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Toxicological basic data for the derivation of EU-LCI values for 1,4-cyclohexane dimethanol, 3-methoxybutanol, 1,2-propylene glycol n-propyl ether, methyl formate and butyl formate

Final report

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Toxicological basic data for the derivation of EU-LCI values for 1,4-cyclohexane dimethanol, 3-methoxybutanol, 1,2-propylene glycol n-propyl ether, methyl formate and butyl formate

Final report

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Abstract: Toxicological basic data for the derivation of EU-LCI values for 1,4-cyclohexane dimethanol, 3-methoxybutanol, 1,2-propylene glycol n-propyl ether, methyl formate and butyl formate

The subject of this report is the preparation of substance reports for the derivation of EU-LCI values for the substances mentioned in the title of this report. 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) from the varying evaluation lists of emissions from 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 has 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 (Voss et al., 2017; 2018; 2020).

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 (2017) Toxicological basic data for the derivation of EU LCI values for triethylamine (CAS No. 121-44-8), tributyl phosphate (CAS No. 126-73-8), triethyl phosphate (CAS No. 78-40-0), methyl methacrylate (CAS No. 80-62-6), and ethyl methyl ketone (CAS No. 78-93-3). German Environment Agency, Berlin, Germany

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

Gegenstand des Berichts ist die Erstellung von Stoffberichten für die Ableitung von EU-LCI-Werten für die im Titel genannten Stoffe. 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 "The EU-LCI Working Group" 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 (Voss et al., 2017; 2018; 2020).

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

3MB	3-Methoxy-butan-1-ol
3MMB	3-Methoxy-3-methylbutan-1-ol
ACGIH	American Conference of Governmental Industrial Hygienists
AgBB	Ausschuss zur gesundheitlichen Bewertung von Bauprodukten (Committee for Health-related Evaluation of Building Products)
CAS	Chemical abstract service
CLP	Classification, labelling and packaging
CNS	Central nervous system
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation)
DNEL	Derived no effect level
DPGPE	dipropylene glycol mono propyl ether
ECHA	European Chemicals Agency
EU	European Union
F	Female(s)
GD	Gestation day
GLP	Good laboratory practice
ICR	Institute for Cancer Research
IUPAC	International union of pure and applied chemistry
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)
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 mono methyl ether
PGnPE	Propylene glycol n-propyl ether
PND	Postnatal day
REACH	Registration, evaluation, authorization and restriction of chemicals
SCOEL	Scientific Committee on Occupational Exposure Limits

Summary

Substance profile and EU-LCI value for 1,4-cyclohexanedimethanol

1,4-Cyclohexanedimethanol (CHDM) is a colourless, water-soluble solid at room temperature with a faint hydrocarbon-like odour. No natural sources are known. CHDM is a large-scale technical product used in the production of polyester resins in coatings, but also in the manufacture of cosmetic products. The technical product consists of about 70 % trans-CHDM and 30 % cis-CHDM; all available toxicological studies have been carried out with this technical mixture.

No data are available on the occurrence of CHDM in indoor air or other compartments.

Toxicokinetic or toxicological findings in humans are not available.

In a toxicokinetic study with oral administration of ^{14}C-CHDM to rats, the substance was rapidly and nearly completely absorbed and largely eliminated via the kidneys as metabolites within 48 h (89 - 96 %). Cyclohexanedicarboxylic acid was identified as main metabolite (68 %), followed by 4-hydroxymethylcyclohexanoic acid (31 %) and small amounts (< 2 %) of unidentified metabolites. A maximum of 3 % of the administered ^{14}C activity was excreted with the faeces and only traces in the exhaled air.

The acute toxicity of CHDM is low. No clinical signs or systemic toxicity were observed in rats during or after inhalation of 1250 mg CHDM/m^3 for 6 h. However, concentrated solutions of CHDM are severely irritant to the eyes.

In a subchronic oral toxicity study following OECD guideline 408, reductions in mean body weights, body weight gains, and/or feed consumption, and haematuria were the main systemic adverse effects after exposure of Sprague-Dawley rats with CHDM in drinking water for 90 days. The NOAELs of the study were considered to be 479 mg/(kg bw x d) for males and 754 mg/(kg bw x d) for females.

CHDM was not genotoxic *in vitro* in assays with bacteria (Ames test) and did not induce chromosomal aberrations in mammalian cells. Also *in viv*o, no clastogenic activity in bone marrow was observed in rats and in a micronucleus assay with mice. Carcinogenicity studies with CHDM are not available. The available data on genotoxicity and from repeated dose toxicity studies do not provide evidence for concern regarding carcinogenic effects of CHDM.

A developmental toxicity study with rats provided a NOAEL for maternal toxicity of 300 mg/(kg bw x d) and a higher NOAEL for developmental toxicity of 1000 mg/(kg bw x d). In a similar study with rabbits, a NOAEL of 200 mg/(kg bw x d) was obtained for maternal toxicity. At higher concentrations, the dams suffered from severe local effects with gastric erosions and ulceration; however, no developmental toxicity was observed up to the highest tested dose level of 400 mg/(kg bw x d).

The NOAEL of 479 mg/(kg bw x d) obtained in the subchronic oral (drinking water) toxicity study with CHDM in rats is used as POD for the derivation of an EU-LCI value. The results of the toxicokinetic study with CHDM in rats indicate that the substance is nearly completely absorbed after oral exposure. Absorption after inhalation is, in the absence of experimental data, assumed to be complete by default. Thus, no factor to account for differences in absorption after oral or inhalation exposure will be considered, and the following assessment factors are used for the derivation:

- Route-to-route extrapolation (rats): 1.15 m^3 (kg bw x d)
- Adjusted study length factor (subchronic exposure study): 2
- Allometric scaling: already included in route-to-route extrapolation
- Interspecies extrapolation: 2.5
- Intraspecies extrapolation: 10

Total assessment factor: 50 x 1.15 = 57.5 m^3 (kg bw x d). This leads to a concentration of 479 mg/(kg bw x d) : 57.5 m^3 (kg bw x d) = 8.330 mg/m^3.

The proposed value is based on a NOAEL for systemic effects observed in a study with oral exposure of rats. The data basis is not sufficient to derive an EU-LCI value for CHDM on the basis of inhalation toxicity data. However, no signs of respiratory irritation have been noted in rats in a short-term (10 day) inhalation study at 1000 – 3000 mg CHDM/m^3, i.e., at more than 100fold higher concentrations, indicating that acute respiratory irritation is unlikely at the proposed EU-LCI value.

Comparisons with the effects of two other glycols, i.e., ethylene glycol and propylene glycol, indicate that long-term local respiratory effects do not seem to be of concern in the absence of short-term local effects following inhalation. A similar conclusion can be drawn for the glycol CHDM.

An EU-LCI value for 1,4-cyclohexanedimethanol (CHDM) of 8300 $\mu g/m^3$ is proposed.

Since no odour threshold is available for CHDM, no conclusions can be drawn regarding olfactory perception of the substance at the proposed EU-LCI.

Substance profile and EU-LCI value for 3-methoxybutan-1-ol

3-Methoxybutan-1-ol (3MB) is a colourless, water-soluble liquid at room temperature with a mild odour. No natural sources are known. Technical 3MB is the racemate of the two enantiomers; no toxicity data are available for the individual isomers. 3MB may be used in adhesives and sealants, coating products and paint removers. However, very few measurements of 3MB concentrations are available for indoor air. According to these data, concentrations around 2 - 4 $\mu g/m^3$ (median values) with up to about 70 $\mu g/m^3$ (95^{th} percentile) could be detected.

Toxicokinetic data for 3MB are not available. Glycol ethers such as 3MB are known to be generally well absorbed orally, after inhalation and via the skin. The metabolism of glycol ethers follows two main oxidative pathways. One pathway involves oxidation by microsomal cytochrome P450 monooxygenases at the ether bond via O-dealkylation. In case of 3MB, this will lead to production of the corresponding glycol, i.e., 1,3-butanediol, which is further oxidised in the body with the formation of 3-hydroxybutanoic acid and acetoacetic acid. Both of these are known as “ketone bodies” and represent normal products in the intermediary metabolism of humans. The other pathway of glycol ether metabolism involves oxidation of the unchanged compound by alcohol dehydrogenase and further oxidation by aldehyde dehydrogenase with the formation of alkoxyalkanoic acids, i.e., 3-methoxybutanoic acid in case of 3MB.

The acute toxicity of 3MB is low. In older studies, inhalation exposure of cats, rabbits and guinea pigs to 3MB-saturated air (about 6200 mg/m^3) for up to 6 h led to slight irritation of mucous membranes and to drowsiness in one cat after 6 h. 3MB was not irritating to the skin in a guideline study with rabbits and mildly irritating to the eyes.

In a combined oral dose toxicity and reproductive developmental toxicity study (OECD guideline 422) with exposure of Sprague-Dawley rats by gavage, haematology and blood chemistry tests showed some slight changes of several parameters at 1000 mg/(kg bw x d). A NOAEL of 300 mg/(kg bw x d) can be obtained from this study.

Read-across data are available from studies with repeated exposure of rats to 3-methoxy-3-methylbutan-1-ol (3MMB). This substance differs from 3MB by the presence of an additional 3-methyl group. In a subacute inhalation study with 3MMB, no local or toxicological relevant systemic changes were observed in Sprague-Dawley rats after whole-body exposure with up to 500 ppm 3MMB 4h/day, 5d/week for a total of 20 exposures. A subchronic oral toxicity study in rats with 3MMB provided a NOAEL of 250 mg/(kg bw x d) and a LOAEL for systemic toxicity of 1000 mg/(kg bw x d), based on slight changes in haematological and clinical chemical parameters.

3MB and its acetate ester were not genotoxic *in vitro* bacteria and mammalian cells. Carcinogenicity studies with 3MB are not available, but the lack of structural alerts and negative genotoxicity results provide sufficient information to indicate that the substance is unlikely to be carcinogenic or mutagenic.

No reproductive toxicity of 3MB was observed in rats in the combined oral dose toxicity and reproductive developmental toxicity study mentioned above at up to 1000 mg/(kg bw x d), the highest concentration tested. Also, no developmental toxicity was observed in rats in a study after oral exposure to 1000 mg 3-methoxybutyl acetate/(kg bw x d). Studies with 3MMB revealed slight skeletal variations at a maternally toxic dose of 2000 mg/(kg bw x d) but not at 1000 mg/(kg bw x d).

The NOAEL of 300 mg/(kg bw x d) obtained in the combined oral dose toxicity and reproductive developmental toxicity study is considered a suitable key study for the derivation of an EU-LCI value for 3MB. The following assessment factors are used for the derivation:

- Route-to-route extrapolation (rats): 1.15 m^3 (kg bw x d)
- Adjusted study length factor (subchronic exposure study): 2
- Allometric scaling: already included in route-to-route extrapolation
- Interspecies extrapolation (systemic effects): 2.5
- Intraspecies extrapolation (interindividual variability, general population): 10
- Quality of whole database (limited data base, limited read-across): 3

Total assessment factor: 172.5 m^3 (kg bw x d). This leads to a concentration of 300 mg/(kg bw x d) : 172.5 m^3 (kg bw x d) = 1.739 mg/m^3.

