were measured (AGÖF, 2013).

DPGME was measured in indoor air in schools in Schleswig-Holstein, Germany. The database consisted of 285 measurements, of which 3 % were above the detection limit of 2 µg/m^3. The mean was below the detection limit, but at least one measurement showed a high DPGME concentration, as the maximum was 120 µg/m^3 (Ad-hoc-AG, 2013; Ostendorp et al., 2009).

In 1278 measurements in indoor air DPGME was measured and the calculated median was low (0.5 µg/m^3). The maximum of 760 µg/m^3 and 95th percentile of 17.1 µg/m^3 indicate that a few measurements detected a high DPGME concentration in indoor air (UBA, 2008).

Table 18: Data on the occurrence of DPGME in indoor air from homes, schools, children day care centres and offices

Indoor	N	LoD (µg/m³)	N > LoD	Median (µg/m³)	P95 (µg/m³)	Maximum (µg/m³)	Source
Indoor air (not further specified), Germany, 2006-2012	2871	not reported	not reported	<1	7.0 *	not reported	(AGÖF, 2013)
Indoor air in schools, Germany, 1985-2009	285	2 **	3 %	<2	<2	120	(Ad-hoc-AG, 2013; Ostendorp et al., 2009)
Indoor air, Germany, 2002-2006	1278	not reported	434	0.5	17.1	760	(UBA, 2008)

* given as P90 value

** determined as toluene equivalent

3.3.2 Other sources

There are no substance-specific data available.

3.4 Toxicokinetics

Male F344 rats exposed to a single oral dose of 1289 mg/kg bw of ^{14}C-labelled DPGME excreted most of the radioactivity in the urine (60 %), 27 % in the exhaled air and less than 3 % in the faeces within 48 h after dosing. In the urine DPGME, glucuronides and sulphates of DPGME, propylene glycol, dipropylene glycol, and propylene glycol methyl ether (PGME) were identified (BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; OECD, 2001).

In general, the main metabolic pathway of DPGME is conjugation with glucuronic acid and sulphate as well as hydrolysis of the methoxy group to form dipropylene glycol. A minor metabolic pathway of DPGME is the hydrolysis of the dipropylene residue of DPGME, which leads to PGME and propylene glycol. Microsomal O-demethylation is the significant pathway of metabolism of DPGME. In comparison with its degradation products, studies showed that DPGME is equal or less toxic than propylene glycol, dipropylene glycol and PGME (OECD, 2001).

An *in vitro* dermal absorption study (according to OECD TG 428) used human skin and applied 30 µl DPGME/cm^2 (undiluted, radioactive labelled) under occlusive conditions for 10 and 60 minutes and determined in the receptor fluid and skin 71.7 µg and 146.2 µg, respectively. The calculated absorption rate was 654.6 µg/cm^2 x h for 10 min exposure and 228.5 µg/cm^2 x h for 60 min exposure (ECHA Dissemination, 2023).

Furthermore, several expert committees have concluded that dermal absorption of DPGME is expected to contribute in a relevant way to systemic toxicity (ACGIH, 2001; OECD, 2001; SCOEL, 1993).

3.5 Health effects

3.5.1 Acute toxicity, sensory irritation, and local effects

The acute toxicity of DPGME is low via the oral, inhalation and dermal route (OECD, 2001).

No symptoms nor signs of irritation were reported by workers painting with water-based paints containing DPGME at levels of 5 - 7 ppm DPGME (30 - 40 mg/m^3 [3]) in indoor air (BUA, 1996). In an inhalation study DPGME concentrations of 100 ppm could be *"voluntarily tolerated without complaint"* by volunteers, while 300 ppm were identified to be unpleasant (ACGIH, 2001; BUA, 1996; ECETOC, 2005; Henschler & MAK Commission, 1987; OECD, 2001). Another study reported that a DPGME concentration of 35 ppm caused slight irritation to the nose/upper respiratory tract, and above 75 ppm irritation to the respiratory tract, eyes and throat was observed, but was still tolerable (BUA, 1996; Henschler & MAK Commission, 1987; OECD, 2001).

In case reports where humans drank a liquid containing DPGME exclusively or also other substances (e.g., reed diffusor liquid) the following symptoms occurred: hypersalivation, hypoxia, stridor, bronchospasm, vomiting, drowsiness and seizures (Langbroek et al., 2022; Panchal et al., 2016). After ingestion of a large dose of DPGME exclusively, lactic acidosis with an elevated osmolal gap was observed (Langbroek et al., 2022).

In an inhalation risk test from 1979 (similar to OECD TG 403), Sprague-Dawley rats (12 per sex/group) were exposed whole-body to 275 ppm DPGME as vapour (1667 mg/m^3) for 7 hours. The observed clinical signs were clear nasal discharge, wiping of snout, *"scrubby fur"*, mucosa

[3] Please note that deviations in the reported concentration in ppm and mg/m^3 are possible depending on the conversion factor used by the expert committee or author(s).

irritation, and dyspnoea. There were no mortalities and therefore an LC0 of more than 275 ppm was derived (ECHA Dissemination, 2023).

No mortality was observed in two older acute inhalation studies in which female CFE albino and male white rats exposed for up to 7 or 8 h to vapour concentrations of DPGME up to the maximum attainable concentration at room temperature of 500 or 552.6 ppm (corresponding to 3100 and 3404.47 mg/m^3, respectively). Mild narcosis was seen in male rats, the animals recovered quickly (BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987).

The acute dermal toxicity of DPGME was investigated in rabbits and rats under occlusive conditions for 4 h (rats) or 24 h (rabbits) resulting in transient narcosis with a quick recovery. LD50 values of 9510 - > 19020 mg/kg bw in rabbits and 19020 mg/kg bw in rats were determined (ACGIH, 2001; ECETOC, 2005; ECHA Dissemination, 2023; OECD, 2001).

Acute oral LD50 values greater than 5000 mg/kg bw (ranging from 5000 - 9100 mg/kg bw) were determined in rats. Observed signs of toxicity included CNS depression (e.g., unsteady gait, narcosis). In dogs, respiratory paralysis was seen after single administration of DPGME and an oral LD50 value of 7125 - 7500 mg/kg bw was derived (ACGIH, 2001; BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; OECD, 2001).

Irritation

In humans, DPGME was not found to be a skin irritant in patch tests (ACGIH, 2001; ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; OECD, 2001).

Studies on skin irritation with undiluted DPGME in rabbits showed under open or occlusive conditions no signs of skin irritation (ACGIH, 2001; ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; OECD, 2001).

The ocular application of a 20 % DPGME solution (0.04 ml, vehicle: water) to one eye of volunteers resulted in slight burning sensation for 30 - 40 sec, lacrimation, eyelid spasm for 1 min, injection of conjunctival vessels and slightly increased intraocular pressure during the first hour after application (BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023). The observed effects were rapidly reversible (ECHA Dissemination, 2023; Henschler & MAK Commission, 1987).

In eye irritation studies undiluted DPGME caused slight irritation in rabbits' eye (ACGIH, 2001; ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; OECD, 2001).

Sensitisation

In patch tests on a total of 250 volunteers, no skin sensitising potential of DPGME was observed (ACGIH, 2001; BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; OECD, 2001).

Animal data on skin sensitising potential of DPGME is not available (ECETOC, 2005).

3.5.2 Repeated dose toxicity

Human data

In three out of seven lithographers, who were exposed to various glycol ether vapours (e.g., DPGME, ethylene glycol monoethyl ether) and organic solvents (e.g., methoxyethanol, substituted benzenes, n-propanol) and several aliphatic, aromatic, and halogenated hydrocarbons, normal peripheral blood parameters but bone marrow lesions (stromal injury) were observed. Due to the mixed exposure to a variety of substances, the observed effects

cannot be causally related to DPGME exposure (ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; OECD, 2001).

Animal data

In F344 rats and B6C3F1 mice exposed to DPGME at concentrations of 0, 50, 140 or 330 ppm (0, 305, 854, 2013 mg/m^3) by whole-body, 6 h/d, 5 d/week for two weeks (total of nine exposures), slight increases in liver weights were observed. The authors of the study considered these effects to be adaptive, as no concomitant histopathological changes were observed, and therefore derived a NO(A)EC of 330 ppm (BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; Landry & Yano, 1984).

In a subchronic inhalation study (similar to OECD TG 413) groups of F344 rats and New Zealand White rabbits (7/sex/group) were exposed to DPGME by whole body inhalation at concentrations of 0, 15, 50, or 200 ppm (0, 91.5, 305 or 1220 mg/m^3), 6 h/d, 5 d/week for 13 weeks. No toxicologically significant changes in clinical chemistry, haematology, cell morphology, gross or microscopic lesions were observed for any of the treated groups. Therefore, a NO(A)EC of 200 ppm in rats and rabbits was derived (ACGIH, 2001; BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; Landry & Yano, 1984; SCOEL, 1993).

In inhalation studies, rats, rabbits, guinea pigs and monkeys were exposed whole-body to saturated DPGME concentrations of 300 - 400 ppm (1830 - 2440 mg/m^3), 7 h/d, 5 d/week for 26 - 31 weeks. In rats, slight form of narcosis was observed, which was transient. In guinea pigs, rabbits and monkeys, changes in liver histology (vacuoles and granulation of cytoplasm) were found (ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; OECD, 2001).

In a subacute dermal toxicity study male Wistar rats were exposed daily to 0, 100 or 1000 mg DPGME/(kg bw x d) under open or occluded conditions for 4 h/d, 5 d /week for 4 weeks. Examination of body weights, food consumption, haematology, clinical chemistry, organ weights, gross pathology, and histopathology determined no statistically significant changes. Therefore, a NOAEL of > 1000 mg/(kg bw x d) was derived (BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; OECD, 2001).

DPGME was applied to male rabbits daily under occlusive conditions in doses of 1.0, 3.0, 5.0 or 10.0 ml DPGME/kg (950 - 9500 mg/(kg bw x d) for 5 d/week for 13 weeks. At 5 ml/kg and above, narcosis and deaths due to the effects of narcosis occurred. Microscopic changes were observed in the kidneys (granular and hydrophic changes) of the high dose animals. A NOEL of 2850 mg/(kg bw x d) and a LOEL of 4750 mg/(kg bw x d) were derived (BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; OECD, 2001).

3.5.3 Genotoxicity and carcinogenicity

Genotoxicity

DPGME was not mutagenic in *in vitro* bacterial mutation assays (Ames test) with and without exogenous metabolic activation system (S9 mix) in tested strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, TA1538) and *E. coli* (WP2uvrA) (BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; OECD, 2001; SCOEL, 1993). The substance induced no chromosomal aberrations in mammalian cells (Chinese Hamster Ovary cells) or unscheduled DNA synthesis in rat hepatocytes in the absence or presence of S9 mix (BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; OECD, 2001; SCOEL, 1993).

In vivo genetic toxicity data for DPGME are not available.

Read-across: No increase in the frequency of micronuclei in bone marrow polychromatic erythrocytes was observed *in vivo* with propylene glycol methyl ether (PGME), a structurally related glycol ether, when mice were administered doses up to 6000 mg/kg bw (OECD, 2001).

Carcinogenicity

Carcinogenicity studies with DPGME are not available.

Read across: No evidence of carcinogenicity was observed in a two-year carcinogenicity study (according to OECD TG 453) in which F344 rats or B6C3F1 mice (50 M + 50 F/group) were exposed to PGME by inhalation at the highest concentration tested (3000 ppm) (ECHA Dissemination, 2023; OECD, 2001).

3.5.4 Toxicity to reproduction

Fertility

No studies are available on the reproductive toxicity or fertility of DPGME.

Read-across:

A reproductive toxicity study is available for PGME, structurally related propylene glycol ether. The following study was also described in a previous project funded by the German Environment Agency (Voss et al., 2021).

A two-generation reproductive toxicity study (according to OECD TG 416 from 1997) was performed with propylene glycol methyl ether (PGME) (98.1 % 1-methoxy-2-hydroxypropane or propylene glycol methyl ether (alpha isomer, CAS No. 107-98-2) and 1.9 % 2-methoxy-1-hydroxypropane or propylene glycol methyl ether (beta isomer)). Sprague-Dawley rats (30 M + 30 F/group) were exposed whole-body to 0, 300, 1000 or 3000 ppm PGME (0, 1110, 3710, 11170 mg/m^3) via inhalation, for 6 h/d, 5 d/week prior to mating and 6 h/d, 7 d/week during mating, gestation and lactation for two generations.

Inhalation exposure of adult male and female rats to 1000 (females only) and 3000 (males and females) ppm PGME resulted in dose-related parental effects. Toxicity in P1 and P2 males and females at 3000 ppm PGME was evidenced by an increased incidence of sedation for several weeks early in the exposure regimen and significant decreases in body weights. Reduced body weights in the P1 and P2 high concentration females generally persisted throughout the pre-breeding, gestation, and lactation phases of the study. Additional effects observed in adult P1 and P2 females exposed to 3000 ppm PGME included lengthened oestrous cycles, decreased fertility, decreased ovarian weights and an increased incidence of histological ovarian atrophy. The effects on fertility, oestrous cyclicity, and ovarian weight/histology appeared to be interrelated and related to the significant decreases in weights and general toxicity/nutritional stress at 3000 ppm PGME in females throughout the test period. No treatment-related differences in sperm count or motility were observed among P1 or P2 adult males. Neonatal effects observed at 3000 ppm PGME consisted of decreased pup body weights, reduced pup survival and litter size, increased time to vaginal opening or preputial separation, and histopathological observations in the liver and thymus of weanling rats. These neonatal effects were considered secondary to maternal toxicity. In the 1000 ppm PGME group, mild parental toxicity was evidenced by slightly decreased pre-mating body weights among P1 and P2 females but was not accompanied by any statistically significant effects on parental reproduction or neonatal survival, growth, or development. There were no treatment-related parental or neonatal effects related to exposure of rats to 300 ppm PGME. In conclusion, the no-observed-

effect-level (NOEC) for fertility and reproductive effects in this two-generation inhalation reproduction study was 1000 ppm (3710 mg/m^3) PGME. Mild parental toxicity was noted at this concentration (ECHA Dissemination, 2023; OECD, 2001).