A read-across with data from the oral subchronic toxicity study with 3MMB provides support for the conclusion that the proposed EU-LCI does not underestimate the systemic toxicity of 3MB. Furthermore, no or at most slight respiratory irritation of 3MB was reported during or after acute inhalation exposure of various species against air saturated with 3MB-vapour (about 6200 mg/m^3) for 6 h. The proposed EU-LCI is about 3600fold lower than this concentration. Moreover, no respiratory tract effects or signs of irritation were reported in a subacute inhalation study with rats exposed against vapours of 3MMB. Considering 500 ppm, the highest concentration used in that study, as a NOAEC for local effects, and taking into account the usual standard factors leads to a value of 1.703 mg/m^3, a value similar to the proposed EU-LCI value

for 3MB. It is concluded that the described comparisons support the derived proposed EU-LCI value for 3MB.

An EU-LCI value for 3-methoxybutan-1-ol (3MB) of 1700 µg/m^3 is proposed.

Since no odour threshold is available for 3MB, no conclusions can be drawn regarding olfactory perception of the substance at the proposed EU-LCI.

Substance profile and EU-LCI value for 1-propoxypropan-2-ol

1-Propxypropan-2-ol (propylene glycol n-propyl ether, PGnPE) is a water-miscible liquid with a mild, ether-like odour. No natural sources of PGnPE are known. PGnPE is a large-scale technical product mainly consisting of 1-propoxypropan-2-ol (α-isomer, > 95 %, mostly > 99 %) with 2-propoxypropan-1-ol (ß-isomer) as a minor component. All available data refer to the technical mixture.

PGnPE is used in coatings and inks and as an ingredient in cleaning products for auto, commercial, industrial and home use. Very few data are available regarding the occurrence of PGnPE in indoor air. In a study in Germany, PGnPE could only be detected in 0.3 % of 1897 measurements (median: 6 µg/m^3, maximum 23 µg/m^3).

Substance-specific toxicokinetic studies with PGnPE are not available. Propylene glycol ethers as a class are known to be rapidly absorbed and distributed throughout the body when introduced by inhalation or exposure. Glycol ethers may also be well absorbed via the skin, even in the vapour state. Propylene glycol ethers may be conjugated at the OH-group with glucuronide or sulphate and excreted as conjugates via the kidneys into the urine. However, the main pathway in the metabolism of propylene glycol ethers involves oxidation. Propylene glycol ethers esterified at the primary hydroxy group such as PGnPE are oxidised by microsomal cytochrome P450 monooxygenases at the ether bond with subsequent O-dealkylation. In case of 1-propoxypropan-2-ol this leads to oxidation products of the corresponding glycol, i.e., propan-1,2-diol (1,2-propylene glycol), and propan-1-ol. These two products may finally enter the intermediary metabolism via the citric acid cycle and may be completely metabolised to CO_2 and water.

No data are available on the toxicity of PGnPE in humans. In animals, acute symptoms of toxicity include depressant effects on the CNS at high inhalation concentrations or dermal or oral doses, and local irritation of the skin and, especially, the eyes after contact with liquid PGnPE.

Subacute inhalation toxicity studies with rats, guinea pigs and rabbits revealed CNS-depression with narcosis (followed by death in some of the rabbits) during or shortly after exposure to 2000 ppm (9740 mg/m^3). Exposure to PGnPE also led to increased liver and kidney weights, probably as an adaptive response, but no histopathological lesions were noted in these or other organs. Especially in F344 rats, ocular lesions with corneal damage were observed after exposure to PGnPE vapour. Mechanistic investigations indicated that the observed ocular changes were linked to a high incidence of corneal dystrophy in the rats used in the above-mentioned studies. Excluding animals with this spontaneous lesion prior to first exposure resulted in a NOAEC of ≥ 600 ppm (the highest concentration tested) in subacute inhalation studies with F344 and Sprague-Dawley rats.

In a subchronic toxicity study (following OECD guideline 413) with “whole body exposure” of Sprague-Dawley and F344 rats, the eyes of the animals did not show any exposure-related alterations. Only in female, but not in male F344 or in female and male Sprague-Dawley rats body weight gain was consistently lower at 300 ppm during exposure but not during the 4-week recovery period. As the decreased body weight gain was only observed in one sex of one strain

and as it was reversible during the recovery period, it was considered as not adverse and a NOAEC of 300 ppm (1461 mg/m^3) established from this study.

In vitro studies provided no evidence for genotoxic effects of PGnPE in bacteria and mammalian cells. *In vivo* studies with PGnPE are not available, but no genotoxicity was observed in studies with the two structurally related propylene glycol ethers dipropylene glycol n-butyl ether (DPGnBE) and propylene glycol methyl ether (PGME).

Carcinogenicity studies with PGnPE are not available. The available data from genotoxicity studies *in vitro* and from repeated dose toxicity studies with PGnPE do not provide evidence for concern regarding carcinogenic effects of the substance. Also, glycol n-alkyl ethers in general are not regarded as to reveal a carcinogenic potential for humans.

PGnPE had no effects on reproductive organs in male and female rats in the subchronic inhalation study with rats mentioned above. Read-across using data from rat studies with PGME or dipropylene glycol mono propyl ether (DPGnPE) provides no evidence for effects on fertility at concentrations or doses which do not also cause general systemic toxicity. In a developmental toxicity study with rats, slight maternal toxicity and a slight delayed ossification in foetuses but no embryotoxicity or teratogenicity were noted at 1500 ppm PGnPE (7305 mg/m^3). Maternal toxicity was more pronounced in a similar developmental toxicity study in rabbits, including mortality of dams at 1500 ppm; however, no developmental toxicity was observed up to 1500 ppm, the highest concentration tested. It is concluded that the available data provide no concern for developmental toxicity of PGnPE.

The subchronic inhalation toxicity study with rats summarised above is considered a suitable key study for the derivation of an EU-LCI value for PGnPE. The following standard assessment factors are used:

- Adjustment for continuous exposure: 5.6
- Adjusted study length factor (subchronic exposure): 2
- Interspecies extrapolation: 2.5
- Intraspecies extrapolation: 10

Total assessment factor: 280. This leads to a concentration of 1461 mg/m^3: 280 = 5.218 mg/m^3.

An EU-LCI value (rounded value) for PGnPE of 5200 µg/m^3 is proposed.

Since no odour threshold is available for PGnPE, no conclusions can be drawn regarding olfactory perception of the substance at the proposed EU-LCI.

Substance profile and EU-LCI value for methyl formate

Methyl formate is a colourless liquid with a pleasant characteristic odour. The substance is a large-scale industrial product used as an intermediate during the production of formic acid and methanol, employed in organic syntheses, as solvent or as a fumigant and larvicide for food and tobacco crops.

Few data are available regarding the occurrence of methyl formate in indoor air. According to a study which analysed 58 building materials, methyl formate was emitted from 3 building materials with determined peak concentrations in the range of 0.09 to 0.13 µg/m^3.

After absorption via inhalation, the dermal or oral route, methyl formate is rapidly and almost completely (97%) cleaved by esterases via an enzymatic hydrolytic reaction to methanol and

formate. Data from inhalation studies in humans and animals showed that the most critical effects of methyl formate are its systemic effect on the central nervous system as well as impairments to the olfactory and respiratory epithelium of rats. In volunteers, a single exposure to 100 ppm (250 mg/m^3) methyl formate resulted in subjective tiredness without causing significant effects in neurobehavioural tests. Workplace studies with foundry worker in which exposures to median concentrations of 47 or 58 ppm methyl formate (maximum: up to 150 ppm) occurred showed also no explicit effects caused by methyl formate exposure. These findings were supported by a subchronic inhalation study in rats which were exposed to concentrations up to 1600 ppm methyl formate. A NOAEC of 400 ppm was derived based on local effects on the respiratory tract in the nose and a NOAEC of 100 ppm for systemic effects on body weight development and organ weights.

In 2019, the MAK commission derived a limit value of 50 ppm (120 mg/m^3), which is also the occupational exposure level (OEL) value in force in Germany, based on the previous mentioned data base. Additionally, the derived MAK/OEL limit value is also protecting against developmental effects caused by methanol during pregnancies.

In *in vitro* and *in vivo* genotoxicity studies methyl formate was neither mutagenic nor genotoxic. Data on carcinogenicity of methyl formate are not available.

As a starting point for the derivation of an EU-LCI value, the NOAEC of 100 ppm (250 mg/m^3) determined in a volunteer study and supported by workplace studies is regarded as appropriate.

The following standard assessment factors are used:

- Adjustment for continuous exposure: 4.2
- Adjusted study length factor (subchronic exposure): 2
- Intraspecies extrapolation (interindividual variability, general population): 10

In a conservative approach, an extrapolation factor of 2 was applied for study length in order to consider that a few of the foundry workers have not been exposed chronically. No extrapolation factor was used for interspecies extrapolation.

Total assessment factor: 84. This leads to a concentration of 250 mg/m^3: 84 = 2976 µg/m^3 (1.194 ppm).

An EU-LCI value of (rounded) 3000 µg/m^3 is proposed for methyl formate.

The proposed EU-LCI value is below the odour threshold ranging from 1500 to 5000 mg/m^3.

Substance profile and EU-LCI value for butyl formate

Butyl formate is a colourless to pale yellow liquid with a fruity, plum-like odour. The substance is mainly used as a flavouring agent and to a lesser degree as a solvent or fragrance.

Regarding the occurrence of butyl formate in indoor air some data are available. In indoor air samples from offices, homes, and (pre)schools in Germany, the substance could only be measured in low concentrations as indicated by a mean of 0.5 µg/m^3.

Data on absorption, distribution, excretion, and metabolism of butyl formate is not available. Systemic effects following inhalation indicate that the substance is taken up via this route of exposure. Reliable quantitative data are, however, not available. Acute exposure is reported to be irritating to eyes, mucous membranes, and skin. An inhaled concentration of 10418 ppm butyl formate caused adverse effects on the respiratory tract and lung in humans. Studies on the genotoxicity of butyl formate or other toxicity studies are not available.

Therefore, additional data was obtained by read-across from studies conducted with methyl or ethyl formate. After a single exposure to 100 ppm (250 mg/m^3) methyl formate in volunteers, subjective tiredness was observed, but neurobehavioural tests were unobtrusive. Workplace studies in which exposures to median concentrations of 47 or 58 ppm methyl formate (maximum: up to 150 ppm) occurred showed also no adverse effects of methyl formate. Furthermore, a subchronic study in rats, which were exposed to concentrations up to 1600 ppm methyl formate, supported the observations in humans and derived a NOAEC of 400 ppm for local effects on the respiratory tract in the nose and a NOAEC of 100 ppm for systemic effects.

Similar lesions of the olfactory nasal epithelium of rats have been described in a subchronic inhalation study conducted with ethyl formate. From the study, NOAEC of 330 ppm (1000 mg/m^3) was derived based on observed nasal irritation (olfactory damage, squamous metaplasia) as well as systemic effects on central nervous system and body weight.

Both read-across substances were not genotoxic in *in vitro* assays and methyl formate was also not clastogenic in an *in vivo* micronucleus test in male mice. For the read-across substances no data on carcinogenicity studies as well as on fertility/reproduction or developmental toxicity studies are available. However, studies with their respective metabolites did not give indications for a concern regarding reproduction or developmental toxicity.