Developmental toxicity

In a developmental toxicity study (equivalent or similar to OECD Guideline 414), pregnant F344 rats (32 - 37 F/group) were exposed 6 h/d by inhalation to 0, 50, 150, and 300 ppm DPGME on GD 6 - 15. No maternal toxicity, treatment-related effects on pups or changes in external, visceral or skeletal malformations were observed. A NOAEC of 300 ppm (49 mg/m^3) was derived for maternal toxicity and for developmental toxicity (BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; OECD, 2001; SCOEL, 1993).

In a similar study, rabbits (16 F/group) were continuously exposed to 0, 50, 150, and 300 ppm DPGME from GD 7-19. Neither maternal toxicity, embryo-/fetotoxicity nor teratogenicity was observed. Therefore, A NOAEC of 300 ppm (49 mg/m^3) was derived for maternal toxicity and for developmental toxicity (BUA, 1996; ECETOC, 2005; OECD, 2001; SCOEL, 1993).

3.5.5 Odour perception

DPGME's odour is reported as mild, pleasant, ethereal odour (ACGIH, 2001; ECETOC, 2005).

In the literature, an odour threshold of 35 ppm (210-216 mg/m^3) is reported (ECETOC, 2005; SCOEL, 1993).

3.6 Evaluation

3.6.1 Existing regulations and classifications

There is no harmonised classification for DPGME (ECHA C&L Inventory, 2023).

Existing guide values for DPGME in air are summarised in Table 19.

A NIK (Lowest Concentration of Interest) value of 3100 µg/m^3 is reported for DPGME by the Committee for Health-related Evaluation of Building Products (AgBB). This value is based on the European occupational exposure limit for DPGME (EC, 2013).

In its assessment to derive an indicative occupational exposure limit value (IOELV) for DPGME, SCOEL used the subchronic inhalation study in rats as basis and applied an assessment factor of five for lacking human data. Considering the preferred value approach an IOELV of 308 mg/m^3 (50 ppm) was derived (SCOEL, 1993).

In the registration dossier for DPGME, a DNEL of 308 mg/m^3 (50 ppm) for workers was given, which is based on the IOELV established by SCOEL. In addition, for the protection of the general population via inhalation route a DNEL of 37.2 mg/m^3 has been reported. The dose descriptor used was the long-term worker DNEL for the inhalation route, corrected for differences in exposure duration between workers and consumers (24 h/d, 7 d/week) and intraspecies differences (ECHA Dissemination, 2023).

In 2000, the MAK Commission updated the MAK value and derived a value of 310 mg/m^3 (50 ppm). A short-term value was not derived. The MAK value was derived on the basis of nasal irritation at 35 ppm and eye and upper respiratory tract irritation at 75 ppm and above observed in humans (Greim & MAK Commission, 2000).

The German Ad-hoc Working Group on Indoor Guidelines has evaluated the toxicity of DPGME. The Guidance value I ("Richtwert I") is based on a subchronic inhalation toxicity study in rats

that observed no effects in the highest concentration group at 200 ppm (1240 mg/m³) DPGME. To derive the lowest adverse effect level for chronic exposure a factor of 5.6 for considering the adjusted exposure duration, a factor of 2 for extrapolation to chronic exposure, a factor of 2.5 for interspecies extrapolation, a standard factor of 10 for intraspecies extrapolation, and as well a factor of 2 for sensitive population (e.g., children) were used, resulting in 2.2 mg DPGME/m³. The guidance value II was obtained by applying a factor of 3 for NOAEC to LOAEC extrapolation and the calculated value was rounded to approx. 7 mg/m³ (Ad-hoc-AG, 2013).

Table 19: Guide values for DPGME (for explanation, see text)

Guide value Parameter/Organisation	(AGBB, 2021)	(SCOEL, 1993)	(ECHA Dissemination, 2023)	(ECHA Dissemination, 2023)	(Greim & MAK Commission, 2000)	(Ad-hoc-AG, 2013)
Name	NIK value, ascribed EU-LCI value[4]	Indicative occupa-tional exposure limit value	DNEL (chronic, workers)	DNEL (chronic, general population)	MAK value	Guidance value I and II
Value (mg/m³)	3.1	308 (50 ppm)	308	37.2	310 (50 ppm)	Guidance value I: 2 Guidance value II: 7
Organ/ critical effect	-	No effects observed	No effects observed	-	Irritation in upper respirator y system (nose, eyes, throat)	No effects observed
Species	rat	rat	rat	rat	humans	rat
Basis	-	NOAEC: 1232 mg/m³ (200 ppm)	NOAEC: 1232 mg/m³ (200 ppm)	DNEL (chronic, workers)	Odour threshold, slight nasal irritation at 35 ppm and eye and throat irritation at 75 ppm	NOAEC: 1240 mg/m³ (200 ppm)
Adjusted for cont. exposure	-	-	-	4.2	-	5.6
Extrapolation factors		*				
Time	-	-	-	-	-	2
LOAEC-NOAEC	-	-	-	-	-	-
Interspecies	-	-	5	-	-	2.5

[4] Agreed EU-LCI values. December 2023. Available at: https://ec.europa.eu/docsroom/documents/56194, accessed on 02.08.2024

Guide value Parameter/Organisation	(AGBB, 2021)	(SCOEL, 1993)	(ECHA Dissemination, 2023)	(ECHA Dissemination, 2023)	(Greim & MAK Commission, 2000)	(Ad-hoc-AG, 2013)
Intraspecies	-	-	-	2	-	10, 2 (sensitive population)
Remarks	-	The IOELV was derived after taking into account the preferred value approach and the mild effect seen in the studies	The guide value corresponds to the derived occupational exposure limit value by SCOEL and the German MAK commission.	The used dose descriptor was the worker-DNEL long-term via inhalation which was corrected for differences in duration of exposure between worker (8 h per day, 5 days a week) and consumer (24 h per day, 7 days per week) and intraspecies difference (5 for workers and in addition a factor of 2 for consumers).	-	Further due to a higher susceptibility of children a factor of 2 was added. For the derivation of guidance value II, a factor of 3 (NOAEC-> LOAEC) was applied.

* A factor of 5 is applied for absence of human data.

3.6.2 Derivation of an EU-LCI value

The data basis for DPGME is limited. Additional data are available from studies with structurally related propylene glycol ethers, e.g., PGME.

After a single oral dose of radioactive labelled DPGME rats excreted 60 % of radioactivity in the urine, 27 % in exhaled air and <3 % in faeces within 48 h after dosing. DPGME is metabolised via microsomal O-demethylation and metabolites are formed by conjugation with glucuronic acid and sulphate as well as hydrolysis of the methoxy group to form dipropylene glycol. Of minor significance is the metabolism via hydrolysis of the dipropylene residue of DPGME, which leads to PGME and propylene glycol. In comparison with its degradation products, studies showed that DPGME is equal or less toxic than propylene glycol, dipropylene glycol and PGME (OECD, 2001).

An *in vitro* dermal absorption study (according to OECD TG 428) with human skin showed that DPGME can permeate the skin and an absorption rate of 228.5 µg/cm^2 x h for 60 min exposure was measured (ECHA Dissemination, 2023). The absorption of DPGME through the skin may contribute in a relevant way to the systemic toxicity (ACGIH, 2001; OECD, 2001; SCOEL, 1993).

Workers painting with water-based paints containing DPGME at levels of 5 - 7 ppm DPGME (30 - 40 mg/m^3) in indoor air reported no symptoms nor signs of irritation (BUA, 1996). Another study reported that a DPGME concentration of 35 ppm caused slight irritation to the nose/upper respiratory tract, and above 75 ppm irritation to the respiratory tract, eyes and throat was observed, but was still tolerable (BUA, 1996; Henschler & MAK Commission, 1987; OECD, 2001).

Volunteers in an inhalation study identified 300 ppm DPGME as to be unpleasant (ACGIH, 2001; BUA, 1996; ECETOC, 2005; Henschler & MAK Commission, 1987; OECD, 2001).

Case reports after oral ingestion of a liquid containing DPGME exclusively or also other substances (e.g., reed diffusor liquid) observed hypersalivation, hypoxia, stridor, bronchospasm, vomiting, drowsiness, lactic acidosis with an elevated osmolal gap and seizures. (Langbroek et al., 2022; Panchal et al., 2016).

In acute inhalation studies rats were exposed for up to 7 or 8 h to vapour concentrations of DPGME up to the maximum attainable concentration at room temperature of 500 or 552.6 ppm (corresponding to 3100 and 3404.47 mg/m^3, respectively). Mild narcosis was seen in male rats, which recovered quickly (BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987). The acute dermal toxicity of DPGME is low as supported by determined LD50 values of 9510 - > 19020 mg/kg bw in rabbits and 19020 mg/kg bw in rats (ACGIH, 2001; ECETOC, 2005; ECHA Dissemination, 2023; OECD, 2001). In rats, acute oral LD50 values greater than 5000 mg/kg bw (ranging from 5000 - 9100 mg/kg bw) were determined and signs of toxicity observed included CNS depression (e.g., unsteady gait, narcosis) (ACGIH, 2001; BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; OECD, 2001).

DPGME was not skin irritating in studies in rabbits and in patch tests in humans (ACGIH, 2001; ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; OECD, 2001). In studies with humans and rabbits, transient eye irritating effects of DPGME were observed (ACGIH, 2001; BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; OECD, 2001).

In patch tests on a total of 250 volunteers, no skin sensitising potential of DPGME was observed (ACGIH, 2001; BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; OECD, 2001). Animal data on skin sensitising potential of DPGME is not available (ECETOC, 2005).

In a subchronic inhalation study (similar to OECD TG 413) with DPGME groups of F344 rats and New Zealand White rabbits (7/sex/group) were exposed to DPGME by whole body inhalation at concentrations of 0, 15, 50, or 200 ppm (0, 91.5, 305 or 1220 mg/m^3), 6 h/d, 5 d/week for 13 weeks. No toxicologically significant effects were observed. Therefore, a NO(A)EC of 200 ppm in rats and rabbits was derived (ACGIH, 2001; BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; Landry & Yano, 1984; SCOEL, 1993).

In inhalation studies, rats, rabbits, guinea pigs and monkeys were exposed whole-body to saturated DPGME concentrations of 300 - 400 ppm, 7 h/d, 5 d/week for 26 - 31 weeks. In rats, slight form of narcosis was observed, which was transient. In guinea pigs, rabbits and monkeys, changes in liver histology (vacuoles and granulation of cytoplasm) were found (ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; OECD, 2001).

DPGME was applied to male rabbits daily under occlusive conditions in doses of 1.0, 3.0, 5.0 or 10.0 ml DPGME/kg (950 - 9500 mg/(kg bw x d) for 5 d/week for 13 weeks. At 5 ml/kg and above, narcosis and deaths due to the effects of narcosis occurred. Microscopic changes were observed in the kidneys (granular and hydrophic changes) of the high dose animals. A NOEL of 2850 mg/(kg bw x d) and a LOEL of 4750 mg/(kg bw x d) were derived (BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; OECD, 2001).

DPGME was not genotoxic in *in vitro* assays with bacteria (Ames test), Chinese Hamster Ovary cells (chromosome aberration test) or rat hepatocytes (UDS-test) (BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler & MAK Commission, 1987; OECD, 2001; SCOEL, 1993).

In vivo genetic toxicity data for DPGME are not available. The structurally related glycol, PGME, was not genotoxic in a micronucleus test in mice (OECD, 2001).

Carcinogenicity studies with DPGME are not available. In 2-year carcinogenicity studies performed in mice and rats, PGME showed no evidence of carcinogenicity (ECHA Dissemination, 2023; OECD, 2001).

No studies are available on the reproductive toxicity or fertility of DPGME. Read-across data from a two-generation reproductive toxicity study in rats with PGME did not provide evidence of specific reproduction toxicity of this propylene glycol ether. Observed effects on reproductive parameters or organs in females appeared to be related and associated with systemic toxicity, and neonatal effects were considered to be secondary to maternal toxicity. The no-observed-effect-level (NOEL) for fertility and reproductive effects was 1000 ppm (OECD, 2001).

The subchronic inhalation toxicity study in rats (Landry & Yano, 1984) summarised above is considered a suitable key study for the derivation of an EU-LCI value for DPGME. The authors of this evaluation use the NOAEC of 200 ppm (1220 mg/m^3 at 23 °C) from this study as POD for the calculation.

The following assessment factors are used (EC, 2013; ECHA, 2018):

- Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6
- Adjusted study length factor: 2
- Interspecies extrapolation: 2.5 (allometric scaling not performed since route of exposure is inhalation)
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 280 leading to a value of 1220 mg/m^3 : 280 = for 4.357 mg/m^3 (rounded to 4400 µg/m^3).

An EU-LCI value of 4400 µg/m^3 is proposed for DPGME.

The odour threshold of DPGME is 35 ppm (210 - 216 mg/m^3) (ECETOC, 2005; SCOEL, 1993). Therefore, the odour is not expected to be perceived at the proposed EU LCI value.

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C Appendix

C.1 Data collection and fact sheet for dipropylene glycol monomethyl ether (DPGME)

Table 20: Data collection sheet for DPGME

Compound	**DPGME**	**Data collection sheet**			
Nº CAS (34590-94-8) 1 ppm = 6.10 mg/m³ at 23 °C	**EU-Classification:** not classified **CLP:** not included				
Organisation name	**AgBB**	**SCOEL**	**REACH registrant**	**MAK commission**	**German Ad-hoc Working Group on Indoor Guidelines**
Risk value name	NIK ('Lowest Concentration of Interest')	Indicative occupational exposure limit	DNEL (chronic, general population)	MAK value	Guidance value I and II ("Richtwert I und II")
Risk value (mg/m³)	3.1	308 (50 ppm)	37.2	310 (50 ppm)	Guidance value I: 2 Guidance value II: 7
Reference period	Chronic (general population)	Chronic (workers)	Chronic (general population)	Chronic (workers)	Chronic (general population)
Risk value (mg/m³) Short term (15 min)	-	-	-	-	-
Year	2021	1993	2023	2000	2013
Key study	-	Landry et al. 1984	Derived OEL value	Inhalation study in volunteers	Landry et al. 1984
Study type	-	subchronic inhalation toxicity study (similar to OECD TG 413)	subchronic inhalation toxicity study (similar to OECD TG 413)	Inhalation study in volunteers	subchronic inhalation toxicity study (similar to OECD TG 413)
Species	-	Rat, F344	Rat, F344	Human	Rat, F344
Duration of exposure in key study	-	90 days	90 days	once	90 days

Compound	DPGME	Data collection sheet			
Critical effect	-	No effects observed	No effects observed	Odour threshold, slight nasal irritation at 35 ppm and eye and throat irritation at 75 ppm	No effects observed
Critical dose value	-	NOAEC: 1232 mg/m³ (200 ppm)	DNEL (chronic, workers): 37.2 mg/m³ (based on a NOAEC: 1232 mg/m³ (200 ppm))	75 ppm	NOAEC: 1240 mg/m³ (200 ppm)
Adjusted critical dose	-		Adjustment for continuous exposure (6/24): 4.2		
Single assessment factors	-	UF_D 5	UF_S 2, UF_H 2		UF_S 2, UF_A 2.5, UF_H 10, $UF_{children}$ 2 RW II to RW I, additional UF_L 3
Other effects					
Remarks		The IOELV was derived after taking into account the preferred value approach and the mild effect seen in the studies.			

AgBB = Committee for Health-related Evaluation of Building Products

UF_A interspecies variability; UF_D data deficiencies; UF_H Intraspecies variability; UF_L Used for LOAEC-NOAEC extrapolation; UF_S Used subchronic study.

Table 21: Fact sheet for DPGME

Compound	Dipropylene glycol monomethyl ether (DPGME) C7H16O3		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	4400
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2024
General information			
CLP-Index No.	4	INDEX	-
EC-No.	5	EINECS	252-104-2
CAS-No.	6	Chemical Abstract Service number	34590-94-8
Harmonised CLP classification	7	Human health risk related classification	Not classified
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	148.2 1 ppm = 6.10 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	Landry et al. 1984 (Subchronic Inhalation Toxicity: 90-Day)
Read across compound	10	Where applicable	-
Species	11	Rat, human, etc.	Rat, F344
Route / type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic, etc.	Subchronic (90 d)
Exposure duration	14	h/d, d/w	6 h/d, 5 d/week
Critical endpoint	15	Effect (s), site of	No effects observed
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEC
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	200 ppm (1220 mg/m³)
Assessment factors (AF)			
Adjustment for exposure duration	19	Study exposure h/d, d/w	5.6
Study length	20	sa→sc→c	2
Route-to-route extrapolation factor	21	-	-

Compound	Dipropylene glycol monomethyl ether (DPGME) C7H16O3		Fact sheet
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	1
	22b	Severity of effect (R8 6d)	1
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	1
	23b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		
Other adjustment factors Quality of database	26	Quality of database	1
Results			
Summary of assessment factors	27	Total Assessment Factor	280
POD/TAF	28	Calculated value [µg/m³ and ppb]	4357 µg/m³ (714 ppb)
Molar adjustment factor	29		
Rounded value	30	[µg/m³]	5000
Additional comments	31		
Rationale selection	32		

Rationale for critical effects

For DPGME the available data basis is limited. Additional data are available from studies with structurally related propylene glycol ethers, e.g., PGME.

Workers painting with water-based paints containing DPGME at levels of 5 - 7 ppm DPGME (30 - 40 mg/m^3) in indoor air reported no symptoms nor signs of irritation (BUA, 1996). Another study reported that a DPGME concentration of 35 ppm caused slight irritation to the nose/upper respiratory tract, and above 75 ppm irritation to the respiratory tract, eyes and throat was observed, but was still tolerable (BUA, 1996; Henschler und MAK Commission, 1987; OECD, 2001). A concentration of 300 ppm DPGME was identified by volunteers as to be unpleasant (ACGIH, 2001; BUA, 1996; ECETOC, 2005; Henschler und MAK Commission, 1987; OECD, 2001).

The acute dermal and oral toxicity of DPGME was low in animals (LD50 values > 5000 mg/kg bw) (ACGIH, 2001; BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler and MAK Commission, 1987; OECD, 2001). In two older acute inhalation studies in which female CFE albino and male white rats were exposed for up to 7 or 8 h to vapour concentrations of DPGME up to the maximum attainable concentration at room temperature of 500 or 552.6 ppm (corresponding to 3100 and 3404.47 mg/m^3, respectively) no mortalities occurred. Mild

narcosis was seen in male rats, the animals recovered quickly (BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler and MAK Commission, 1987).

DPGME was not skin irritating in humans or animals. The ocular application of a 20 % DPGME solution (0.04 ml, vehicle: water) to one eye of volunteers resulted in slight burning sensation for 30 - 40 sec, lacrimation, eyelid spasm for 1 min, injection of conjunctival vessels and slightly increased intraocular pressure during the first hour after application (BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023). In rabbits, undiluted DPGME caused a slight irritation to the eyes (ACGIH, 2001; ECETOC, 2005; ECHA Dissemination, 2023; Henschler and MAK Commission, 1987; OECD, 2001).

In humans (250 volunteers) no skin sensitising potential of DPGME was observed in patch tests (ACGIH, 2001; BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler and MAK Commission, 1987; OECD, 2001). Animal data on skin sensitisation are not available.

Relevant repeated dose toxicity studies or observations with DPGME in humans are not available.

In a subchronic inhalation study (similar to OECD TG 413) groups of F344 rats and New Zealand White rabbits (7/sex/group) were exposed to DPGME by whole body inhalation at concentrations of 0, 15, 50, or 200 ppm (0, 91.5, 305 or 1220 mg/m^3), 6 h/d, 5 d/week for 13 weeks. No toxicologically significant effects were observed. Therefore, a NOAEC of 200 ppm in rats and rabbits was derived (ACGIH, 2001; BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler and MAK Commission, 1987; Landry and Yano, 1984; SCOEL, 1993).

In *in vitro* studies (Ames test, chromosome aberration test, UDS-test), DPGME was not genotoxic (BUA, 1996; ECETOC, 2005; ECHA Dissemination, 2023; Henschler and MAK Commission, 1987; OECD, 2001; SCOEL, 1993). *In vivo* genetic toxicity data for DPGME are not available. For the structurally related glycol, PGME, a negative test result is available from a micronucleus test in mice (OECD, 2001).

Carcinogenicity studies with DPGME are not available. In 2-year carcinogenicity studies performed in mice and rats, PGME showed no evidence of carcinogenicity (ECHA Dissemination, 2023; OECD, 2001).

No studies are available on the reproductive toxicity or fertility of DPGME. Data on PGME was used as read-across. In a two-generation reproductive toxicity study in rats, PGME did not provide evidence of specific reproduction toxicity. Observed effects on reproductive parameters or organs in females appeared to be related and associated with systemic toxicity, and neonatal effects were considered to be secondary to maternal toxicity. A no-observed-effect-level (NOEL) for fertility and reproductive effects of 1000 ppm was derived (OECD, 2001).

Rationale for starting point

The subchronic inhalation toxicity study in rats (Landry and Yano, 1984) summarised above is considered a suitable key study for the derivation of an EU-LCI value for DPGME. Up to the highest tested concentration no significant effects were observed. Therefore, the NOAEC of 200 ppm (1220 mg/m^3 at 23 °C) from this study is used as POD for the calculation.

Rationale for assessment factors

The following assessment factors are used (EC, 2013; ECHA, 2018):

- Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6
- Adjusted study length factor: 2

- Interspecies extrapolation: 2.5 (allometric scaling not performed since route of exposure is inhalation)
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 280 leading to a value of 1220 mg/m³: 280 = 4.357 mg/m³ (rounded to 4400 µg/m³).

An EU-LCI value of 4400 µg/m³ is proposed for DPGME.

In the literature, an odour threshold of 35 ppm (210-216 mg/m³) is reported for DPGME (ECETOC, 2005; SCOEL, 1993). Therefore, it is not to be expected that the odour will be perceived at the proposed EU-LCI value.

References

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BUA, Beratergremium für umweltrelevante Altstoffe (1996) Propylenglykolmethylether, Dipropylenglykolmethylether, BUA-Stoffberichte 173 und 174. S. Hirzel Verlag Stuttgart

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SCOEL, Scientific Committee for Occupational Exposure Limits (1993) Recommendation of the Scientific Expert Group on Occupational Exposure Limits for Dipropylene glycol monomethylether. SEG/SUM/45 final 1993. European Commission; Employment, Social Affairs and Inclusion

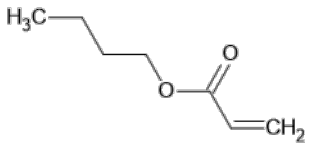
4 Toxicological evaluation of n-butyl acrylate as basis for the derivation of an EU-LCI value

4.1 Substance identification

n-Butyl acrylate (BA) belongs to the group of acrylic acid esters. The substance identification of BA is shown in Table 22.

The toxicological data basis for BA has been summarised and evaluated in a number reviews, for example by the GDCh Advisory Committee on Existing Chemicals (BUA) (1992), by ECETOC (1994), within the AEGL project (U.S.EPA, 2007), IARC (1999), Greim et al. (1995), within the framework of the HPV (OECD SIDS, 2002, 2007) and several times by the MAK Commission (most recently in 2017/2018) (DFG, 2017; Hartwig & MAK Commission, 2018). An indicative occupational exposure limit (IOEL)[5] and a SCOEL recommendation (SCOEL, 1993) were published. A registration dossier (ECHA Dissemination, 2023) and a substance evaluation report (Kemi, 2019) are also available.

Table 22: Substance identification of n-butyl acrylate (ECHA Dissemination, 2023)

Cas-No. EU-No. CLP-Index-No.	Systematic name, common name	Sum formula	Structural formula
141-32-2 205-480-7 607-062-00-3	n-butyl prop-2-enoate, n-butyl acrylate,	$C_7H_{12}O_2$	

4.2 Substance properties and uses

The physicochemical properties of n-butyl acrylate (BA) are shown in Table 23. At room temperature, BA is a colourless liquid with an odour described as "strong fruity" or "pungent, fragrant, acrid, fruity" (van Thriel et al., 2023). BHT is only slightly soluble in water but soluble in most organic solvents (ECHA Dissemination, 2023).

n-Butyl acrylate is an industrially produced ester of acrylic acid that does not occur naturally (IARC, 1999). The substance is produced industrially on a large scale (tonnage band in the EU 500,000 to 1,000,000 tonnes/a (Kemi, 2019) and is mainly used in the production of polymers and resins for textile and leather finishing, solvent-based coatings, adhesives, paints, binders and emulsifiers (IARC, 1999). The REACH registration dossier states that butyl acrylate per se is not intended for consumer use. However, end-use consumer products may contain trace amounts of acrylic acid and its esters due to the polymerisation process as residuals (ECHA Dissemination, 2023).

[5] Commission Directive 2000/39/EC (first list of indicative OELs) https://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2000L0039:20100108:EN:PDF

Table 23: Physicochemical properties of n-butyl acrylate (ECHA Dissemination, 2023)

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa)	Conversion 1 ppm = x mg/m³ (23 °C)	log pow	Solubility in water (mg/L)
128.17	-64.6 at 1013.25 hPa	147 at 1013.25 hPa	5 at 22.2 °C	5.3	2.38 at 25 °C	1700 at 20 °C

4.3 Exposure

4.3.1 Indoor air

Few data are available on measured concentrations of BA in indoor air (Table 24). (Hofmann & Plieninger, 2008) could detect BA in less than 5 % out of 896 measurements, with a maximum of 12 µg/m³ and a median below the limit of detection. In a larger number of measurement data, the 95th percentile was reported to be below 1.0 µg/m³ (AGÖF, 2013)

Table 24: Data on the occurrence of n-butyl acrylate in indoor air

Indoor	N	LoD (µg/m³)	N > LoD	Median (µg/m³)	P95 (µg/m³)	Maximum (µg/m³)	Source
Offices, homes, (pre)-schools, Germany	896	1.0	33 (3.7 %)	0.5	2.5	12	(Hofmann & Plieninger, 2008)
Indoor air (not further specified), Germany, 2006-2012	1807	not reported		< 1.0	< 1.0		(AGÖF, 2013)

*: 90th percentile

4.4 Toxicokinetics

Studies in rats show that following oral administration butyl acrylate is rapidly absorbed, mainly hydrolysed by carboxyl esterase to acrylic acid and butanol and ultimately eliminated as CO_2. A minor portion (ca. 10 %) is conjugated to glutathione and excreted in urine (Kemi, 2019).