Due to the lack of inhalation toxicity data for butyl formate the inhalation data of the read-across substance, ethyl formate, is considered as suitable for the derivation of an EU-LCI value for butyl formate. Within the chemical class of carboxylic acid esters, ethyl formate is the closest homologue for which suitable toxicity data are available for the derivation of an EU-LCI value. The key assumption underlying the read-across is that both compounds have the same critical endpoint (nasal irritation (olfactory damage and squamous metaplasia) and systemic effects on the central nervous system) and this is caused by the common functional group (and not by the additional CH2 groups).

The subacute inhalation toxicity study with ethyl formate in rats is considered a suitable key study for the derivation of an EU-LCI value for butyl formate. The NOAEC of 330 ppm observed for rats in that study is used as POD for the calculation.

The following standard assessment factors are used:

- Adjustment for continuous exposure: 5.6
- Adjusted study length factor (subchronic exposure): 2
- Interspecies extrapolation: 2.5
- Intraspecies extrapolation: 10

Total assessment factor: 280. This leads to a concentration of 1000 mg/m^3: 280 = 3571 µg/m^3 (1.16 ppm).

It is proposed to adopt this value for butyl formate on a molar basis 23 °C and 1013 hPa (102.13 g/mol (butyl formate) : 74.08 g/mol (ethyl formate) = 1.379):

3571 µg/m^3 x 1.379 = 4924 µg/m^3.

An EU-LCI value (rounded value) for butyl formate of 4900 µg/m^3 is proposed.

For butyl formate, an odour threshold of 0.37 mg/m^3 is reported in the literature.

Zusammenfassung

Stoffprofil und EU-LCI-Wert für 1,4-Cyclohexandimethanol

1,4-Cyclohexandimethanol (CHDM) ist bei Raumtemperatur ein farbloser, wasserlöslicher Feststoff mit einem schwach kohlenwasserstoffähnlichen Geruch. Natürliche Vorkommen sind nicht bekannt. CHDM ist ein großtechnisches Produkt, das zur Herstellung von Polyesterharzen in Beschichtungen, aber auch zur Herstellung kosmetischer Produkte eingesetzt wird. Das technische Produkt besteht zu etwa 70 % aus trans-CHDM und zu 30 % aus cis-CHDM; alle vorliegenden toxikologischen Untersuchungen sind mit diesem technischen Gemisch durchgeführt worden.

Zum Vorkommen von CHDM in der Innenraumluft oder anderen Kompartimenten liegen keine Angaben vor.

Toxikokinetische oder toxikologische Befunde am Menschen liegen nicht vor.

In einer toxikokinetischen Untersuchung mit oraler Verabreichung von ^{14}C-CHDM an Ratten wurde der Stoff rasch und weitestgehend resorbiert und binnen 48 h größtenteils (89 – 96 %) über die Nieren in Form von Metaboliten wieder eliminiert. Als Hauptmetabolit wurde Cyclohexandicarbonsäure identifiziert (68 %), daneben 4-Hydroxymethylcyclohexansäure (31 %), in geringen Anteilen (< 2 %) außerdem nicht näher identifizierte Metabolite. Maximal 3 % der verabreichten ^{14}C-Aktivität wurden mit den Faeces ausgeschieden und nur Spuren in der Ausatemluft.

Die akute Toxizität von CHDM ist gering. Bei Ratten wurden während oder nach 6-stündiger Inhalation von 1250 mg CHDM/m^3 keine klinischen Symptome oder systemische Toxizität beobachtet. Konzentrierte Lösungen von CHDM sind jedoch stark augenreizend.

In einer subchronischen oralen Toxizitätsstudie (in Anlehnung an die OECD-Richtlinie 408) traten bei Sprague-Dawley-Ratten nach oraler Verabreichung von CHDM im Trinkwasser für 90 Tage im Vergleich zur Kontrolle geringeres Körpergewicht, verminderte Gewichtszunahme, verminderte Futteraufnahme sowie Hämaturie als die wesentlichen systemischen Wirkungen auf. Die NOAELs der Studie wurden mit 479 mg/(kg KG x d) für männliche und 754 mg/(kg KG x d) für weibliche Tiere angesetzt.

CHDM war *in vitro* in Assays mit Bakterien (Ames-Test) nicht genotoxisch und induzierte keine Chromosomenaberrationen in Säugetierzellen. Auch *in vivo* wurde keine klastogene Aktivität im Knochenmark bei Ratten und in einem Mikronukleus-Assay bei Mäusen beobachtet.

Karzinogenitätsstudien mit CHDM sind nicht verfügbar. Die verfügbaren Daten zur Gentoxizität und aus Studien zur Toxizität bei wiederholter Verabreichung geben keinen Anlass zur Besorgnis hinsichtlich kanzerogener Wirkungen von CHDM.

Eine Studie zur Entwicklungstoxizität mit Ratten ergab einen NOAEL für maternale Toxizität von 300 mg/(kg KG x d) und einen höheren NOAEL für Entwicklungstoxizität von 1000 mg/(kg KG x d). In einer vergleichbaren Studie mit Kaninchen wurde ein NOAEL von 200 mg/(kg KG x d) für die maternale Toxizität ermittelt. Bei höheren Konzentrationen traten bei den Muttertieren schwere lokale Effekte mit Magenerosionen und Ulzerationen auf; bis zur höchsten getesteten Dosis von 400 mg/(kg KG x d) wurde jedoch keine Entwicklungstoxizität beobachtet.

Der NOAEL von 479 mg/(kg KG x d), der in der subchronischen oralen (Trinkwasser) Toxizitätsstudie mit CHDM bei Ratten ermittelt wurde, wird als POD für die Ableitung eines EU-LCI-Wertes herangezogen.

Die Ergebnisse der toxikokinetischen Studie mit CHDM an Ratten deuten darauf hin, dass die Substanz nach oraler Exposition nahezu vollständig absorbiert wird. Die Absorption nach Inhalation wird in Ermangelung von experimentellen Daten standardmäßig als vollständig angenommen. Daher wird kein Faktor zur Berücksichtigung von Unterschieden in der Absorption nach oraler oder inhalativer Exposition berücksichtigt, und die folgenden Anpassungsfaktoren werden für die Ableitung verwendet:

- Pfad-zu-Pfad-Extrapolation (Ratten): 1,15 m^3 (kg KG x d)
- Zeitextrapolation (subchronische Exposition): 2
- Allometrisches Scaling: in der Pfad-zu-Pfad-Übertragung bereits berücksichtigt
- Interspeziesextrapolation (verbleibende Unterschiede): 2,5
- Intraspeziesextrapolation: 10

Gesamtfaktor: 50 x 1,15 = 57,5 m^3 (kg KG x d). Daraus ergibt sich eine Konzentration von 479 mg/(kg KG x d) : 57,5 m^3 (kg KG x d) = 8330 mg/m^3.

Der vorgeschlagene Wert basiert auf einem NOAEL für systemische Effekte, der in einer Studie mit oraler Exposition von Ratten ermittelt wurde. Die Datenbasis reicht nicht aus, um einen EU-LCI-Wert für CHDM auf der Grundlage von Daten zur Inhalationstoxizität abzuleiten. Allerdings wurden bei Ratten in einer Kurzzeit-Inhalationsstudie (10 Tage) bei 1000 - 3000 mg $CHDM/m^3$, d.h. bei mehr als 100-fach höheren Konzentrationen im Vergleich zum vorgeschlagenen EU-LCI, keine Anzeichen einer Reizung der Atemwege festgestellt, was darauf hinweist, dass eine akute Reizung der Atemwege bei dem vorgeschlagenen EU-LCI-Wert unwahrscheinlich ist.

Der Vergleich mit den Wirkungen zweier andere Glykole, Ethylenglykol und Propylenglykol, weist darauf hin, dass mit lokalen Auswirkungen auf die Atemwege bei langfristiger Exposition nicht zu rechnen sein dürfte, wenn keine kurzfristigen lokalen Auswirkungen bei Inhalation auftreten. Eine ähnliche Schlussfolgerung kann für das Glykol CHDM gezogen werden.

Für 1,4-Cyclohexandimethanol (CHDM) wird ein EU-LCI-Wert von (gerundet) 8300 $\mu g/m^3$ vorgeschlagen.

Zur Geruchsschwelle von CHDM liegen keine Angaben vor.

Stoffprofil und EU-LCI-Wert für 3-Methoxybutan-1-ol

3-Methoxybutan-1-ol (3MB) ist eine bei Raumtemperatur farblose, wasserlösliche Flüssigkeit mit schwachem Geruch. Natürlichen Quellen für 3MB sind nicht bekannt. Technisches 3MB ist das Racemat der beiden Enantiomere; für die einzelnen Isomere sind keine Toxizitätsdaten verfügbar. 3MB kann in Kleb- und Dichtstoffen, Beschichtungsprodukten und Farbentfernern verwendet werden. Für die Innenraumluft liegen nur sehr wenige Messungen zum Vorkommen von 3MB vor. Nach diesen Daten konnten Konzentrationen um 2 - 4 $\mu g/m^3$ (Medianwerte) und bis zu etwa 70 $\mu g/m^3$ (95. Perzentil) nachgewiesen werden.

Toxikokinetische Daten für 3MB sind nicht verfügbar. Glykolether wie 3MB werden oral, nach Inhalation und über die Haut gut resorbiert. Der Metabolismus von Glykolethern folgt im Wesentlichen zwei oxidativen Pfaden. Ein Weg beinhaltet die Oxidation durch mikrosomale Cytochrom P450-Monooxygenasen an der Etherbindung mit O-Dealkylierung. Im Falle von 3MB führt dies zur Bildung des entsprechenden Glykols 1,3-Butandiol, dass im Körper unter Bildung von 3-Hydroxybutansäure und Acetessigsäure weiter oxidiert wird. Beide sind als "Ketonkörper" bekannt und stellen normale Produkte im Intermediärstoffwechsel des

Menschen dar. Der andere Weg des Glykolether-Stoffwechsels beinhaltet die Oxidation der unveränderten Verbindung durch Alkohol-Dehydrogenase und die weitere Oxidation durch Aldehyd-Dehydrogenase mit der Bildung von Alkoxyalkansäuren, im Falle von 3MB also 3-Methoxybutansäure.

Die akute Toxizität von 3MB ist gering. In älteren Studien führte die inhalative Exposition von Katzen, Kaninchen und Meerschweinchen gegenüber 3MB-gesättigter Luft (ca. 6200 mg/m^3) für bis zu 6 h zu einer leichten Reizung der Schleimhäute und zu Schläfrigkeit bei einer Katze nach 6 h. 3MB war in einer Prüfung an Kaninchen nicht hautreizend und leicht augenreizend.

In einer kombinierten Studie zur oralen Toxizität und Reproduktions-/Entwicklungstoxizität (OECD-Richtlinie 422) mit Exposition von Sprague-Dawley-Ratten durch Schlundsonde zeigten sich bei 1000 mg/(kg KG x d) einige leichte Veränderungen mehrerer hämatologischer und blutchemischer Parameter. Aus dieser Studie lässt sich ein NOAEL von 300 mg/(kg KG x d) ableiten.

Es liegen Read-Across-Daten aus Studien mit wiederholter Exposition von Ratten gegenüber 3-Methoxy-3 methylbutan-1-ol (3MMB) vor. Diese Substanz unterscheidet sich von 3MB durch das Vorhandensein einer zusätzlichen 3-Methylgruppe. In einer subakuten Inhalationsstudie mit 3MMB wurden bei Sprague-Dawley-Ratten nach Ganzkörperexposition mit bis zu 500 ppm 3MMB 4h/Tag, 5d/Woche für insgesamt 20 Expositionen keine lokalen oder toxikologisch relevanten systemischen Veränderungen beobachtet. Eine subchronische orale Toxizitätsstudie an Ratten mit 3MMB ergab einen NOAEL von 250 mg/(kg KG x d) und einen LOAEL für systemische Toxizität von 1000 mg/(kg KG x d), basierend auf leichten Veränderungen hämatologischer und klinisch-chemischer Parameter.

3MB und sein Acetatester waren *in vitro* Bakterien und Säugetierzellen nicht genotoxisch. Karzinogenitätsstudien mit 3MB sind nicht verfügbar, aber das Fehlen von entsprechenden reaktiven Strukturen und die negativen Gentoxizitätsergebnisse liefern keine Hinweise darauf, dass der Stoff karzinogen oder mutagen ist.

In der oben erwähnten kombinierten Studie zur oralen Toxizität und Reproduktions-/Entwicklungstoxizität wurde bei Ratten keine Reproduktionstoxizität von 3MB bei bis zu 1000 mg/(kg KG x d), der höchsten getesteten Konzentration, beobachtet. Auch wurde in einer Studie an Ratten nach oraler Exposition mit 1000 mg 3-Methoxybutylacetat/(kg KG x d) keine Entwicklungstoxizität beobachtet. Studien mit 3MMB zeigten leichte Skelettveränderungen bei einer maternal toxischen Dosis von 2000 mg/(kg KG x d), jedoch nicht bei 1000 mg/(kg KG x d).

Der NOAEL von 300 mg/(kg KG x d), der in der kombinierten Studie zur oralen Toxizität und zur Reproduktionsentwicklungstoxizität ermittelt wurde, wird als geeignete Schlüsselstudie für die Ableitung eines EU-LCI-Wertes für 3MB angesehen. Die folgenden Anpassungsfaktoren werden für die Ableitung verwendet:

- Pfad-zu-Pfad-Extrapolation (Ratten): 1,15 m^3 (kg KG x d)
- Zeitextrapolation (subchronische Exposition): 2
- Allometrisches Scaling: in der Pfad-zu-Pfad-Übertragung bereits berücksichtigt
- Interspeziesextrapolation (verbleibende Unterschiede): 2,5
- Intraspeziesextrapolation: 10
- Qualität der Datenbasis (Datenlage begrenzt, begrenzte Read-Across-Daten): 3

Gesamtfaktor: 172,5 m^3 (kg KG x d). Daraus ergibt sich eine Konzentration von 300 mg/(kg KG x d) : 172,5 m^3 (kg KG x d) = 1,739 mg/m^3.

Ein Read-Across mit Daten aus der oralen subchronischen Toxizitätsstudie mit 3MMB unterstützt die Schlussfolgerung, dass der vorgeschlagene EU-LCI die systemische Toxizität von 3MB nicht unterschätzt. Darüber hinaus wurde keine oder höchstens eine leichte Reizung der Atemwege durch 3MB während oder nach akuter inhalativer Exposition verschiedener Spezies gegenüber mit 3MB-Dampf gesättigter Luft (ca. 6200 mg/m^3) für 6 h berichtet. Der vorgeschlagene EU-LCI ist etwa 3600-fach niedriger als diese Konzentration. Weiterhin wurden in einer subakuten Inhalationsstudie mit Ratten, die gegenüber 3MMB-Dämpfen exponiert wurden, keine Auswirkungen auf die Atemwege oder Anzeichen einer Reizung festgestellt. Betrachtet man 500 ppm, die höchste in dieser Studie verwendete Konzentration, als NOAEC für lokale Effekte und berücksichtigt die üblichen Standardfaktoren, so ergibt sich ein Wert von 1,703 mg/m^3, der dem vorgeschlagenen EU-LCI-Wert für 3MB ähnlich ist. Die beschriebenen Vergleiche stützen den abgeleiteten vorgeschlagenen EU-LCI-Wert für 3MB.

Für 3-Methoxybutan-1-ol (3MB) wird ein EU-LCI-Wert von (gerundet) 1700 $\mu g/m^3$ vorgeschlagen.

Da für 3MB keine Geruchsschwellenwerte vorliegen, können hinsichtlich der Geruchswahrnehmung des Stoffes bei dem vorgeschlagenen EU-LCI keine Aussagen getroffen werden.

Stoffprofil und EU-LCI-Wert für 1-Propoxypropan-2-ol

1-Propxypropan-2-ol (Propylenglykol-n-propylether, PGnPE) ist eine mit Wasser mischbare Flüssigkeit mit schwachem etherähnlichen Geruch. Natürlichen Quellen vom PGnPE sind nicht bekannt. PGnPE ist ein großtechnisches Produkt, das hauptsächlich aus 1-Propoxypropan-2-ol (α-Isomer, > 95 %, meist > 99 %) mit 2-Propoxypropan-1-ol (ß-Isomer) als Nebenkomponente besteht. Alle verfügbaren Daten beziehen sich auf das technische Gemisch.

PGnPE wird in Beschichtungen und Druckfarben sowie als Bestandteil von Reinigungsprodukten für den Auto-, Gewerbe-, Industrie- und Haushaltsgebrauch verwendet. Über das Vorkommen von PGnPE in der Innenraumluft liegen nur sehr wenige Daten vor. In einer Studie in Deutschland konnte PGnPE nur in 0,3 % von 1897 Messungen nachgewiesen werden (Median: 6 $\mu g/m^3$, Maximum 23 $\mu g/m^3$).

Substanzspezifische toxikokinetische Studien mit PGnPE sind nicht verfügbar. Propylenglykolether als Stoffgruppe sind dafür bekannt, dass sie bei oraler oder inhalativer Exposition schnell absorbiert und im Körper verteilt werden. Propylenglykolether können auch über die Haut gut resorbiert werden, selbst im dampfförmigen Zustand. Propylenglykolether können an der OH-Gruppe mit Glucuronid oder Sulfat konjugiert werden und als Konjugate über die Nieren mit dem Urin ausgeschieden werden. Der Hauptweg im Metabolismus von Propylenglykolethern ist jedoch die Oxidation. An der primären Hydroxygruppe veresterte Propylenglykolether wie PGnPE werden durch mikrosomale Cytochrom P450-Monooxygenasen an der Etherbindung mit anschließender O-Dealkylierung oxidiert. Im Falle von 1-Propoxy-propan-2-ol führt dies zu Oxidationsprodukten des entsprechenden Glykols, d.h. Propan-1,2-diol (1,2-Propylenglykol) und Propan-1-ol. Diese beiden Produkte können schließlich über den Zitronensäurezyklus im Intermediärstoffwechsel verwertet und vollständig zu CO_2 und Wasser metabolisiert werden.

Es liegen keine Daten zur Toxizität von PGnPE beim Menschen vor. Im Tierversuch wurden als akute Symptome depressive Wirkungen auf das ZNS bei hohen inhalativen Konzentrationen

oder dermalen oder oralen Dosen sowie lokale Reizungen der Haut und insbesondere der Augen nach Kontakt mit flüssigem PGnPE festgestellt.

Subakute Inhalationstoxizitätsstudien mit Ratten, Meerschweinchen und Kaninchen zeigten ZNS-Depression mit Narkose (gefolgt vom Tod bei einigen der Kaninchen) während oder kurz nach der Exposition mit 2000 ppm (9740 mg/m^3). Die Exposition gegenüber PGnPE führte außerdem zu erhöhten Leber- und Nierengewichten, wahrscheinlich als adaptive Reaktion, jedoch ohne histopathologische Läsionen in diesen oder anderen Organen. Insbesondere bei F344-Ratten wurden nach Exposition mit PGnPE-Dampf Hornhautschäden im Auge beobachtet. Mechanistische Untersuchungen sprechen dafür, dass die beobachteten Veränderungen am Auge mit einer hohen Spontaninzidenz von Hornhautdystrophie bei den Ratten zusammenhingen, die in den oben genannten Studien eingesetzt worden waren. Der Ausschluss von Tieren mit dieser spontanen Läsion vor der ersten Exposition führte zu einer NOAEC von ≥ 600 ppm (der höchsten getesteten Konzentration) in subakuten Inhalationsstudien mit F344- und Sprague-Dawley-Ratten.

In einer subchronischen Toxizitätsstudie (in Anlehnung an OECD-Richtlinie 413) mit "Ganzkörperexposition" von Sprague-Dawley- und F344-Ratten zeigten die Augen der Tiere keine expositionsbedingten Veränderungen. Nur bei weiblichen, aber nicht bei männlichen F344- oder bei weiblichen und männlichen Sprague-Dawley-Ratten war die Körpergewichtszunahme bei 300 ppm während der Exposition, aber nicht während der 4-wöchigen Erholungsphase niedriger. Da die verringerte Körpergewichtszunahme nur bei einem Geschlecht eines Stamms beobachtet wurde und während der Erholungsphase reversibel war, wurde sie als nicht advers betrachtet und eine NOAEC von 300 ppm (1461 mg/m^3) abgeleitet.

In-vitro-Studien ergaben keine Hinweise auf gentoxische Wirkungen von PGnPE in Bakterien und Säugetierzellen. *In-vivo*-Studien mit PGnPE liegen nicht vor, aber in Studien mit den beiden strukturell verwandten Propylenglykolethern Dipropylenglykol-n-butylether (DPGnBE) und Propylenglykolmethylether (PGME) wurde keine Gentoxizität beobachtet.

Karzinogenitätsstudien mit PGnPE sind nicht verfügbar. Die verfügbaren Daten aus Gentoxizitätsstudien *in vitro* und aus Toxizitätsstudien mit PGnPE bei wiederholter Verabreichung liefern keine Hinweise hinsichtlich krebserregender Wirkungen des Stoffes. Auch wird bei Glykol-n-alkylethern im Allgemeinen nicht davon ausgegangen, dass sie ein karzinogenes Potenzial für den Menschen aufweisen.

PGnPE hatte in der oben erwähnten subchronischen Inhalationsstudie mit Ratten keine Auswirkungen auf die Fortpflanzungsorgane bei männlichen und weiblichen Ratten. Read-across unter Verwendung von Daten aus Rattenstudien mit PGME oder Dipropylenglykolmonopropylether (DPGnPE) liefert keine Hinweise auf Auswirkungen auf die Fruchtbarkeit bei Konzentrationen oder Dosen, die nicht zugleich systemisch-toxische Wirkungen hervorrufen. In einer Entwicklungstoxizitätsstudie mit Ratten wurde bei 1500 ppm PGnPE (7305 mg/m^3) eine leichte maternale Toxizität und eine leicht verzögerte Verknöcherung bei Föten, aber keine Embryotoxizität oder Teratogenität festgestellt. Die maternale Toxizität war in einer ähnlichen Studie zur Entwicklungstoxizität bei Kaninchen ausgeprägter, einschließlich der Sterblichkeit der Muttertiere bei 1500 ppm; jedoch wurde bis zu 1500 ppm, der höchsten getesteten Konzentration, keine Entwicklungstoxizität beobachtet. Die verfügbaren Daten liefern somit keine Hinweise auf eine Entwicklungstoxizität von PGnPE.