After oral administration to male rats, n-butyl [2,3-^{14}C]acrylate (4, 40, 400 mg/kg bw) was very rapidly absorbed and hydrolysed to acrylic acid, with more than 75 % of the dose eliminated as $^{14}CO_2$. About 10 % of the dose was excreted in the urine and 2 % with the faeces. Two metabolites in urine were identified as the mercapturic acid N-acetyl- S-(2-carboxyethyl)-cysteine and its sulfoxide. Additional unidentified ^{14}C peaks were present in the urine at the highest dose (OECD SIDS, 2002).

4.5 Health effects

4.5.1 Acute toxicity, sensory irritation, and local effects

Acute toxicity

The acute toxicity of n-butyl acrylate is low. Oral LD50 values of 3143 mg/kg bw and 9050 mg/kg bw were obtained for rats (OECD SIDS, 2002).

An inhalation LC50 (4-hour) of 10300 mg/m^3 (1940 ppm) was reported for rats, and a dermal LD50 of 2000 to 3024 mg/kg bw for rabbits (OECD SIDS, 2002).

Sensory irritation

The RD50 (concentration leading to decrease in breathing rate by 50 % as sign of respiratory irritation) was determined in mice. The obtained RD50 of 340 ppm (1800 mg/m^3) for n-butyl acrylate was very similar to the RD50 of 315 ppm determined for ethyl acrylate (Hartwig & MAK Commission, 2018).

No data regarding sensory irritation of n-butyl acrylate are available from controlled human studies. However, no evidence of sensory irritation was observed in a study in which volunteers were exposed with 2.5 ppm ethyl acrylate for four hours with a peak of up to 5 ppm (Hartwig & MAK Commission, 2018).

Sensitisation

Sensitisation to butyl acrylate was observed in several patch test (ECHA Dissemination, 2023). A positive cross-reaction with butyl acrylate was described in patients who were sensitised to 2-ethylhexyl acrylate and n-tert-butylmaleic acid monoamide (DFG, 1986). A number of clinical findings revealed skin-sensitising effects of n-butyl acrylate in humans. These and the results of patch tests and some clinical epidemiological studies in small cohorts showed that the number of contact allergic reactions caused by n-butyl acrylate is similar to that caused by ethyl acrylate (Hartwig & MAK Commission, 2018).

Butyl acrylate had a sensitising effect on guinea pigs in various experimental models. Cross-reactions have been demonstrated with several mono- and diacrylates (DFG, 1986). In a Local Lymph Node Assay (following OECD Guideline 429), n-butyl acrylate was shown to be a potential skin sensitiser. The concentration giving rise to a 3 fold increase in lymphocyte proliferation (EC3) was calculated to be 11.2 % (ECHA Dissemination, 2023).

No data are available regarding sensitising effects of n-butyl acrylate on the respiratory tract.

4.5.2 Repeated dose toxicity

Human data

No data are available relevant for the derivation of an EU LCI-value.

Animal data

Administration of butyl acrylate in drinking water to F-344 rats (leading to applied doses of 0, 12, 73, 84 mg/(kg bw x d) in males and 0, 15, 91.111 mg/(kg bw x d) in females) for 13 weeks led to a slightly reduced water intake in all dose groups and slightly delayed body weight gain in males at the highest dose. No other effects were noted (DFG, 1986; OECD SIDS, 2002). No effects were observed in a satellite group receiving 150 mg/(kg bw x d) by gavage (OECD SIDS, 2002).

Sprague-Dawley rats (20 M + 20 F/group) were exposed by inhalation against 0, 21, 108, 211, or 546 ppm (0, 111, 572, 1118, 2894 mg/m^3) on 6 h/d, 5 d/week for 13 weeks. At the highest

concentration of 546 ppm, most animals (31/40) died. The most prominent findings, apart from bloody eye and nasal secretions, were irritation of the nasal mucosa (oedema, hyperaemia, keratinisation), metaplastic changes in the trachea and bronchi, and pulmonary hyperaemia and pneumonia. Irritant effects on the eyes and nasal mucosa, reduced body weight gain and increased relative liver weights were also observed at 211 ppm, as were decreased potassium values (females) and an increase in alkaline phosphatase activity (females). Only minor effects, such as increased liver weights in female animals without histological correlate, were observed at 108 ppm (572 mg/m^3) which represented the NOAEC (DFG, 1986; Hartwig & MAK Commission, 2018; OECD SIDS, 2002).

In a chronic inhalation study (equivalent or similar to OECD Guideline 453: "Combined Chronic Toxicity/ Carcinogenicity Studies"), Sprague-Dawley rats (a total of 86 M + 86 F/concentration) were exposed 6 h/d, 5 d/week, for up to two years whole body against concentrations of 0, 5, 15 and 45 ppm (0, 27, 80, 240 mg/m^3) during the first 13 weeks and thereafter against concentrations of 0, 15, 45, or 135 ppm (0, 80, 240, 720 mg/m^3). There were no indications of systemic toxicity, except for a slight decrease in food consumption and slightly lower relative heart, kidney, liver and thyroid weights at the highest dose. Localised and diffuse stippling of the corneal epithelium, cloudiness of the cornea, and various degrees of vascularisation were observed at ≥ 45 ppm. A NOAEC for local effects in the respiratory tract could not be determined. The severity of nasal mucosa effects increased with concentration and occurred at all doses in males and females. Effects ranged from slight atrophy of the neurogenic part of the olfactory epithelium at 15 ppm to a partial loss of the columnar cell layer and stratified reserve-cell hyperplasia at 45 and 135 ppm (ECHA Dissemination, 2023; OECD SIDS, 2002; Reininghaus et al., 1991).

4.5.3 Genotoxicity and carcinogenicity

Genotoxicity

Overall, the available data for alkyl (methyl, ethyl, butyl, and 2-ethylhexyl) acrylates indicate that acrylate monomers are not genotoxic *in vivo*, and that positive findings *in vitro* are typically observed at cytotoxic concentrations (Suh et al., 2018).

The *in vitro* gene mutation studies in bacteria with n-butyl acrylate are negative, both in the absence or presence of exogenous metabolic activation system (ECHA Dissemination, 2023).

An *in vitro* Mammalian Cell Gene Mutation test (OECD TG 490) was conducted with mouse lymphoma cells, with and without metabolic activation. Cells were exposed to butyl acrylate up to concentrations which caused 20 % cytotoxicity. Mutation frequencies were close to or within the respective vehicle control. Thus, under tested conditions butyl acrylate did not induce mutations *in vitro* (Kemi, 2019).

A UDS test (unscheduled DNA synthesis) with SHE (Syrian hamster embryo) cells yielded negative results. No clastogenic effects were observed in two micronucleus tests with SHE cells *in vitro*. In CHO (Chinese hamster ovary) cells chromosomal aberrations were induced only after exposure to highly cytotoxic concentrations in the absence of a metabolic activation system. In the presence of a metabolic activation system, a slight increase was observed, which was less than twice the control value. The significance of this result was deemed questionable. Similarly, a slight increase in the incidence of sister chromatid exchange (SCE) was observed with CHO cells which was less than twice the control value (DFG, 1996).

In vivo, n-butyl acrylate did not produce an increase in sex-linked recessive lethal mutations in the fruit fly *Drosophila melanogaster* at concentrations of 1800 ppm administered with the diet or injected (DFG, 1996). No chromosomal aberrations were observed in the bone marrow of Chinese hamsters and Sprague-Dawley rats exposed to 4300 mg BA/m^3 (⅓ of the LC50) for 5 – 6

h/d for four days when examined 5 h after cessation of exposure. However, n-butyl acrylate induced chromosomal aberrations in the bone marrow of rats dosed by intraperitoneal injection (IARC, 1999; Kemi, 2019). An increase in the incidence of chromosomal aberrations was observed in the bone marrow of rats after single oral doses of 300 and 600 mg/kg w (¼ and ½ of the LD50) and after two oral doses weekly for 8 weeks of 300 mg/kg bw (DFG, 1996).

Based on a WoE (weight of evidence) analysis of the currently available data which took into account data from genotoxicity tests with methyl and ethyl acrylate (negative or weakly positive at cytotoxic concentrations only) and the negative results of the long-term carcinogenicity studies with acrylates, it was concluded that there is no concern for mutagenicity of n-butyl acrylate (Kemi, 2019).

Carcinogenicity

No evidence of an increase in the incidence of tumours was observed in the chronic inhalation toxicity study with rats (see chapter 4.5.2) (Reininghaus et al., 1991).

No treatment-related tumours were observed in C3H/HeJ mice after skin applications of n-butyl acrylate for lifetime (ECHA Dissemination, 2023; IARC, 1999).

4.5.4 Toxicity to reproduction

Rats were exposed in a range finding reproductive toxicity study with 0, 40, 160 and 400 mg BA/(kg bw x d) by gavage. Animals at the highest dose and, to a lesser extent at the mid-dose, showed salivation and red material around the eyes, nose and mouth. Macroscopic examinations showed thickened and eroded stomach at the highest dose. Systemic or reproductive toxicity was not observed (Kemi, 2019).

In an extended one-generation reproductive toxicity study (EOGRTS, OECD guideline 443) Sprague-Dawley rats (30 M + 30 F/group) received oral doses of 0, 20, 50 and 150 mg BA/(kg bw x d) by gavage. Thickened stomach was observed in 3 of 30 high-dose P0 males. Microscopic findings were in the nonglandular stomach, liver and kidneys. Nonglandular stomach findings were minimal to moderate epithelial hyperplasia and hyperkeratosis. At 150 mg/(kg bw x d) minimal oedema and congestion was observed in the submucosa adjacent to the hyperplasia and hyperkeratosis in one female. In the F1 animals, test substance-related microscopic changes were observed in the nonglandular stomach in males and females at all doses. Hyperkeratosis was observed in all treated animals, while epithelial hyperplasia was observed at 50 and 150 mg/kg bw/d. These findings were not associated with clinical pathology changes, but slightly less severe when compared to the F0 generation and were considered adverse at 150 mg/kg bw/d (ECHA Dissemination, 2023; Kemi, 2019). There was no evidence of reproductive toxicity at any dosage level based on evaluation of reproductive performance in the F0 generation and sperm measurements and oestrous cyclicity in the F0 and F1 generations (ECHA Dissemination, 2023).

In an inhalation developmental toxicity study, pregnant Sprague-Dawley rats (30/ group) were exposed to 0, 25, 135 or 250 ppm BA for 6 h/d on GD6-15. Respiratory tract irritation and reduced body weight gain were observed in dams at concentrations ≥ 135 ppm. These concentrations also led to increased embryo lethality, but no teratogenic effect could be observed at any dose. The NOAEC for maternal toxicity and developmental toxicity was 25 ppm (135 mg/m^3) (DFG, 2007b; ECHA Dissemination, 2023).

In a further developmental toxicity study, pregnant Sprague-Dawley rats (at least 24/group) were exposed by inhalation to 0, 100, 200 or 300 ppm BA for 6 h/d on GD 6 - 20. Reduced feed intake and reduced body weight gain occurred at all concentrations. The foetal body weight was

reduced at ≥ 200 ppm. A non-significant increase in the proportion of foetuses with skeletal variations per litter observed at 300 ppm was not considered to be substance-related due to the high incidence in the control animals and the high variability. There was no increase in malformations. 100 ppm (530 mg/m^3) represented a NOAEC for developmental toxicity and a LOAEC for maternal toxicity (DFG, 2007b).

In an oral developmental toxicity study, CD-1 mice (at least 24/group) received n-butyl acrylate by gavage at doses of 0, 100, 1000, 1500, 2000, 2500, 3000 or 4000 mg/(kg bw x d) GD 6 – 15. At the highest dose all dams died. Body weight gain was reduced at ≥ 1500 mg/(kg bw x d) and liver weight increased at ≥ 2500 mg/(kg bw x d). Developmental toxicity was noted at ≥ 1500 mg/(kg bw x d) (reduced foetal weights) and at ≥ 2500 mg/(kg bw x d) (increased resorption rates). Although the incidence of the sum of foetuses with "malformations" per litter was significantly increased at ≥ 1000 mg/(kg bw x d), the specific findings at 1000, 1500 and 2000 mg/(kg bw x d) were neither consistent nor dose-dependent and mostly also occurred in the control foetuses. The changes observed at up to 2000 mg/(kg bw x d) were therefore considered to be spontaneous findings and not substance-related. A clear and dose-dependent increase in the incidence of malformations was recognised at 2500 and 3000 mg/(kg bw x d). Findings included cleft palate, exencephaly, open eyes, fused arches and fused ribs. Such findings typically occur more frequently in mice under stress conditions. No effects on dams or foetuses were observed at 100 mg/(kg bw x d). Taking into account the relevance and dose dependence of the findings, 1000 mg/(kg bw x d) was considered the NOAEL for maternal and developmental toxicity (DFG, 2007b).