Die oben zusammengefasste subchronische Inhalationstoxizitätsstudie mit Ratten wird als geeignete Schlüsselstudie für die Ableitung eines EU-LCI-Wertes für PGnPE angesehen. Es werden die folgenden Standardextrapolationsfaktoren verwendet:

- Adjustierung auf kontinuierliche Exposition: 5,6
- Zeitextrapolation (subchronische Exposition): 2
- Interspeziesextrapolation: 2,5
- Intraspeziesextrapolation: 10

Gesamtextrapolationsfaktor: 280.

Als EU-LCI-Wert (gerundet) für 1-Propoxypropan-2-ol (Propylenglykol-n-propylether, PGnPE) wird somit eine Konzentration von 5200 µg/m^3 vorgeschlagen.

Zur Geruchsschwelle von PGnPE liegen keine Angaben vor.

Stoffprofil und EU-LCI-Wert für Methylformiat

Methylformiat ist eine farblose Flüssigkeit mit einem angenehmen, charakteristischen Geruch. Die Substanz ist ein großtechnisches Produkt, das als Zwischenprodukt bei der Herstellung von Ameisensäure und Methanol, bei organischen Synthesen, als Lösungsmittel oder als Begasungsmittel und Larvizid für Lebensmittel und Tabakernten eingesetzt wird.

Über das Vorkommen von Methylformiat in der Innenraumluft liegen nur wenige Daten vor. Gemäß einer Studie, in der 58 Baumaterialien analysiert wurden, wurde Methylformiat aus 3 Baumaterialien mit ermittelten Spitzenkonzentrationen im Bereich von 0,09 bis 0,13 µg/m^3 emittiert.

Nach Aufnahme durch Inhalation, den dermalen oder oralen Pfad wird Methylformiat schnell und fast vollständig (97 %) von Esterasen über eine enzymatische hydrolytische Reaktion zu Methanol und Formiat gespalten. Daten aus Inhalationsstudien an Mensch und Tier zeigten, dass die kritischsten Wirkungen von Methylformiat die systemische Wirkung auf das zentrale Nervensystem sowie Beeinträchtigungen des Riech- und Atmungsepithels bei Ratten sind. Bei Probanden führte eine einmalige Exposition mit 100 ppm (250 mg/m^3) Methylformiat zu subjektiver Müdigkeit, ohne signifikante Effekte in neurologischen Verhaltenstests zu verursachen. Arbeitsplatzstudien mit Gießereiarbeitern, bei denen Expositionen mit mittleren Konzentrationen von 47 oder 58 ppm Methylformiat (Maximum: bis zu 150 ppm) auftraten, zeigten ebenfalls keine ausgeprägten Effekte infolge der Methylformiat-Exposition. Diese Ergebnisse wurden durch eine subchronische Inhalationsstudie an Ratten gestützt, die Konzentrationen von bis zu 1600 ppm Methylformiat ausgesetzt waren. Es wurde ein NOAEC von 400 ppm für lokale Effekte auf die Atemwege in der Nase und ein NOAEC von 100 ppm für systemische Effekte auf die Körpergewichtsentwicklung und Organgewichte abgeleitet.

Im Jahr 2019 hat die MAK-Kommission auf Basis der oben genannten Datenlage einen Grenzwert von 50 ppm (120 mg/m^3) abgeleitet, der auch der in Deutschland geltende Arbeitsplatzgrenzwert (AGW) ist. Zusätzlich schützt der abgeleitete MAK/OEL-Grenzwert auch vor entwicklungsbedingten Wirkungen von Methanol während der Schwangerschaft.

In *In-vitro*- und *In-vivo*-Gentoxizitätsstudien wirkte Methylformiat weder mutagen noch genotoxisch. Daten zur Karzinogenität von Methylformiat liegen nicht vor.

Als Ausgangspunkt für die Ableitung eines EU-LCI-Wertes wird die in einer Probandenstudie ermittelte und durch Arbeitsplatzstudien gestützte NOAEC von 100 ppm (250 mg/m^3) als angemessen angesehen.

Die folgenden Standardextrapolationsfaktoren werden herangezogen:

- Adjustierung auf kontinuierliche Exposition: 4,2
- Zeitextrapolation (subchronische Exposition): 2
- Intraspeziesextrapolation (interindividuelle Variabilität, allgemeine Bevölkerung): 10

In einem konservativen Vorgehen wurde für die Studiendauer ein Extrapolationsfaktor von 2 angewandt, um zu berücksichtigen, dass ein Teil der Gießereiarbeiter nicht chronisch exponiert war. Für die Interspeziesextrapolation wurde kein Extrapolationsfaktor verwendet.

Gesamtbewertungsfaktor: 84. Daraus ergibt sich eine Konzentration von 250 mg/m^3: 84 = 2976 µg/m^3 (1,194 ppm).

Für Methylformiat wird ein EU-LCI-Wert von (gerundet) 3000 µg/m^3 vorgeschlagen.

Der vorgeschlagene EU-LCI-Wert liegt unterhalb der Geruchsschwelle im Bereich von 1500 bis 5000 mg/m^3 (600 bis 2000 ppm).

Stoffprofil und EU-LCI-Wert für Butylformiat

Butylformiat ist eine farblose bis blassgelbe Flüssigkeit mit einem fruchtigen, pflaumenartigen Geruch. Die Substanz wird hauptsächlich als Aromastoff und in geringerem Maße als Lösungsmittel oder Duftstoff verwendet.

Über das Vorkommen von Butylformiat in der Innenraumluft liegen einige Daten vor. In Innenraumluftproben aus Büros, Wohnungen und (Vor-)Schulen in Deutschland konnte die Substanz nur in geringen Konzentrationen gemessen werden, was durch einen Mittelwert von 0,5 µg/m^3 belegt wird.

Daten zur Absorption, Verteilung, Ausscheidung und zum Metabolismus von Butylformiat sind nicht verfügbar. Systemische Effekte nach Inhalation weisen darauf hin, dass der Stoff über diesen Expositionsweg aufgenommen wird. Verlässliche quantitative Daten sind jedoch nicht vorhanden. Es wird berichtet, dass eine akute Exposition reizend für Augen, Schleimhäute und Haut ist. Eine eingeatmete Konzentration von 10418 ppm Butylformiat verursachte beim Menschen schädliche Wirkungen auf die Atemwege und die Lunge. Aufgrund einer begrenzten Datenlage sind Studien zur Gentoxizität von Butylformiat oder andere Toxizitätsstudien nicht vorhanden.

Daher wurden zusätzliche Daten durch Read-Across aus Studien gewonnen, die mit Methyl- oder Ethylformiat durchgeführt wurden. Nach einer einmaligen Exposition mit 100 ppm (250 mg/m^3) Methylformiat wurde bei Probanden subjektive Müdigkeit beobachtet, die Tests zum Neuroverhalten waren jedoch unauffällig. Studien am Arbeitsplatz, in denen Expositionen mit mittleren Konzentrationen von 47 oder 58 ppm Methylformiat (Maximum: bis zu 150 ppm) auftraten, zeigten ebenfalls keine schädigenden Wirkungen von Methylformiat. Darüber hinaus unterstützte eine subchronische Studie an Ratten, die gegenüber Konzentrationen von bis zu 1600 ppm Methylformiat exponiert waren, die Beobachtungen am Menschen und leitete eine NOAEC von 400 ppm für lokale Effekte an den Atemwegen in der Nase und eine NOAEC von 100 ppm für systemische Effekte ab.

Analoge Läsionen des olfaktorischen Nasenepithels von Ratten wurden in einer subchronischen Inhalationsstudie beschrieben, die mit Ethylformiat durchgeführt wurde. Aus der Studie wurde eine NOAEC von 330 ppm (1000 mg/m^3) abgeleitet, basierend auf der beobachteten nasalen

Reizung (olfaktorische Schädigung, Plattenepithelmetaplasie) sowie systemischen Effekten auf das zentrale Nervensystem und das Körpergewicht.

Beide Read-Across-Substanzen wirkten in *In-vitro*-Tests nicht gentoxisch und Methylformiat war auch in einem *In-vivo*-Mikronukleustest bei männlichen Mäusen nicht klastogen. Für die Read-Across-Substanzen liegen keine Daten zu Kanzerogenitätsstudien sowie zu Fertilitäts-/Reproduktions- oder Entwicklungstoxizitätsstudien vor. Studien mit den jeweiligen Metaboliten ergaben jedoch keine Hinweise auf eine Besorgnis hinsichtlich Reproduktions- oder Entwicklungstoxizität.

Wegen fehlender Inhalationsstudien mit Butylformiat werden Befunde zur Read-Across-Substanz Ethylformiat als geeignete Basis zur Ableitung eines EU-LCI-Werts für Butylformiat herangezogen. Innerhalb der Stoffklasse der Carbonsäureester ist Ethylformiat das nächstgelegene Homolog, für das geeignete Toxizitätsdaten für die Ableitung eines EU-LCI-Wertes verfügbar sind. Die Hauptannahme, die dem Read-Across zugrunde liegt, ist, dass beide Verbindungen denselben kritischen Endpunkt haben (nasale Reizung (olfaktorische Schädigung und Plattenepithelmetaplasie) und systemische Wirkungen auf das zentrale Nervensystem) und dies durch die gemeinsame funktionelle Gruppe (und nicht durch die zusätzlichen CH2-Gruppen) verursacht wird.

Die subakute inhalative Toxizitätsstudie mit Ethylformiat an Ratten wird als geeignete Schlüsselstudie für die Ableitung eines EU-LCI-Wertes für Butylformiat angesehen. Die in dieser Studie für Ratten beobachtete NOAEC von 330 ppm wird als POD für die Berechnung verwendet.

Die folgenden Standardextrapolationsfaktoren werden herangezogen:

- Adjustierung auf kontinuierliche Exposition: 5,6
- Zeitextrapolation (subchronische Exposition): 2
- Interspeziesextrapolation: 2,5
- Intraspeziesextrapolation: 10

Gesamtextrapolationsfaktor: 280. Daraus ergibt sich eine Konzentration von 1000 mg/m^3: 280 = 3571 µg/m^3 (1,16 ppm).

Es wird vorgeschlagen, diesen Wert auf molarer Basis für Butylformiat zu übernehmen 23 °C und 1013 hPa (102,13 g/mol (Butylformiat) : 74,08 g/mol (Ethylformiat) = 1,379): 3571 µg/m^3 x 1,379 = 4924 µg/m^3.

Als EU-LCI-Wert (gerundet) für Butylformiat wird somit eine Konzentration von 4900 µg/m^3 vorgeschlagen.

Für Butylformiat wird in der Literatur eine Geruchsschwelle von 0,37 mg/m^3 angegeben.

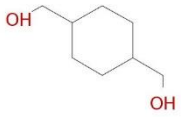
1 Toxicological evaluation of 1,4-cyclohexanedimethanol as basis for the derivation of an EU-LCI value

1.1 Substance identification

Substance identification data and physicochemical properties of 1,4-cyclohexanedimethanol (CHDM) are shown in Table 1 and Table 2.

No natural sources of CHDM are known. CHDM is registered according to REACH in a total tonnage band 1000 – 10000 tonnes/a. Technical CHDM is a mixture of about 70 % trans-CHDM and 30 % cis-CHDM; the ratio can be varied by the production method. No toxicity data are available for the individual isomers (ECHA Dissemination, 2021).