In a range-finding study for a development toxicity study, New Zealand White rabbits (5/group) received 0, 50, 125, 250 and 400 mg/(kg bw x d) by gavage. Body weight gain and food consumption were decreased at 400 mg/(kg bw x d) throughout the treatment period. Otherwise, no significant clinical observations or treatment-related findings were reported at any dose. In the main study (OECD guideline 414), pregnant New Zealand White rabbits (25/group) were dosed with 0, 50, 150 and 400 mg/(kg bw x d) on GD7-28. No effects were observed on body or organ weights. The numbers of foetuses (litters) were 219(25), 214(24), 199(25) and 214(24) in the control, 50, 150 and 400 mg/(kg bw x d) groups, respectively. No treatment-related malformations were observed. It was concluded that there was no concern for developmental toxicity (ECHA Dissemination, 2023; Kemi, 2019).

4.5.5 Odour perception

Measurements using the triangle odour bag method revealed an odour threshold for BA of 0.00055 ppm (0.0029 mg/m^3) (Nagata, 2003). An even lower odour threshold of 0.0015 mg/m^3 (1.5 µg/m^3) has also been reported (van Thriel et al., 2023).

4.6 Evaluation

4.6.1 Existing regulations and classifications

There is no harmonised classification for n-butyl acrylate regarding carcinogenicity, mutagenicity, or toxicity for reproduction. Butyl acrylate is classified (harmonised classification) as irritating to eyes, skin and respiratory tract (Eye Irrit. 2, H319; Skin Irrit. 2; H315; STOT SE H335) and as skin sensitising (Skin Sens. 1, H317) (ECHA C&L Inventory, 2023).

The IARC evaluated BA in 1999 and classified the substance in group 3, since no epidemiological data relevant to the carcinogenicity of n-butyl acrylate were available, and the evidence in

experimental animals for the carcinogenicity of n-butyl acrylate was inadequate. Overall, BA was *not classifiable as to its carcinogenicity to humans* (IARC, 1999).

Existing guide values for n-butyl acrylate in air are summarised in Table 25 and Table 26.

No DNEL for the general population were derived. The registration dossier states that "*butyl acrylate per se is not intended for consumer use. However, end-use consumer products may contain trace amounts of acrylic acid and its esters due to the polymerization process as residuals. As a consequence, consumer exposure to acrylate monomers including butyl acrylate can be considered at least as very low or as negligible, if any. But even in the case of very low exposure to tiny amounts of butyl acrylate it was shown that even long-term inhalation exposure with its high bioavailability did not led to carcinogenicity or systemic toxicity up to the highest biologically feasible concentration (135 ppm = 0.773 mg/L). In addition, butyl acrylate was not carcinogenic, when applied to the skin of mice throughout their lifetime at 1 % corresponding to about 8 mg/kg bw. Therefore, no DNELs were derived.*"

The 8-h TWA derived by SCOEL (1993) was adopted as DNEL for employees. The derivation of the SCOEL is based on the LOAEC of 15 ppm obtained in a chronic inhalation study with rats (see chapter 4.5.2).

The results of the same chronic inhalation study were also used by the MAK-commission. Benchmark concentrations of the 2-year study using the US EPA BMDS programme provided a $BMDL_{05}$ in the range of 3 ppm. A NAEC of 5 ppm was obtained from the LOAEC of 15 ppm by dividing the LOAEC by a factor of 3. MAK values of 1 and 2 ppm were calculated from the $BMDL_{05}$ and the NAEC to extrapolate the effects in the olfactory epithelium of rats to a NOAEC for humans (1:2), taking into consideration the preferred value approach. The MAK commission additionally took into account data for ethyl acrylate. The RD50 of ethyl acrylate is similar to that of n-butyl acrylate, ethyl acrylate and n-butyl acrylate were found to have very similar NOAEC in medium-term inhalation studies in rats (ethyl acrylate: 25 ppm, n-butyl acrylate: 21 ppm), and a NOAEC of 5 ppm for ethyl acrylate was obtained in a 2-year inhalation study in rats. As there was no evidence of sensory irritation in a 4-hour volunteer study with ethyl acrylate concentrations of 2.5 ppm and peaks of up to 5 ppm, a MAK value of 2 ppm was established (Hartwig & MAK Commission, 2018). The 8-h TWA/ MAK value was adopted for the German AGW (AGS, 2023).

Regarding the MoA (mode action), the MAK commission stated that *in vitro* studies showed that the hydrolysis of the acrylate ester and the accompanying formation of acrylic acid is a detoxification mechanism. The commission concluded that not the release of acid is decisive for the toxicity of short-chain acrylates and methacrylates, but the reactivity of the Michael system (alpha-beta unsaturated compounds) with nucleophilic compounds such as glutathione (Hartwig & MAK Commission, 2018). This explanation contrasts with that of the MoA described in the rationale for 2-ethylhexyl acrylate (DFG, 2007a) where it was concluded that acrylic acid is crucial for the development of nasal lesions in the rat by exposure to alkyl acrylates (DFG, 2007a) (see chapter 5.6.1).

Table 25: Guide values for n-butyl acrylate, part I (for explanation, see text)

Guide value Parameter/Organisation	**(ECHA Dissemination, 2023)**	**(AGBB, 2021)**
Name	DNEL (chronic, general population)	NIK value
Value (mg/m³)	No value derived	0.110
Organ/critical effect		
Species		
Basis		
Adjusted for cont. exposure		
Extrapolation factors Time LOAEC to NAEC Interspecies Intraspecies Route-to-route Total		"Ascribed" EU-LCI value
Remarks		

Table 26: Guide values for n-butyl acrylate, part II (for explanation, see text)

Guide value Parameter/ Organisation	(ECHA Dissemination, 2023)	(Hartwig & MAK Commission, 2018)	(AGS, 2023)	(SCOEL, 1993)
Name	DNEL (chronic, workers)	MAK value (workplace)	AGW	8h-TWA
Value (mg/m³)	11	11	11	11 (2 ppm)
Organ/critical effect		Reserve cell hyper-plasia with loss of ciliated or olfactory cells in nasal olfactory epithelium		Atrophy of the olfactory epithelium
Species		Rat		Rat
Basis		BML_{05}: ≈ 3 ppm (16 mg/m³) LOAEC/3 = 5 ppm (27 mg/m³)		LOAEC: 15 ppm (80 mg/m³)
Adjusted for cont. exposure		-		-
Extrapolation factors Time NOAEC to NEC Interspecies Intraspecies Total		 - - 2		 5
Remarks	Based on SCOEL, 1993	Derivation supported by read-across to data from ethyl acrylate for sensory irritation in humans (no sensory irritation at 2.5 ppm)	Based on MAK and SCOEL	"Preferred value approach"

#

4.6.2 Derivation of an EU-LCI value

The chronic inhalation toxicity study with rats (Reininghaus et al., 1991) is taken as the basis for the derivation of the EU-LCI. This study provided a LOAEC of 15 ppm (79.5 mg/m³) but no NOAEC since adverse effects were observed down to the lowest applied concentration.

A benchmark calculation (using RIVM PROAST[6] Web application, version 70.1) was performed for the incidence of reserve cell hyperplasia with loss of olfactory or ciliated cells in the nasal olfactory epithelium of male or female rats, respectively. The model averaging approach provided a $BMDL_{05}$ of 4.86 ppm for male rats but no satisfactory calculation was possible for the

[6] https://proastweb.rivm.nl/

incidence in female rats (data not shown). Since the $BMDL_{05}$ of 4.86 ppm is nearly identical with the value of 5 ppm obtained by the conventional extrapolation using a factor of three to extrapolate from a LOAEC to a NOAEC, the conventional LOAEC to NOAEC approach may be used as well.

The following assessment factors are used:

- LOAEC to NOAEC: 3
- Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6
- Adjusted study length factor: 1
- Interspecies extrapolation: 2.5 (allometric scaling not performed since route of exposure is inhalation)
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 420 leading to a value of 79.5 mg/m^3: 420 = 0.189 mg/m^3 (rounded to 200 $\mu g/m^3$).

(Note: On a molar basis, the non-rounded values for n-butyl acrylate and 2-ethylhexyl acrylate (see chapter 5.6.2) are identical, i. e. 35.7 ppb for both substances).

An EU-LCI value of 200 $\mu g/m^3$ is proposed for n-butyl acrylate.

According to Nagata (2003), BA has a very low odour threshold 2.9 $\mu g/m^3$. It is therefore to be expected that the odour will be perceived at the proposed EU-LCI value.

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The links listed in the bibliography were last checked and confirmed on 2. May 2024.

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D Appendix

D.1 Data collection and fact sheet for n-butyl acrylate

Table 27: Data collection sheet for n-butyl acrylate

Compound	**n-Butyl acrylate**	**Data collection sheet**				
N° CAS: 141-32-2 1 ppm = 5.3 mg/m³ at 23 °C	**EU-Classification:** **CLP, harmonised classification:** H319: Eye Irrit. 2, H315: Skin Irrit. 2, H335: STOT SE: irritating to the respiratory tract, H317: Skin Sensit. 1					
Organisation name	**REACH registrant**	**AgBB**	**REACH registrant**	**DFG**	**AGS**	**SCOEL**
Risk value name	DNEL (general population)	NIK ('Lowest Concentration of Interest')	DNEL (workers)	MAK value (workplace)	AGW (workplace)	TWA (workplace)
Risk value (mg/m³)	not derived	0.110	11	11	11	11
Reference period				Chronic (workplace)		
Risk value (mg/m³) **Short term (15 min)**				11		53
Year	2023	2021	2023	2018	2023	1993
Key study		see below		Reininghaus et al., 1991		Reininghaus et al., 1991
Study type				Chronic inhalation toxicity study		

Compound	n-Butyl acrylate	Data collection sheet				
Species				Rat, Sprague-Dawley (n = 86 M + 86 F/group)		Rat, Sprague-Dawley (n = 86 M + 86 F/group)
Duration of exposure in key study				6 h/d, 5 d/week, 2 years		6 h/d, 5 d/week, 2 years
Critical effect				Nasal epithelial lesions (Reserve cell hyper-plasia with loss of ciliated or olfactory cells in nasal olfactory epithelium)		Atrophy of the olfactory epithelium
Critical dose value				LOAEC: 80 mg/m³ BML_{05}: 16 mg/m³		LOAEC 80 mg/m³
Adjusted critical dose						
Single assessment factors				UF_L 3, UFA 2		Overall UF: 5
Other effects						
Remarks	No value derived ("no hazard identified"	Adopted ascribed EU-LCI-value	Based on SCOEL, 1993	Derivation supported by read-across to data from ethyl acrylate for sensory irritation in humans (no sensory irritation at 2.5 ppm)	Based on MAK and SCOEL	UF considered appropriate to allow for absence of NOAEL and of reliable human data, "preferred value approach"

AgBB = Committee for Health-related Evaluation of Building Products

UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_{SA} Used subacute study; UF_D data deficiencies.

Table 28: Fact sheet for n-butyl acrylate

Compound	n-Butyl acrylate C7H12O2		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	200
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2024
General information			
CLP-Index No.	4	INDEX	607-062-00-3
EC-No.	5	EINECS	205-480-7
CAS-No.	6	Chemical Abstract Service number	141-32-2
Harmonised CLP classification	7	Human health risk related classification	H315, H319, H335, H317
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	128.17 1 ppm = 5.3 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	Reininghaus et al., 1991
Read across compound	10	Where applicable	-
Species	11	Rat, human, etc.	Rat, Sprague-Dawley
Route / type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic, etc.	Chronic (two years)
Exposure duration	14	h/d, d/w	6 h/d, 5 d/week
Critical endpoint	15	Effect (s), site of	Degeneration of the olfactory epithelium
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	LOAEC
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	80 mg/m³ (15 ppm)
Assessment factors (AF)			
Adjustment for exposure duration	19	Study exposure h/d, d/w	5.6
Study length	20	sa→sc→c	1
Route-to-route extrapolation factor	21	-	-

Compound	n-Butyl acrylate C7H12O2		Fact sheet
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	3
	22b	Severity of effect (R8 6d)	1
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	1
	23b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		
Other adjustment factors Quality of database	26	Quality of database	1
Results			
Summary of assessment factors	27	Total Assessment Factor	420
POD/TAF	28	Calculated value [µg/m³ and ppb]	189 µg/m³ (35.7 ppb)
Molar adjustment factor	29		
Rounded value	30	[µg/m³]	200
Additional comments	31		
Rationale selection	32		

Rationale for critical effects

The acute toxicity of n-butyl acrylate (BA) is low. An inhalation LC50 (4-hour) of 10300 mg/m³ was reported for rats (OECD SIDS, 2002). No data on sensory irritation of BA from controlled human studies is available. Results of a study with volunteers exposed to 2.5 ppm ethyl acrylate vapour for four hours (with peak exposures up to 5 ppm) showed no evidence of sensory irritation. An RD50 (concentration leading to decrease in breathing rate by 50 % as sign of respiratory irritation) of 340 ppm BA was determined in mice (Hartwig und MAK Commission, 2018). Several patch tests and some clinical findings showed skin-sensitising effects of BA in humans. BA also showed a sensitising effect on guinea pigs in various experimental models. No data is available concerning sensitising effects of BA on the respiratory tract (ECHA Dissemination, 2023).

Relevant data from repeated dose toxicity studies in humans is not available.