Table 1: Substance identification of 1,4-cyclohexanedimethanol (CHDM, cyclohex-1,4-ylene dimethanol) (OECD SIDS, 2008)

CAS-No. EU-No. CLP-Index-No.	Systematic name, common name	Sum formula	Structural formula
105-08-8 203-268-9 -	1,4-cyclohexanedimethanol (CHDM, cyclohex-1,4-ylene dimethanol)	$C_8H_{16}O_2$	

1.2 Substance properties and uses

Table 2: Substance identification of 1,4-cyclohexanedimethanol (CHDM, cyclohex-1,4-ylene dimethanol) (OECD SIDS, 2008)

Molar mass (g/mol)	Mp. (° C)	Boiling point (° C)	Vapour pressure (Pa) (at 25 °C)	Conversion 1 ppm = x mg/m³ (23 °C)	log pow	Solubility in water (g/L)
144.21	34.6 43 (cis) 67 (trans)	285.5 286 (cis) 283 (trans)	0.041	5.93	1.49	920

Cyclohexanedimethanol (CHDM) is a colourless low-melting solid with a mild "hydrocarbon-like" odour. The substance is used in the production of polyester resins (HSDB, 2014).

According to the Substance Infocard provided on the corresponding ECHA website, CHDM may be used in the following products: coating products and cosmetics and personal care products (ECHA, 2021).

1.3 Exposure

1.3.1 Indoor air

There are no quantitative data available.

1.3.2 Other sources

There are no data available.

1.4 Toxicokinetics

Toxicokinetic data for CHDM were obtained in a non-guideline study conducted with CD-COBS rats (4 M + 4 F/group) which received a single oral gavage dose of 40 (males only) or 400 (both sexes) mg/(kg bw x d) of [^{14}C]-labelled CHDM. The substance was rapidly absorbed, metabolised and eliminated with most of the radioactivity recovered in urine (89-96%) and only small amounts in faeces (1.2-3.0%). Only traces were found as $^{14}CO2$ in exhaled breath. Very little radioactivity (< 0.5 %) was retained in the body. Additional studies revealed a very short half-life of about 13 min for CHDM in the blood of rats. In addition to the parent compound (cis- and trans-CHDM), cis- and trans-isomers of 4-hydroxymethylcyclohexanecarboxylic acid were detected in the blood. No CHDM could be detected in the urine. Excretion with urine occurred within 48 h of dosing, the major metabolites identified in urine were cyclohexanedicarboxylic acid (68 %) and 4-hydroxymethylcyclohexane carboxylic acid (31 %). The cis-trans ratio of the metabolites excreted in the urine was the same as in the original dose. Less than 2 % of the ^{14}C-activity in urine was not fully characterised; at least some of this may be attributed to a glycine conjugate of one or more of the oxidation products of CHDM (ECHA Dissemination, 2021).

1.5 Health effects

1.5.1 Acute toxicity, sensory irritation and local effects

The acute oral toxicity of CHDM is low (LD50 > 2000 mg/kg bw). Dermal exposure with up to 20 g/kg bw caused local irritation (oedema and erythema) but no mortality. In an acute inhalation study with rats exposed against 1.25 CHDM mg/L of air for 6 h, no deaths occurred and no abnormal clinical signs or signs of systemic toxicity were evident during the 14-day observation period (ECHA Dissemination, 2021).

CHDM is not irritating to the skin, but is a severe irritant with corrosive effects on the eyes. The available data do not indicate that CHDM is a skin sensitiser (ECHA Dissemination, 2021).

1.5.2 Repeated dose toxicity

In an inhalation study with short-term repeated exposure, rats (n=3) were exposed against CHDM at a concentration of 1-3 mg/l, 6 h/d, for 10 days. No deaths occurred; abnormal clinical signs or signs of systemic toxicity were limited to minor reversible central nervous system effects during the exposures. All clinical signs were reversible before the start of the next exposure (ECHA Dissemination, 2021).

In a subchronic oral toxicity study following OECD guideline 408, Sprague-Dawley rats (12 M + 10 F/group) were exposed to CHDM in drinking water at concentrations of 0, 0.4, 0.8 and 1.25 % for a total of 13 weeks. The concentrations corresponded to delivered body doses of 0, 256, 479, 861 mg/(kg bw x d) (males) and 0, 440, 754, 1754 mg/(kg bw x d) (females). Reductions in mean body weights, body weight gains, and/or feed consumption values were seen in high-dose animals; there were no treatment-related effects on water consumption in any group. Softened or reduced faeces occurred in animals in all groups but severity and incidence were slightly greater among treated groups. Urine analysis revealed traces of blood in urine from 2-3 male rats per group (reported to be common for male rats of this strain and age), while moderate to large amounts of blood were detected in 3 male rats from the high-dose group and one male in the low-dose group. Large amounts of blood were also detected in the urine from 3 females from

the high-dose group. A slight dose-dependent increase in urinary protein concentration was observed with control and low-dose values ranging from a trace to 30 mg/dl, mid-dose group values generally between 30-100 mg/dl, and 62 % of the high-dose animals with values between 100 mg/dl and 300 mg/dl (10 rats) or > 2000 mg/dl (3 rats). The slight changes at the mid-dose were considered as not related to treatment or adverse. A dose-dependent decrease in urinary pH was also observed with values between 7.0-8.0 for control, 6.0-7.0 for low-dose animals, 6.0-6.5 for mid-dose animals, and 6.0 for high-dose animals. There were no adverse effects on glucose or specific gravity values, volume or clarity. No treatment-related changes in clinical chemistry, haematology, or cell morphology were observed. No toxicologically significant gross or microscopic lesions were observed at necropsy for any of the treated groups. Based on reduced weight gain and terminal weight and on clinical effects at the highest dose, the NOAELs of the study were considered to be 479 mg/(kg bw x d) for males and 754 mg/(kg bw x d) for females (Eastman Kodak, 2000).

In another subchronic toxicity study (conducted before the availability of standard guidelines), albino rats were fed CHDM at target concentrations of 0, 0.1 %, and 1 % for 36 days. The dose levels achieved were not reported. There were no significant treatment related effects on mortality, body weight, food consumption, or any of the other parameters in either sex of rats up to highest dose level (ECHA Dissemination, 2021).

1.5.3 Genotoxicity and carcinogenicity

Genotoxicity

No mutagenicity of CHDM was observed *in vitro* in the absence or presence of exogenous metabolic activation system in assays with bacteria (Ames test) and no chromosomal aberrations were induced in mammalian cells (human lymphocytes, Chinese Hamster lung cells). No clastogenic activity in bone marrow was observed *in vivo* in rats and in a micronucleus assay with mice. Furthermore, 1,4-cyclohexanedicarboxylic acid, the terminal oxidation product of CHDM in mammals, was not mutagenic *in vitro* in a mouse L5178Y lymphoma cell assay in the absence or presence of exogenous metabolic activation system (ECHA Dissemination, 2021; OECD SIDS, 2008).

Carcinogenicity

Carcinogenicity studies with CHDM are not available.

1.5.4 Toxicity to reproduction

The subchronic toxicity study described above was combined with a reproductive/developmental toxicity study according to OECD TG 421 and included a satellite group of 12 F/dose for assessing reproductive effects. Sprague-Dawley rats received CHDM in drinking water at doses of 0, 4.0, 8.0 and 12.5 mg/L during pre-mating (56 days), mating (up to 14 days), gestation (21–22 days), and early lactation (four days). The approximate dose levels achieved were 0, 256/385, 479/854 and 861/1360 mg/(kg bw x d) in males/females, respectively. Clinical abnormalities were observed mainly in the high dose groups and included mortality, bloody or brown/red discoloured urine, softened and/or reduced faeces, dehydration, reductions in body weight and body weight gains, and decreased feed consumption (similar to the effects described above in the parallel conducted repeated dose toxicity part of the study). High-dose males had decreased sperm motility, but reproductive performance was not affected. Several high-dose dams had litters with decreased postnatal pup survival and clinical abnormalities (decreased pup body weights and weight gains). The NOAEL for systemic and also for reproductive/

developmental effects in this study was considered to be 479 mg/(kg bw x d) (ECHA Dissemination, 2021).

In a developmental toxicity study (following OECD Guideline 414), pregnant Sprague-Dawley rats were gavaged with CHDM at doses of 0, 100, 300, and 1000 mg/(kg bw x d) GD3–19. The relative adrenal weight of pregnant females was significantly increased at the highest dose, but no clinical signs, no change in absolute adrenal weight, and no morphologic changes to the adrenals were observed. There was no evidence of foetotoxicity. The NOAEL for maternal toxicity, based on the increased relative adrenal weight, was 300 mg/(kg bw x d), the NOAEL for developmental toxicity was 1000 mg/(kg bw x d) (ECHA Dissemination, 2021).

In a similar (OECD Guideline 414) study with New Zealand White rabbits, pregnant females received 0, 100, 200, 300, and 400 mg/(kg bw x d) CHDM by gavage (dose volume 5 ml/kg) on GD7-28. Increased mortality of dams occurred at 300 and 400 mg/(kg bw x d). Most of these animals showed substantial body weight losses and reduced food consumption prior to death, and adverse clinical observations. Closer inspection revealed gastric erosions and/or ulceration, renal tubular degeneration, and adrenal cortical vacuolation. Test substance-related lower mean body weight gains were also noted for the surviving females in the 300 and 400 mg/(kg bw x d) groups. Mean body weights, weight gains, and gravid uterine weights were unaffected at 100 and 200 mg/(kg bw x d). Haematology and serum chemistry values were unaffected by test substance administration. There were no test substance-related effects on foetal morphology at any dosage level. A dose of 200 mg/(kg bw x d) was considered to be the NOAEL for maternal toxicity. Based on the absence of test substance-related effects on intrauterine growth and survival and foetal morphology at any dosage level, the highest dose of 400 mg/(kg bw x d) represented the NOAEL for developmental toxicity in this study (ECHA Dissemination, 2021).

CHDM did not reveal endocrine disrupting activity in a uterotrophic assay with ovariectomized female Sprague-Dawley rats after oral administration of a mixture of CHDM with 2,2,4,4-tetramethyl-1,3-cyclobutanediol (TMCD) and dimethyl terephthalate (DMT) once daily at dose levels of 0, 0.001, 0.01, 0.1, 1, or 10 mg/(kg bw x d) for three consecutive days. This mixture also displayed no androgenic or anti-androgenic activity in a Hershberger assay in orchid-epididymectomised male Sprague-Dawley rats after oral gavage of 0, 0.001, 0.01, 0.1, 1, or 10 mg/(kg bw x d) for 10 consecutive days (ECHA Dissemination, 2021).

1.5.5 Odour perception

There are no data available.

1.6 Evaluation

1.6.1 Existing regulations and classifications

There is no harmonised classification for CHDM (ECHA C&L Inventory, 2021).

Existing guide values for PGnPE in air are summarised in Table 3.

Table 3: Guide values for CHDM (for explanation, see text)

Guide value Parameter/ Organisation	AGBB	ECHA Dissemination (2021)	ECHA Dissemination (2021)
Name (reference period)	NIK value (2013)	DNEL (chronic, general population)	DNEL (chronic, workers)
Value (mg/m³)	1.6	7.5	30.4
Organ/critical effect	Haematuria	Not specified	Not specified
Species	Rat	Rat	Rat
Basis	NOAEL: 479 mg/(kg bw x d)	NOAEL: 479 mg/(kg bw x d)	NOAEL: 479 mg/(kg bw x d)
Adjusted for continuous exposure			
Extrapolation factors Route-to-route Time LOAEC to NOAEC Interspecies Intraspecies Other Total	 1.15 m³/(kg bw x d) 2 - 2.5 10 5 250 x 1.15	 1.15 m³/(kg bw x d) 2 - 2.5 10 - 50 x 1.15	 1.15 m³/(kg bw x d) 2 - 2.5 5 - 25 x 1.15
Remarks	A factor of 5 was included because of insecurities in the data base and incomplete data on local irritation of the respiratory tract	The oral bioavailability was corrected to 90 % based on the available toxicokinetic data	The oral bioavailability was corrected to 90 % based on the available toxicokinetic data

The NIK value of the German AGBB (2013, unpublished) is based on the NOAEL of 479 mg/(kg bw x d) obtained in the subchronic oral toxicity study with rats (see chapter 1.5.2). Route-to-route extrapolation was performed according to the procedure following ECHA guidance (ECHA, 2012) assuming identical (100 %) absorption after oral and inhalation exposure. A factor of 5 was additionally applied to account for incomplete data basis, e. g. missing details in reporting in incidence/severity of dehydration observed in the mid-dose group and incomplete data on local irritation of the respiratory tract.

In the registration dossier, a DNEL of 7.5 mg/m³ is derived for the protection of the general population via inhalation. This DNEL is also based on the NOAEL obtained in the subchronic oral toxicity study with rats by means of a route-to-route extrapolation. Other than the derivation of the NIK value, the oral bioavailability was estimated as 90 % based on the results from the kinetic study with CDHM (see chapter 1.4) while inhalation uptake was set 100 %, leading to a correction factor of 0.9. No additional factor for any "incompleteness of data" was used in the derivation of the DNEL. For workers, the same data basis and factors were used except that the intraspecies factor was reduced to 5 (ECHA Dissemination, 2021).

1.6.2 Derivation of an EU-LCI value

No data are available on the toxicity of CHDM in humans.

Toxicokinetic data obtained in rats show that the substance is rapidly and nearly completely absorbed after oral administration. Once absorbed, the substance is rapidly metabolised by

oxidation of the OH-group with the formation of corresponding mono- and dicarboxylic acid. These acids are the dominant metabolites and are rapidly excreted with urine within 48 h. No accumulation in the body is observed (ECHA Dissemination, 2021).

The acute toxicity of CHDM is low. No clinical signs or systemic toxicity was observed in rats during or after inhalation of 1.25 mg CHDM/L (1250 mg/m^3) for 6 h. However, concentrated solutions of CHDM are severely irritant to the eyes (ECHA Dissemination, 2021).

In the only study with repeated inhalation exposure, no local respiratory or systemic effects were noted in rats after exposure against 1-3 mg/L (1000-3000 mg/m^3) for 10 days. This subacute study is too limited to serve as the sole basis for the derivation of an EU-LCI value (ECHA Dissemination, 2021).

In a subchronic oral toxicity study following OECD guideline 408, reductions in mean body weights, body weight gains, and/or feed consumption, and haematuria were the main systemic adverse effects after exposure of rats with CHDM in drinking water for 90 days. The NOAELs of the study were considered to be 479 mg/(kg bw x d) for males and 754 mg/(kg bw x d) for females (Eastman Kodak, 2000).

CHDM was not genotoxic *in vitro* in assays with bacteria (Ames test) and did not induce chromosomal aberrations in mammalian cells. Also *in viv*o, no clastogenic activity in bone marrow was observed in rats and in a micronucleus assay with mice (ECHA Dissemination, 2021; OECD SIDS, 2008).

Carcinogenicity studies with CHDM are not available. The available data on genotoxicity and from repeated dose toxicity studies do not provide evidence for concern regarding carcinogenic effects of CHDM.

A developmental toxicity study (OECD Guideline 414) with rats provided a NOAEL of 300 mg/(kg bw x d) for maternal toxicity based on the increased relative adrenal weight and a higher NOAEL of 1000 mg/(kg bw x d) for developmental toxicity, the highest dose tested (ECHA Dissemination, 2021). In a similar study with rabbits, a NOAEL of 200 mg/(kg bw x d) was obtained for maternal toxicity, but no developmental toxicity was observed up to the highest tested dose level of 400 mg/(kg bw x d). At this concentration, the dams suffered from severe local effects with gastric erosions and ulceration (ECHA Dissemination, 2021). CHDM is known to be highly irritating or corrosive to the eye and similar effects are to be expected at the mucosal epithelia of the gastrointestinal tract by gavage exposure. Therefore, the effects observed in the gavage study with rabbits are not suitable as basis for the derivation of an EU-LCI for CHDM.

The NOAEL of 479 mg/(kg bw x d) obtained in the subchronic oral (drinking water) toxicity study with CHDM in rats is used as POD for the derivation of an EU-LCI value.

The results of the toxicokinetic study with CHDM in rats indicate that the substance is nearly completely absorbed after oral exposure. Absorption after inhalation is, in the absence of experimental data, assumed to be complete by default. Thus, no factor to account for differences in absorption after oral or inhalation exposure will be taken into account, and the following assessment factors (EC, 2013; ECHA, 2012) are used for the derivation:

- Route-to-route extrapolation (rats): 1.15 m^3 (kg bw x d)
- Adjusted study length factor (subchronic exposure study): 2
- Allometric scaling: already included in route-to-route extrapolation

- Interspecies extrapolation (systemic effects): 2.5
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 50 x 1.15 = 57.5 m^3 (kg bw x d).

This leads to a concentration of 479 mg/(kg bw x d) : 57.5 m^3 (kg bw x d) = 8.330 mg/m^3.

The proposed value is based on a NOAEL for systemic effects observed in a study with oral exposure of rats. As noted above, the data basis is not sufficient to derive an EU-LCI value for CHDM on the basis of inhalation toxicity data. However, no signs of respiratory irritation have been noted in rats in a short-term (10 day) inhalation study at 1000 – 3000 mg CHDM/m^3 (see chapter 1.5.2), i.e., at more than 100fold higher concentrations, indicating that acute respiratory irritation is unlikely at the proposed EU-LCI value.

Further support for the derivation can be deduced from read-across with the EU-LCI values derived for two other glycols, i.e., ethylene glycol and propylene glycol (EU-LCI Working Group, 2021). The EU-LCI values for these substances are based on local irritation effects in humans and rats. Although in case of propylene glycol one of the POD was taken from a subchronic toxicity study with rats, the minimal irritation observed was acute in nature and fully reversible within two days. Similarly, the EU-LCI value for ethylene glycol is based on acute respiratory irritation effects in humans and is also protective against long-term systemic effects.

It is concluded that for these glycols long-term local respiratory effects do not seem to be of concern. In the absence of short-term local effects following inhalation, a similar conclusion can be drawn for the glycol CHDM[1].

An EU-LCI value of 8300 µg/m^3 is proposed for 1,4-cyclohexanedimethanol (CHDM).

Since no odour threshold is available for CHDM, no conclusions can be drawn regarding olfactory perception of CHDM at the proposed EU-LCI.

[1] On a molar basis, the proposed EU-LCI value for CHDM is 1400 ppb, similar to the EU-LCI value for ethylene glycol (1307 ppb) and about a factor of two higher than the EU-LCI value for propylene glycol (675 ppb).

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A Appendix

A.1 Fact and data sheet for 1,4-cyclohexanedimethanol

Table 4: Data collection sheet for 1,4-cyclohexanedimethanol

Compound	1,4-Cyclohexanedimethanol	Data collection sheet
Nº CAS 105-08-8 1 ppm = 5.93 mg/m³ at 23 °C	**EU-Classification: -** **CLP,** harmonised classification: none	
Organisation name	AgBB	Reach registrants
Risk value name	NIK ('Lowest Concentration of Interest')	DNEL
Risk value (mg/m³)	1.6	7.5
Reference period	Chronic (general population)	Chronic (general population)
Risk value (mg/m³) Short term (15 min)	-	not derived (no hazard identified)
Year	2013	2020
Key study	Eastman Kodak (2000)	Eastman Kodak (2000)
Study type	Oral study with 0, 4, 8, 12.5 mg/ml (nominal) CHDM in drinking water	Oral study with 0, 4, 8, 12.5 mg/ml (nominal) CHDM in drinking water
Species	Sprague-Dawley rat (n=12 M + 10 F/dose)	Sprague-Dawley rat (n=12 M + 10 F/dose)
Duration of exposure in key study	13 weeks	13 weeks
Critical effect	Haematuria	Haematuria
Critical dose value	NOAEL: 479 mg/(kg bw x d)	NOAEL: 479 mg/(kg bw x d)
Adjusted critical dose	479 mg/(kg bw x d) : 1.15 m³/)kg bw x d) = 416.5 mg/m³	479 mg/(kg bw x d), corrected for 90 % bioavailability: 431.1 mg/(kg bw x d) : 1.15 m³/(kg bw x d) = 374.9 mg/m³
Single assessment factors	UF_S 2, UF_A 2.5, UF_H 10, UF_d 5 = 250	UF_S 2, UF_A 2.5, UF_H 10 = 50
Other effects		
Remarks	A factor of 5 was included because of insecurities in the data base and incomplete data on local irritation of the respiratory tract	The oral bioavailability was corrected to 90 % based on the available toxicokinetic data

AgBB = Ausschuss zur gesundheitlichen Bewertung von Bauprodukten
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study UF_D data deficiencies.

Table 5: Fact sheet for 1,4-cyclohexanedimethanol (CHDM)

Compound	**1,4-Cyclohexanedimethanol (CHDM) C8H16O2**		**Fact sheet**
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	8300
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2021
General information			
CLP-Index No.	4	INDEX	-
EC-No.	5	EINECS	203-268-9
CAS-No.	6	Chemical Abstract Service number	105-08-8
Harmonised CLP classification	7	Human health risk related classification	-
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	144.21
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	ECHA (2021) Subchronic oral toxicity study with rats (OECD guideline 408) (2000)
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	Rat, Sprague-Dawley (12 M, 10 F/dose)
Route / type of study	12	Inhalation, oral feed, etc.	Oral (drinking water)
Study length	13	Days, subchronic, chronic, etc.	13 weeks
Exposure duration	14	h/d, d/w	daily
Critical endpoint	15	Effect (s), site of	Haematuria: increased haematuria in M and F at 1.25 mg CHDM/ml, not observed at 0.8 mg/ml
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEL (males)
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	479 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	2
Route-to-route extrapolation factor	21	-	1.15 m³/kg bw

Compound	1,4-Cyclohexanedimethanol (CHDM) C8H16O2		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		1
Other adjustment factors Quality of database	26	Quality of database	1
Results			
Summary of assessment factors	27	Total Assessment Factor	50 x 1.15
POD/TAF	28	Calculated value [µg/m³ and ppb]	8330 µg/m³ (1405 ppb)
Molar adjustment factor	29		
Rounded value	30	[µg/m³]	8300
Additional comments	31		
Rationale selection	32		

Data compilation and evaluation for 1,4-cyclohexanedimethanol is based on a project funded by the German Environment Agency (Voss et al., 2021).