In a subchronic inhalation toxicity study, Sprague-Dawley rats were exposed against 0, 21, 108, 211, or 546 ppm (0, 111, 572, 1118, 2894 mg/m³) 6 h/d, 5 d/week for 13 weeks. Most animals (31/40) died at the highest concentration. Reported effects were bloody eye and nasal secretions, irritation of the nasal mucosa, metaplastic changes in the trachea and bronchi, and pulmonary hyperaemia and pneumonia. At 211 ppm irritant effects on the eyes and nasal mucosa, reduced body weight gain and increased relative liver weights were observed. The

NOAEC of the study was considered to be 108 ppm (572 mg/m^3). At this concentration only minor effects, such as increased liver weights in female animals without histological correlate were observed (DFG, 1986; Hartwig und MAK Commission, 2018; OECD SIDS, 2002).

In a chronic inhalation study (equivalent or similar to OECD Guideline 453), Sprague-Dawley rats were exposed whole body against concentrations of 0, 5, 15 and 45 ppm (0, 27, 80, 240 mg/m^3) during the first 13 weeks and thereafter against concentrations of 0, 15, 45, or 135 ppm (0, 80, 240, 720 mg/m^3) for up to two years. The severity of nasal mucosa effects increased with concentration and occurred at all doses in males and females. A NOAEC for local effects in the respiratory tract could not be determined. There were no indications of systemic toxicity, except for a slight decrease in food consumption and slightly lower relative heart, kidney, liver, and thyroid weights at the highest dose (ECHA Dissemination, 2023; OECD SIDS, 2002; Reininghaus et al., 1991).

In vitro genotoxicity studies in bacteria and in mammalian cells (gene mutation in mouse lymphoma cells, unscheduled DNA synthesis in Syrian hamster embryo (SHE) cells, sister chromatid exchange in Chinese hamster ovary (CHO) cells, clastogenicity in SHE cells and CHO cells) were negative or, at most, questionably positive at high cytotoxic concentrations (ECHA Dissemination, 2023; DFG, 1996; Kemi, 2019). *In vivo*, no chromosomal aberrations were observed in the bone marrow of Chinese hamsters and Sprague-Dawley rats exposed to 4300 mg BA/m^3 for four days when examined 5 h after cessation of exposure. However, chromosomal aberrations in the bone marrow of rats were observed after intraperitoneal injection of BA (IARC, 1999; Kemi, 2019; DFG, 1996).

Overall, the available data for alkyl (methyl, ethyl, butyl, and 2-ethylhexyl) acrylates indicate that acrylate monomers are not genotoxic *in vivo*, and that positive findings *in vitro* are typically observed at cytotoxic concentrations (Suh et al., 2018). Based on a WoE (weight of evidence) analysis of the currently available data which took into account data from genotoxicity tests with methyl and ethyl acrylates and the negative results of the long-term carcinogenicity studies with acrylates, it was concluded that there is no concern for mutagenicity of BA (Kemi, 2019).

No evidence of an increase in the incidence of tumours was observed in the chronic inhalation toxicity study with rats (see above), and no treatment-related tumours were observed in C3H/HeJ mice after skin applications of BA for lifetime (ECHA Dissemination, 2023; IARC, 1999).

In an extended one-generation reproductive toxicity study (OECD guideline 443) Sprague-Dawley rats received oral doses of 0, 20, 50 and 150 mg BA/(kg bw x d) by gavage. Test substance-related local microscopic changes were observed in the non-glandular stomach at all doses (ECHA Dissemination, 2023; Kemi, 2019). There was no evidence of reproductive toxicity at any dosage level based on evaluation of reproductive performance in the F0 generation and sperm measurements and oestrous cyclicity in the F0 and F1 generations (ECHA Dissemination, 2023).

In an inhalation developmental toxicity study, pregnant Sprague-Dawley rats exposed to 0, 25, 135 or 250 ppm BA for 6 h/d on gestation day 6 – 15 showed respiratory tract irritation and reduced body weight gain at ≥ 135 ppm. These concentrations also led to increased embryo lethality, but no teratogenic effect could be observed at any dose. The NOAEC for maternal toxicity and developmental toxicity was 25 ppm (135 mg/m^3) (DFG, 2007; ECHA Dissemination, 2023). In a further developmental inhalation toxicity study with pregnant Sprague-Dawley rats exposed to 0, 100, 200 or 300 ppm BA for 6 h/d on GD 6 – 20, the lowest test concentration of 100 ppm (530 mg/m^3) represented a NOAEC for developmental toxicity and a LOAEC for maternal toxicity. An oral developmental toxicity study with CD-1 mice provided a NOAEL for maternal and developmental toxicity of 1000 mg/(kg bw x d). A dose-dependent increase in the

incidence of malformations was recognised at 2500 and 3000 mg/(kg bw x d); such findings typically occur more frequently in mice under stress conditions (DFG, 2007). In rabbits, maternal toxicity (reduced weight gain) was observed at 400 mg/(kg bw x d) (only in range-finding study) but no embryotoxicity or teratogenicity (ECHA Dissemination, 2023; Kemi, 2019).

Rationale for starting point

The chronic inhalation toxicity study with rats (Reininghaus et al., 1991) is taken as the basis for the derivation of the EU-LCI. This study provided a LOAEC of 15 ppm (79.5 mg/m^3) but no NOAEC since adverse effects were observed down to the lowest applied concentration. A benchmark calculation for the incidence of reserve cell hyperplasia with loss of olfactory or ciliated cells in the nasal olfactory epithelium of male or female rats was performed. No satisfactory calculation was possible for the incidence in female rats. The calculated BMDL05 of 4.86 ppm for male rats is almost identical to the NOAEC obtained by the extrapolation from LOAEC to NOAEC using the standard assessment factor of three.

Rationale for assessment factors

The LOAEC of 15 ppm was chosen as POD. The following assessment factors are used:

- LOAEC to NOAEC: 3
- Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6
- Adjusted study length factor: 1
- Interspecies extrapolation: 2.5 (allometric scaling not performed since route of exposure is inhalation)
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 420 leading to a value of 79.5 mg/m^3: 420 = 0.189 mg/m^3 (rounded to 200 µg/m^3).

An EU-LCI value of 200 µg/m^3 is proposed for n-butyl acrylate.

According to Nagata (2003), n-butyl acrylate has a very low odour threshold 2.9 µg/m^3. It is expected that the odour will be perceived at the proposed EU-LCI value.

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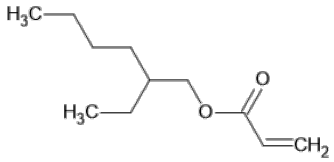
5 Toxicological evaluation of 2-ethylhexyl acrylate as basis for the derivation of an EU-LCI value

5.1 Substance identification

2-Ethylhexyl acrylate (EHA) belongs to the group of acrylic acid esters. The substance identification of EHA is shown in Table 29.

The toxicological data basis for EHA has been summarised and evaluated in a number reviews (DFG, 1997, 2007; ECB, 2005; ECHA Dissemination, 2023a; IARC, 1994, 2019; OECD SIDS, 2003).

Table 29: Substance identification of 2-ethylhexyl acrylate

Cas-No. EU-No. CLP-Index-No.	Systematic name, common name	Sum formula	Structural formula
103-11-7 203-080-7 607-107-00-7	2-ethylhexyl prop-2-enoate, 2-ethylhexyl acrylate, acrylic acid 2-ethylhexyl ester	$C_{11}H_{20}O_2$	

5.2 Substance properties and uses

The physicochemical properties of 2-ethylhexyl acrylate (EHA) are shown in Table 30. At room temperature, EHA is a colourless liquid which is only slightly soluble in water but soluble in most organic solvents (ECHA Dissemination, 2023b).

2-Ethylhexyl acrylate is a high production volume chemical that is produced worldwide. It is used as a plasticising co-monomer in the production of resins for pressure-sensitive adhesives, latex paints, reactive diluents and/or cross-linking agents, textile and leather finishes, and coatings for paper (IARC, 2019). The tonnage band in the EU is between 100000 and 1000000 tonnes/year (ECHA Dissemination, 2023a).

Table 30: Physicochemical properties of 2-ethylhexyl acrylate (ECHA Dissemination, 2023a)

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa)	Conversion 1 ppm = x mg/m³ (23 °C)	log pow	Solubility in water (mg/L)
184.28	-90	215	0.24 at 25 °C	7.6	ca. 4	9.6 at 25 °C

5.3 Exposure

5.3.1 Indoor air

Few data are available on measured concentrations of EHA in indoor air (Table 31). Hofmann and Plieninger (2008) could detect EHA in about 15 % out of 157 measurements but at low concentrations which did not exceed a maximum of 3 µg/m³. In a larger number of measurement data, the 95th percentile was reported to be below 1.0 µg/m³ (AGÖF, 2013).

Measurements of EHA residual monomers after painting with paints containing 940 ppm and 2000 ppm a room with restricted ventilation revealed room air peak concentrations of 2.5 ppm (19 mg/m^3) and 8 ppm (60.8 mg/m^3). EHA was not detectable 25 hours after painting (ECB, 2005).

Table 31: Data on the occurrence of 2-ethylhexyl acrylate in indoor air

Indoor	N	LoD (µg/m³)	N > LoD	Median (µg/m³)	P95 (µg/m³)	Maximum (µg/m³)	Source
Offices, homes, (pre)-schools, Germany	157	1.0	24 (15 %)	0.5	0.8	3	(Hofmann & Plieninger, 2008)
Indoor air (not further specified), Germany, 2006-2012	806	not reported		< 1.0	< 1.0	-	(AGÖF, 2013)

*: 90th percentile

5.4 Toxicokinetics

Studies on rats have indicated that short-chain acrylates in general are hydrolysed by carboxylesterases with the formation of acrylic acid and the corresponding alcohol. Using purified porcine liver carboxylesterase, the enzymatic hydrolysis of several acrylates was characterised to determine K_m and V_{max}-values. Increasing chain length of the alkyl group of the acrylate ester significantly affected the enzymatic hydrolysis. Butyl acrylate had a K_m value four times lower compared with that for ethyl acrylate, but at the same time, the V_{max} for butyl acrylate was about six times slower than the V_{max} of ethyl acrylate. Data on 2-ethylhexyl acrylate are not available (ECB, 2005).

The hydrolysis properties of a number of acrylate esters (methyl- (MA), ethyl- (EA), n-butyl- (n-BA), iso-butyl- (i-BA), t-butyl- (t-BA) and 2-ethylhexyl acrylates) were determined in liver S9 fraction and blood plasma of male Wistar rats *in vitro.* In liver S9 fraction, the half-lives for the degradation of acrylates and the formation of acrylic acid were 1.40, 0.84, 0.74 and 1.15 min for EA, n-BA, i-BA and EHA, respectively (no data for methyl acrylate, and due to steric hindrance by the butyl group, t-BA was not hydrolysed). Other *in vitro* data indicate that the hydrolysis of the acrylate esters in rat liver microsomes is mainly mediated by esterases. The degradation therefore takes place mostly via ester cleavage (ECHA Dissemination, 2023a).

The degradation times of alkyl acrylates in plasma were slower than in liver S9 fraction. The half-lives were 34.62, 8.45, 8.15, 6.48 min for MA, n-BA, i-BA and EHA, respectively (ECHA Dissemination, 2023a).

Acrylate esters are also expected to undergo conjugation with GSH to form thio compounds, with the main urinary conjugate identified as N-acetyl-S-(2-carboxyethyl)cysteine. There is no evidence to suggest that the vinyl moiety undergoes epoxidation (ECHA Dissemination, 2023a).

2-Ethylhexyl acrylate is believed to undergo carboxylesterase-catalysed hydrolysis to 2-ethyl-hexanol and acrylic acid, like other acrylate esters. To support this hypothesis, the metabolism of

^{14}C-2-ethylhexyl acrylate or ^{14}C-2-ethylhexanol were compared following a single gavage administration of equimolar doses (100 or 70.6 mg/kg body weight) of EHA and EH, respectively, in male rats. No ^{14}C-2-ethylhexyl acrylate could be detected in any blood samples. ^{14}C-2-ethylhexanol was the only major metabolite observed (ECHA Dissemination, 2023a).

After oral or i.p. administration of 14C-2-ethylhexyl acrylate (labelled on the vinyl carbons) to rats, the highest specific radioactivity was found three hours after i.p. administration in liver and kidneys, followed by spleen, lungs, brain, adipose tissue and blood. After oral dosing about 90 % was eliminated during the first 24 hours (50 % of the radioactivity as CO_2 via the expired air and 38 % via the urine). A small portion (about 1 % of the dose) was excreted via the faeces (ECB, 2005).

5.5 Health effects

5.5.1 Acute toxicity, sensory irritation, and local effects

Acute toxicity

Human data on the acute toxicity of EHA are not available.

The acute toxicity of 2-EHA in animal studies is low. Acute oral toxicity in rats is characterised by LD50 values of 4000-6000 mg/kg bw with clinical effects, e, g. decreased spontaneous motoric activity and ataxia. A dermal LD50 value > 10000 mg/kg is reported for rabbits (ECB, 2005).

LC50 values for inhalation toxicity are not available.

None of six rats exposed to saturated EHA vapour died within the 8-hour inhalation phase or within the 14-day postexposure observation period. Hyperactivity on removal from exposure chamber was documented, and gross pathology revealed nasal and ocular irritation (ECHA Dissemination, 2023a).

No mortality was observed after 30-min exposure of mice to 1130, 1226, or 7713 mg/m^3 EHA (probably vapour and aerosol). Clinical signs included incoordination, increased rate of respiration, and restlessness (ECHA Dissemination, 2023a).

Irritation

No data are available regarding local irritation or corrosion caused by 2-ethylhexyl acrylate in humans. 2-Ethylhexyl acrylate caused serious lesions to the skin of rabbits but the data basis indicates only mild eye irritation (ECB, 2005).

No data regarding sensory irritation of 2-ethylhexyl acrylate are available from controlled human studies. However, no evidence of sensory irritation was observed in a study in which volunteers were exposed with 2.5 ppm ethyl acrylate for four hours with a peak of up to 5 ppm (Hartwig & MAK Commission, 2018).

Animal studies with inhalation exposure demonstrate an irritating potential of the test substance. Quantitative data (RD50 values) are not available.

Sensitisation

Individual case reports were published on the allergenic effect of 2-ethylhexyl acrylate on human skin with positive results in the epicutaneous test. However, no sensitisation could be detected in occupational medical examinations, and only a low sensitisation rate was determined in retrospective studies. As more detailed information on the extent of exposure is lacking, the sensitising effect in humans cannot be clearly assessed and the positive reactions

described in the epicutaneous test to 2-ethylhexyl acrylate may therefore be partly an expression of an immunological cross-reaction (DFG, 2007).

A weak dermal sensitisation potential was observed in a local Lymph node assay (LLNA) in mice (EC3 = 18.96 %). Various former tests with guinea pigs, with and without adjuvants, also provided evidence that 2-ethylhexyl acrylate is a skin sensitiser (DFG, 2007).

5.5.2 Repeated dose toxicity

Human data

No relevant data were available.

Animal data

In a subchronic inhalation toxicity study, Wistar rats (10 M + 10 F/group) were exposed "whole body" to 0, 10, 30, and 100 ppm 2-ethylhexyl acrylate vapour (0, 76, 230, 760 mg/m^3) for 6 h/d, 5 d/week for 13 weeks. The study was conducted in accordance with the then current version of OECD Guideline 413 (lung tissues were not perfused, and laryngopharynx was not examined) (ECHA Dissemination, 2023a).

There were no treatment-related premature deaths. Clinical signs at the high and mid concentration were lethargy and ptosis during exposure. Body weight gain and body weight (males only) at termination of the study were lower at the highest concentration. Clical-chemical parameters altered were ALAT and alkaline phosphatase (elevated in high dose females), total protein, albumin and glucose (lowered at the highest concentration in males and females). Reduced protein and albumin values were also seen in males and females at 30 ppm. Organ weight changes included reduced absolute liver weight in high dose males and relative adrenal weights in high dose males and females. The reduced body weight gain and the effects on clinical-chemical parameters as well as a reduced lipid accumulation in liver cells were assumed to be induced by a lower food consumption possibly resulting from the irritation effect on the respiratory tract of exposed animals (ECHA Dissemination, 2023a).

Local effects were observed in the nasal epithelia. Microscopic examination revealed focal or diffuse degeneration of the olfactory epithelium of the cranial nasal cavity in animals of both sexes at ≥ 30 ppm. All rats at 100 ppm showed degeneration of the olfactory mucosa in the anterior part of the nasal cavity. The incidence of degeneration of the olfactory mucosa but not the severity was increased in mid dose rats. Degeneration of the olfactory epithelium was characterised by a reduction of cell layers, reduction or loss of apical cytoplasmic structures such as olfactory knobs and microvilli, and by necrosis. EHA induced no lesions of the trachea and the lungs, data of the pharynx/larynx were not available. No treatment-related lesions of the nasal cavity or otherwise were diagnosed at 10 ppm. The NOAEC for local effects on the respiratory tract was 10 ppm (76 mg/m^3), and the NOAEC for systemic toxic effects was 30 ppm (230 mg/m^3) (ECHA Dissemination, 2023a).

Initial loss of body weight, lethargy and laboured breathing were observed in rats (2 M + 2 F/group, strain not specified) exposed against an atmosphere saturated with 2-ethylhexyl acrylate vapour (about 130 ppm) 6 h/d, 5 d/week for 13 days. No such effects were observed at 50 ppm (DFG, 2007; ECHA Dissemination, 2023a).

Small groups of Wistar rats (2 M + 2 F/group) were exposed by inhalation to vapour concentrations of 0, 10, 30, and 100 ppm (0, 75, 230, 760 mg/m^3) 6 h/d, 5 d/week for 90 days. No evidence was observed of peroxisome proliferation in the liver (DFG, 2007).

5.5.3 Genotoxicity and carcinogenicity

Genotoxicity

Three *in vitro* gene mutation studies in bacteria (Ames test) with 2-ethylhexyl acrylate are negative, both in the absence or presence of exogenous metabolic activation system (ECHA Dissemination, 2023a).

The MAK commission summarised the available data basis with tests on mammalian cells *in vitro* as follows (DFG, 2007):

No increased frequency of sister chromatid exchanges (SCE) was observed in CHO cells in the absence of metabolic activation. In the presence of metabolic activation, an increased SCE frequency was observed at high concentrations, but the effect was not concentration-dependent. A questionable stimulation of unscheduled DNA synthesis was reported in rat hepatocytes, a weakly positive result was obtained at only one concentration. No mutagenic effect was noted in a HPRT gene mutation test on CHO (Chinese Hamster Ovary) cells with and without exogenous metabolic activation system. Thymidin kinase assays (TK+/- gene mutation test) with mouse lymphoma cells provided no consistent results: one test was negative without metabolic activation and gave a questionable positive result with metabolic activation. Another test showed a weak increase (factor 1.6 – 1.9) in mutant frequencies without metabolic activation but only in the range of strong cytotoxicity and with no clear dependence. A weak induction of chromosomal aberrations was also demonstrated in this study but again at cytotoxic concentrations and without clear dose-response relationship. In a parallel experiment, no induction of micronuclei was observed (DFG, 2007).

Overall, the available studies showed that 2-ethylhexyl acrylate has a weak genotoxic potential *in vitro*, with the data suggesting a clastogenic effect. However, the results were negative at concentrations with no or only weak cytotoxicity (DFG, 2007).

In vivo, no genotoxic potential of 2-ethylhexyl acrylate could be demonstrated. 2-ethylhexyl acrylate did not induce an increase in DNA repair synthesis in rat hepatocytes following oral treatment (1000 or 2000 mg/kg bw) in an UDS test conducted in accordance with OECD test guideline 486. No induction of chromosomal aberrations were observed in the bone marrow of mice after either a single or a 5-day oral application of a systemically toxic dose (250, 1000, or 2500 mg/kg bw) (DFG, 2007).

Overall, the available data for alkyl (methyl, ethyl, butyl, and 2-ethylhexyl) acrylates indicate that acrylate monomers are not genotoxic *in vivo*, and that positive findings *in vitro* are typically observed at cytotoxic concentrations (Suh et al., 2018).

Carcinogenicity

No carcinogenicity studies with inhalation exposure against 2-ethylhexyl acrylate are available.

Other alkyl acrylates were not carcinogenic in inhalation studies with chronic exposure of rats (methyl and butyl acrylate) or rats and mice (ethyl acrylate) (DFG, 2007).

2-Ethylhexyl acrylate was negative in a cell transformation assay with C3H-10T1/2 fibroblasts at concentrations of 1–30 µl/l (DFG, 2007).

The results of studies with dermal exposure of mice were summarised in the EU Risk Assessment Report for 2-ethylhexyl acrylate (ECB, 2005): EHA induced skin tumours in mice at concentrations which were highly irritative. A lower concentration of 2.5 % EHA which caused only transient irritation showed no tumour response of the skin. Other long-term studies on different mouse strains did not confirm tumour induction of the mouse skin. Additionally, there

is no concern from tumour data of acrylic acid and 2-ethylhexanol, the hydrolysis products of EHA. Furthermore, taking into account the negative results from *in vivo* genotoxicity studies, induction of sin tumours by EHA is likely via non-genotoxic mechanisms. It was concluded, that tumour growth is associated with the highly irritative properties of EHA. Due to the limited reliability of skin painting studies in mice as a tool to identify the carcinogenic potential of a test substance, these studies give some concern but no clear evidence that EHA has carcinogenic potential (ECB, 2005).

5.5.4 Toxicity to reproduction

The draft report of an Extended One-Generation Reproduction Toxicity Study (EOGRT according to OECD TG 443) is available. Wistar rats (25 M + 25 F/group) received food containing 0, 1500, 5000 and 12500 ppm 2-ethylhecyl acrylate (males: 0, 119, 357, 998 mg/(kg bw x d), females: 0, 135, 453, 1136 mg/(kg bw x d)). F0 animals were treated at least for 10 weeks prior to mating to produce a litter (F1 generation). Mating pairs were from the same dose group. Pups of the F1 litter were selected (F1 rearing animals) and assigned to 2 different cohorts (1A and 1B) which were subjected to specific postweaning examinations. The study was terminated with the terminal sacrifice of the F1 rearing animals of cohort 1A (ECHA Dissemination, 2023a).

There were no test substance-related mortalities or adverse clinical observations noted in any of the treatment groups in the F0 parental animals and F1 offspring. Body weights and body weight change of the high-dose male F0 and F1 rats were consistently and, in many parts of the study significantly, below the concurrent control across all cohorts and study periods, including terminal body weight. Female F0 and F1 rats were less sensitive, significant body weight decreases were limited to single episodes during the study. Regarding pathology, target organs were the glandular stomach and the kidneys. An increased number of foci correlated to an increased number of erosions/ulcers histologically detected in the glandular stomach was detected in the glandular stomach of high-dose F0 and F1A females. In high-dose males of all groups an increased incidence of minimal to mild basophilic tubules was detected in the kidneys.

There were no indications from clinical examinations as well as gross and histopathology that EHA adversely affected the fertility or reproductive performance of the F0 parental animals up to and including the administered high concentration of 12500 ppm. A concentration of 12500 ppm was associated with statistically significantly reduced numbers of implants, which subsequently caused a smaller average litter size in F1 offspring of the high-dose group. It is likely that the relatively high implantation number and litter size in control caused a statistical difference to the high-dose number. Overall, no toxicological relevance is assumed for this apparent finding. No test substance-induced signs of developmental toxicity were noted at any concentration. Postnatal survival as well as post-weaning development of the offspring in all treatment groups until puberty remained unaffected by the test substance. Measurement of thyroid hormones revealed no consistent adverse effects caused by the test substance in the F0 and F1 adult animals as well as the F1 preweaning offspring. Neither the anogenital distance/index nor the percentage of male pups showing presence of nipples/areolas revealed any test substance-related effects. A minimal delay in vaginal opening in high-dose F1-offspring is considered as unspecific minimal delay of general development and of no toxicological relevance. The NOAEL for general, systemic toxicity is 5000 ppm in the F0 parental and the F1 adolescent/adult rats, based on evidence for local toxicity in the gastrointestinal tract. The NOAEL for fertility, reproductive performance and developmental toxicity is 12500 ppm, the highest dose tested (ECHA Dissemination, 2023a).

Pregnant New-Zealand White Rabbits (23 – 25/group) were exposed whole-body against 0, 50, 75, or 100 ppm 2-ethylhexyl acrylate (0, 380, 570, 760 mg/m^3) 6 h/d, during GD6-20. Based on

slightly reduced food intake and lower maternal weight gain at the higher exposure level a NOAEC for maternal toxicity of 75 ppm (570 mg/m^3) is derived from this study. No embryo- or foetotoxic effects were observed (NOAEC for developmental toxicity: 100 ppm (760 mg/m^3)) (ECHA Dissemination, 2023a).

The draft report of an oral developmental toxicity study with New Zealand White Rabbits is available. Pregnant rabbits (25/group) received 2-ethylhexyl acrylate in food leading to delivered doses of approximately 0, 39, 119 or 191 mg/(kg bw x d) on GD6-29. The LOAEL for maternal toxicity is 119 mg/(kg bw x d), based on evidence indicative of maternal toxicity (food refusal because of stomach irritation) at the highest dose. There was no evidence for treatment-related adverse effects of the test substance on foetal morphology (NOAEL: 191 mg/(kg bw x d, the highest dose tested) (ECHA Dissemination, 2023a).

5.5.5 Odour perception

The odour of EHA is described as "pleasant" (no further details) (HSDB, 2004). No data are available for an odour threshold for EHA using the triangle odour bag method (Nagata, 2003). For the related acrylate compounds methyl acrylate, ethyl acrylate-, n-butyl acrylate, and isobutyl acrylate very low odour thresholds were reported of 0.0035 ppm, 0.00026, 0.00055, and 0.00090 ppm, respectively (Nagata, 2003).

Odour thresholds between 0.5497 and 1.3554 mg/m^3 (0.072 and 0.178 ppm) were reported for EHA (ECB, 2005; Ruth, 1986). These values must be doubted as probably too high in view of the much lower thresholds reported by (Nagata, 2003) for other acrylate esters.

5.6 Evaluation

5.6.1 Existing regulations and classifications

There is no harmonised classification for 2-ethylhexyl acrylate regarding carcinogenicity, mutagenicity, or toxicity for reproduction. The substance is classified (harmonised classification) as irritating to the skin (Skin Irrit 2, H315), as skin sensitising (Skin Sens. 1, H317) and irritating to the respiratory tract (STOT SE 3, H335) (ECHA C&L Inventory, 2023).

The IARC evaluated EHA in 2019. Based on *inadequate evidence* in humans for the carcinogenicity of 2-ethylhexyl acrylate, and *sufficient evidence* in experimental animals for the carcinogenicity of 2-ethylhexyl acrylate, overall, 2-ethylhexyl acrylate is *possibly carcinogenic to humans* (group 2B) (IARC, 2019). The evidence in experimental animals is based on three skin application studies in male mice; there were no studies available with oral or inhalation exposure of experimental animals.

Existing guide values for 2-ethylhexyl acrylate in air are summarised in Table 32 and Table 33.

No DNEL for the general population or for workers were derived. The registration dossier states that the monomer 2-ethylhexyl acrylate is not intended to be used as such or in a mixture in consumer products (ECHA Dissemination, 2023a). No further explanation is provided.

Table 32: Guide values for 2-ethylhexyl acrylate, part I (for explanation, see text)

Guide value Parameter/Organisation	(ECHA Dissemination, 2023a)	(AGBB, 2021)
Name	DNEL (chronic, general population)	NIK value
Value (mg/m³)	-	0.380
Organ/critical effect		
Species		
Basis		
Adjusted for cont. exposure	-	
Extrapolation factors Time LOAEC to NAEC Interspecies Intraspecies Route-to-route Total		
Remarks	No value derived („no hazard identified“)	Adoption of (ascribed) EU-LCI value

The MAK-value of 10 ppm is based on the NOAEC for nasal epithelial lesions obtained in a subchronic inhalation toxicity study with rats (see chapter 5.5.2). Regarding the mode of action (MoA), the MAK commission stated in the rationale that from the data on the activity of carboxylesterase in the respiratory and olfactory epithelium of humans, cynomolgus monkeys and F344 rats, measured with ethyl acrylate as substrate, it can be concluded that ester cleavage in the olfactory epithelium of rats is much faster than in humans and monkeys. Data on the cleavage of 2-ethylhexyl acrylate are lacking. However, since the long-chain dimethyl esters of succinic, glutaric and adipic acid are also cleaved faster in the olfactory epithelium of rats than in the olfactory epithelium of humans and the same finding was also obtained for methyl methacrylate, a similar species difference should also be expected for 2-ethylhexyl acrylate. Acrylic acid was considered crucial for the development of nasal lesions in rats caused by acrylates. The commission assumed that the human olfactory epithelium is less exposed with acrylic acid from acrylate esters than that of the rat and that the NOAEC of the rat for 2-ethylhexyl acrylate can be adopted without any further safety margin when determining the MAK value for 2-ethylhexyl acrylate (DFG, 2007). This contrasts with the MoA described in the rationale of the MAK commission for butyl acrylate where it is stated that not the formation of acrylic acid is crucial but the reaction of the short-chain acrylate esters with nucleophilic compounds such as glutathione (see chapter 4.6.1).

Table 33: Guide values for 2-ethylhexyl acrylate, part II (for explanation, see text)

Guide value Parameter/ Organisation	(ECHA Dissemination, 2023a)	(DFG, 2007)
Name	DNEL (chronic, workers)	MAK value (workplace)
Value (mg/m³)	-	38 (5 ppm)
Organ/critical effect		
Species		Rat
Basis		NOAEC: 10 ppm
Adjusted for cont. exposure		-
Extrapolation factors Time NOAEC to NEC Interspecies Intraspecies Route-to-route Total		
Remarks	No value derived („no hazard identified“)	

5.6.2 Derivation of an EU-LCI value

The subchronic inhalation toxicity study with rats (chapter 5.5.2) is taken as the basis for the derivation of the EU-LCI. In that study, local effects were observed in the nasal epithelia. Microscopic examination revealed focal or diffuse degeneration of the olfactory epithelium of the cranial nasal cavity in animals of both sexes at ≥ 30 ppm. The NOAEC for local effects on the respiratory tract was 10 ppm (76 mg/m^3), and the NOAEC for systemic toxic effects was 30 ppm (230 mg/m^3) (ECHA Dissemination, 2023a).

The following assessment factors are used:

- Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6
- Adjusted study length factor (subchronic study): 2
- Interspecies extrapolation: 2.5 (allometric scaling not performed since route of exposure is inhalation)
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 280 leading to a value of 76 mg/m^3: 280 = 0.271 mg/m^3 (rounded to 250 µg/m^3).

(Note: On a molar basis, the non-rounded values for EHA and n-butyl acrylate (see chapter 4.6.2) are identical, i. e. 35.7 ppb for both substances).

An EU-LCI value of 250 µg/m³ is proposed for 2-ethylhexyl acrylate.

It should be expected that the odour of 2-ethylhexyl acrylate (see chapter 5.5.5) will be perceived at the proposed EU-LCI value.

5.7 List of References

The links listed in the bibliography were last checked and confirmed on 2. May 2024.

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E Appendix

E.1 Data collection and fact sheet for 2-ethylhexyl acrylate

Table 34: Data collection sheet for 2-ethylhexyl acrylate (EHA)

Compound	**2-Ethylhexyl acrylate**	**Data collection sheet**	
N° CAS: 103-11-7 1 ppm = 7.6 mg/m³ at 23 °C	**EU-Classification:** **CLP, harmonised classification:** H315: irritating to the skin, H317: Skin Sens. 1, H335: irritating to the respiratory tract		
Organisation name	**REACH registrant**	**AgBB**	**DFG**
Risk value name	DNEL (general population and workers)	NIK ('Lowest Concentration of Interest')	MAK value (workplace)
Risk value (mg/m³)	not derived	0.380	38
Reference period			Chronic (workplace)
Risk value (mg/m³) Short term (15 min)			38
Year		2021	2007
Key study		see below	BASF AG (1989
Study type			Subchronic inhalation toxicity study
Species			Rat, Wistar (n = 10 M + 10 F/group)
Duration of exposure in key study			6 h/d, 5 d/week, 13 weeks
Critical effect			Nasal epithelial lesions (degeneration of the olfactory epithelium)
Critical dose value			NOAEC: 76 mg/m³
Adjusted critical dose			
Single assessment factors			
Other effects			

Compound	2-Ethylhexyl acrylate	Data collection sheet	
Remarks	No value derived ("no hazard identified")	Adopted ascribed EU-LCI-value	The MAK-commission assumed that the human olfactory epithelium is less exposed with acrylic acid from acrylate esters than that of the rat and that the NOAEC of the rat for EHA can be adopted without any further safety margin when determining the MAK value for EHA

Table 35: Fact sheet for 2-ethylhexyl acrylate (EHA)

Compound	2-Ethylhexyl acrylate C11H20O2		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	250
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2024
General information			
CLP-Index No.	4	INDEX	607-107-00-7
EC-No.	5	EINECS	203-080-7
CAS-No.	6	Chemical Abstract Service number	103-11-7
Harmonised CLP classification	7	Human health risk related classification	H315, H335, H317
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	184.28 1 ppm = 7.6 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	ECHA Dissemination (2023)
Read across compound	10	Where applicable	-
Species	11	Rat, human, etc.	Rat, Sprague-Dawley
Route / type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic, etc.	Subchronic (13 weeks)
Exposure duration	14	h/d, d/w	6 h/d, 5 d/week
Critical endpoint	15	Effect (s), site of	Degeneration of the olfactory epithelium
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEC
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	10 ppm (76 mg/m³)
Assessment factors (AF)			
Adjustment for exposure duration	19	Study exposure h/d, d/w	5.6
Study length	20	sa→sc→c	2
Route-to-route extrapolation factor	21	-	-

Compound	2-Ethylhexyl acrylate C11H20O2		Fact sheet
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	1
	22b	Severity of effect (R8 6d)	1
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	1
	23b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		
Other adjustment factors Quality of database	26	Quality of database	1
Results			
Summary of assessment factors	27	Total Assessment Factor	280
POD/TAF	28	Calculated value [µg/m³ and ppb]	271 µg/m³ (35.7 ppb)
Molar adjustment factor	29		
Rounded value	30	[µg/m³]	250
Additional comments	31		
Rationale selection	32		

Rationale for critical effects

The acute toxicity of 2-ethylhecyl acrylate (EHA) in animals is low. LD50 values of 4000 – 6000 mg/kg bw were determined in rats. None of six rats exposed to saturated EHA vapour died within the 8-hour inhalation phase or within the 14-day postexposure observation period. Hyperactivity on removal from exposure chamber was documented, and gross pathology revealed nasal and ocular irritation (ECB, 2005; ECHA Dissemination, 2023a).

No data regarding sensory irritation of EHA are available from controlled human studies. However, no evidence of sensory irritation was observed in a study in which volunteers were exposed with 2.5 ppm ethyl acrylate for four hours with a peak of up to 5 ppm (Hartwig und MAK Commission, 2018). Animal studies with inhalation exposure demonstrate an irritating potential of the test substance. Quantitative data (RD50 values) are not available.

EHA led to serious lesions to the skin of rabbits, other data indicates only mild eye irritation. The allergenic effect of EHA on human skin with positive results in the epicutaneous test was mentioned in individual case reports. As more detailed data is missing, it is not possible to clearly assess the sensitising effect in humans. Dermal sensitisation tests in animals provided evidence that EHA is a skin sensitiser (DFG, 2007; Hartwig und MAK Commission, 2018).

Relevant repeated dose toxicity studies with EHA in humans are not available.

In a subchronic inhalation toxicity study, Wistar rats were exposed "whole body" to 0, 10, 30, and 100 ppm EHA vapour (0, 76, 230, 760 mg/m^3) 6 h/d, 5 d/week for 13 weeks. The study was conducted in accordance with the then current version of OECD Guideline 413. Local effects in the nasal epithelia were reported. These included focal or diffuse degeneration of the olfactory epithelium of the cranial nasal cavity in animals of both sexes above 30 ppm. Degeneration of the olfactory mucosa in the anterior part of the nasal cavity was observed in all rats at 100 ppm. In mid-dose rats the incidence of degeneration of the olfactory mucosa but not the severity was increased. No treatment-related lesions of the nasal cavity or otherwise were diagnosed at 10 ppm. A NOAEC for local effects of 10 ppm (76 mg/m^3) and a NOAEC for systemic toxic effects of 30 ppm (230 mg/m^3) could be identified in the study (ECHA Dissemination, 2023).

Regarding genotoxicity, no such effects of EHA were observed *in vitro* in studies with bacteria. Studies with mammalian cells *in vitro* provided variable results, indicating a weak genotoxic potential, i. e. a clastogenic effect. However, the results were negative at concentrations with no or only weak cytotoxicity (DFG, 2007). *In vivo,* no genotoxic potential of EHA could be demonstrated. Overall, the available data for EHA and other related alkyl (methyl, ethyl, butyl) acrylates indicate that acrylate monomers are not genotoxic *in vivo,* and that positive findings *in vitro* are typically observed at cytotoxic concentrations (Suh et al., 2018).

Carcinogenicity studies with inhalation or oral exposure against EHA are not available. Other alkyl acrylates were not carcinogenic in inhalation studies with chronic exposure of rats (methyl and butyl acrylate) or rats and mice (ethyl acrylate) (DFG, 2007). EHA induced skin tumours in mice at concentrations which were highly irritative; at lower concentrations, only transient irritation but no tumour response of the skin could be observed. Other long-term studies on different mouse strains did not confirm tumour induction of the mouse skin. Taking into account the negative results from *in vivo* genotoxicity studies, the induction of skin tumours by EHA is likely via non-genotoxic mechanisms, and tumour growth is associated with the highly irritative properties of EHA (ECB, 2005). Based on skin application studies in mice, the IARC concluded that there is sufficient evidence in experimental animals but inadequate evidence in humans for the carcinogenicity of EHA. Overall, IARC concluded that EHA is possibly carcinogenic to humans (IARC, 2019).

An extended one-generation reproduction toxicity study according to OECD TG 443 with rats exposed to EHA via food provided a NOAEL of 5000 ppm (males: 357 mg/(kg bw x d), females: 453 mg/(kg bw x d)) for general toxicity, based on evidence for effects in the gastrointestinal tract. The NOAEL for fertility, reproductive performance and developmental toxicity was 12500 ppm (males: 998 mg/(kg bw x d), females: 1136 mg/(kg bw x d)), the highest concentration in food tested (ECHA Dissemination, 2023).

Rationale for starting point

The subchronic inhalation toxicity study with rats is taken as the basis for the derivation of the EU-LCI. In that study, local effects were observed in the nasal epithelia. Microscopic examination revealed focal or diffuse degeneration of the olfactory epithelium of the cranial nasal cavity in animals of both sexes at ≥ 30 ppm. The NOAEC for local effects on the respiratory tract was 10 ppm (76 mg/m^3), and the NOAEC for systemic toxic effects was 30 ppm (230 mg/m^3) (ECHA Dissemination, 2023).

The NOAEC of 10 ppm (76 mg/m^3) for local effects is used as POD for the derivation of an EU-LCI value.

Rationale for assessment factors

The following assessment factors are used:

- Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6
- Adjusted study length factor (subchronic study): 2
- Interspecies extrapolation: 2.5 (allometric scaling not performed since route of exposure is inhalation)
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 280 leading to a value of 76 mg/m³: 280 = 0.271 mg/m³ (rounded to 250 µg/m³).

An EU-LCI value of 250 µg/m³ is proposed for 2-ethylhexyl acrylate.

No reliable odour threshold value could be identified for EHA. In view of the low odour thresholds for other alkyl acrylates, it should be expected that the odour of 2-ethylhexyl acrylate will be perceived at the proposed EU-LCI value.

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