Rationale for critical effects

No data are available on the toxicity of CHDM in humans.

Toxicokinetic data obtained in rats show that the substance is rapidly and nearly completely absorbed after oral administration. Once absorbed, the substance is rapidly metabolised by oxidation of the OH-group with the formation of corresponding mono- and dicarboxylic acid. These acids are the dominant metabolites and are rapidly excreted with urine within 48 h. No accumulation in the body is observed (ECHA Dissemination, 2021).

The acute toxicity of CHDM is low. No clinical signs or systemic toxicity was observed in rats during or after inhalation of 1.25 mg CHDM/L (1250 mg/m^3) for 6 h. However, concentrated solutions of CHDM are severely irritant to the eyes (ECHA Dissemination, 2021).

In the only study with repeated inhalation exposure, no local respiratory or systemic effects were noted in rats after exposure against 1-3 mg/L (1000-3000 mg/m^3) for 10 days. This subacute study is too limited to serve as the sole basis for the derivation of an EU-LCI value (ECHA Dissemination, 2021).

In a subchronic oral toxicity study following OECD guideline 408, Sprague-Dawley rats (12 M + 10 F/group) were exposed to CHDM in drinking water at concentrations of 0, 0.4, 0.8 and 1.25 % for a total of 13 weeks. The concentrations corresponded to delivered body doses of 0, 256, 479, 861 mg/(kg bw x d) (males) and 0, 440, 754, 1754 mg/(kg bw x d) (females). Reductions in mean body weights, body weight gains, and/or feed consumption values were seen in high-dose animals; there were no treatment-related effects on water consumption in any group. Softened or reduced faeces occurred in animals in all groups but severity and incidence were slightly greater among treated groups. Urine analysis revealed traces of blood in urine from 2-3 male rats per group (reported to be common for male rats of this strain and age), while moderate to large amounts of blood were detected in 3 male rats from the high-dose group and one male in the low-dose group. Large amounts of blood were also detected in the urine from 3 females from the high-dose group. A slight dose-dependent increase in urinary protein concentration was observed with control and low-dose values ranging from a trace to 30 mg/dl, mid-dose group values generally between 30-100 mg/dl, and 62 % of the high-dose animals with values between 100 mg/dl and 300 mg/dl (10 rats) or > 2000 mg/dl (3 rats). The slight changes at the mid-dose were considered as not related to treatment or adverse. A dose-dependent decrease in urinary pH was also observed with values between 7.0-8.0 for control, 6.0-7.0 for low-dose animals, 6.0-6.5 for mid-dose animals, and 6.0 for high-dose animals. There were no adverse effects on glucose or specific gravity values, volume or clarity. No treatment-related changes in clinical chemistry, haematology, or cell morphology were observed. No toxicologically significant gross or microscopic lesions were observed at necropsy for any of the treated groups. Based on reduced weight gain and terminal weight and on clinical effects at the highest dose, the NOAELs of the study were considered to be 479 mg/(kg bw x d) for males and 754 mg/(kg bw x d) for females (Eastman Kodak, 2000).

CHDM was not genotoxic *in vitro* in assays with bacteria (Ames test) and did not induce chromosomal aberrations in mammalian cells. Also in vivo, no clastogenic activity in bone marrow was observed in rats and in a micronucleus assay with mice (ECHA Dissemination, 2021; OECD SIDS, 2008).

Carcinogenicity studies with CHDM are not available. The available data on genotoxicity and from repeated dose toxicity studies do not provide evidence for concern regarding carcinogenic effects of CHDM.

A developmental toxicity study (OECD Guideline 414) with rats provided a NOAEL for maternal toxicity, based on the increased relative adrenal weight, of 300 mg/(kg bw x d) and a higher NOAEL for developmental toxicity of 1000 mg/(kg bw x d), the highest dose tested (ECHA Dissemination, 2021). In a similar study with rabbits, a NOAEL of 200 mg/(kg bw x d) was obtained for maternal toxicity, but no developmental toxicity was observed up to the highest tested dose level of 400 mg/(kg bw x d). At this concentration, the dams suffered from severe local effects with gastric erosions and ulceration (ECHA Dissemination, 2021). CHDM is known to be highly irritating or corrosive to the eye and similar effects are to be expected at the mucosal epithelia of the gastrointestinal tract by gavage exposure. Therefore, the effects observed in the gavage study with rabbits are not suitable as basis for the derivation of an EU-LCI for CHDM.

Rationale for starting point

The NOAEL of 479 mg/(kg bw x d) obtained in the subchronic oral (drinking water) toxicity study with CHDM in rats is used as POD for the derivation of an EU-LCI value.

Rationale for assessment factors

The results of the toxicokinetic study with CHDM in rats indicate that the substance is nearly completely absorbed after oral exposure. Absorption after inhalation is, in the absence of experimental data, assumed to be complete by default. Thus, no factor to account for differences in absorption after oral or inhalation exposure will be considered, and the following assessment factors (EC, 2013; ECHA, 2012) are used for the derivation:

- Route-to-route extrapolation factor: 1.15 m^3/(kg bw x d) (rat)
- Adjusted study length factor: 2 (subchronic exposure)
- Allometric scaling (rat to human): already included in route-to-route extrapolation
- Interspecies differences: 2.5 (default value for systemic effects)
- Intraspecies differences: 10,

leading to a value of 479 mg/(kg bw x d) : (50 x 1.15) = 8330 µg/m^3 for CHDM.

The proposed value is based on a NOAEL for systemic effects observed in a study with oral exposure of rats. As noted above, the data basis is not sufficient to derive an EU-LCI value for CHDM on the basis of inhalation toxicity data. However, no signs of respiratory irritation have been noted in rats in a short-term (10 day) inhalation study at 1000 – 3000 mg CHDM/m^3, i.e., at more than 100fold higher concentrations, indicating that acute respiratory irritation is unlikely at the proposed EU-LCI value.

Further support for the derivation can be deduced from a comparison with the EU-LCI values derived for two similar glycols, i.e., ethylene glycol and propylene glycol (EU-LCI Working Group, 2021). The EU-LCI values for these substances are based on local irritation effects in humans and rats. Although in case of propylene glycol one of the POD was taken from a subchronic toxicity study with rats, the minimal irritation observed was acute in nature and fully reversible within two days. Similarly, the EU-LCI value for ethylene glycol is based on acute respiratory irritation effects in humans and is also protective against long-term systemic effects.

It is concluded that for these glycols long-term local respiratory effects do not seem to be of concern. In the absence of short-term local effects following inhalation, a similar conclusion can be drawn for the glycol CHDM.

An EU-LCI value of 8300 µg/m^3 is proposed for CHDM.

Since no odour threshold is available for CHDM, no conclusions can be drawn regarding olfactory perception of CHDM at the proposed EU-LCI.

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Voss JU, Bierwisch A, Kaiser E (2021) Toxicological basic data for the derivation of EU LCI values for 1,4-cyclohexanedimethanol, 3-methoxy¬butanol, 1,2-propylene glycol n-propyl ether, methyl formate and butyl formate. UBA Texte, to be published.

2 Toxicological evaluation of 3-methoxy-1-butanol as basis for the derivation of an EU-LCI value

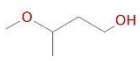
2.1 Substance identification

Substance identification data and physicochemical properties of 3-methoxybutan-1-ol (3MB) are shown in Table 6 and Table 7.

The data base on the toxicity of 3MB is very limited. In a decision on a compliance check, the ECHA has requested the registrants to submit a number of data/studies, i.e., a 90-d oral toxicity study (OECD TG 408), a screening for reproductive/developmental oral toxicity study (OECD 421/422), a prenatal developmental oral toxicity study (OECD TG 414) in a first specie and an *in vitro* gene mutation study in bacteria (OECD TG 471) with selected strains. The requested information shall be submitted in an updated registration dossier by December 2021 (ECHA, 2018). However, no additional data have been presented in the REACH registration dossier yet.

3-Methoxybutan-1-ol is a colourless, water soluble liquid with a mild odour. No natural sources of the substance are known. 3MB is registered according to REACH in a total tonnage band 100 – 1000 tonnes/a. Technical 3MB is the racemate of the two enantiomers (ECHA Dissemination, 2019). No toxicity data are available for the individual isomers.

Table 6: Substance identification of 3-methoxy-butan-1-ol (3MB) (ECHA Dissemination, 2019)

CAS-No. EU-No. CLP-Index-No.	Systematic name, common name	Sum formula	Structural formula
2517-43-3 219-741-8 -	3-methoxy-butan-1-ol, 3-methoxy-1-butanol	$C_5H_{12}O_2$	

2.2 Substance properties and uses

Table 7: Substance identification of 3-methoxy-butan-1-ol (3MB) (ECHA Dissemination, 2019)

Molar mass (g/mol)	Mp. (° C)	Boiling point (° C)	Vapour pressure (Pa) (at 25 °C)	Conversion 1 ppm = x mg/m³ (23 °C)	log pow	Solubility in water (g/L)
104.15	-86	157	0.33	4.29	0.002	500

According to the Substance Infocard provided on the corresponding ECHA website, 3MB may be used in the following products: adhesives and sealants, adsorbents, anti-freeze products, coating products, fillers, putties, plasters, modelling clay, finger paints, non-metal-surface treatment products, polishes and waxes and textile treatment products and dyes (ECHA, 2021). Other uses may include inks for printing or writing and paint or graffiti removers (PubChem,

2021). 3MB was detected in concentrations up to 5 µg/m³ in chamber measurements as a constituent of various lacquers[2].

2.3 Exposure

2.3.1 Indoor air

The above mentioned uses suggest that 3MB may occur in indoor air. However, very few measurements of 3MB concentrations seem to be available in homes, schools or offices.

In an evaluation of altogether 1897 complaint-caused measurements performed in 1866 rooms of 714 public buildings in Germany, 3MB could be detected in 9 cases (0.5 % of samples > LoD, no further details reported). The median value was 2 µg/m³, while the 95th percentile and the maximum value were reported to be 70 µg/m³. In the same study, 3MB-acetate, which is expected to be rapidly hydrolysed after inhalation to 3 MB, was observed in 6 samples (median: 4 µg/m³, 95th percentile and maximum: 10 µg/m³) (Petzold, 2015).

2.3.2 Other sources

There are no data available.

2.4 Toxicokinetics

Toxicokinetic data for 3MB are not available.

Read-across: Glycol ethers in general are known to be well absorbed orally, after inhalation and via the skin. Once absorbed, glycol ethers are readily distributed through the body (ECETOC, 2005).

The metabolism of glycol ethers follows two main oxidative pathways. One pathway involves oxidation by microsomal cytochrome P450 monooxygenases at the ether bond via O-dealkylation (OECD SIDS, 2003). In case of 3MB, this will lead to production of the corresponding glycol, i.e., 1,3-butanediol. This glycol is oxidised in the body by alcohol and aldehyde dehydrogenase with the formation of 3-hydroxybutanoic acid and 3-oxobutanoic acid (acetoacetic acid). Both of these are known as “ketone bodies”, represent normal products in the intermediary metabolism (derived from acetyl-CoA in fatty acid catabolism) and may be used as substrates in oxidative metabolism for ATP-generation.

The other pathway of glycol ether metabolism involves oxidation of the unchanged compound by alcohol dehydrogenase and further oxidation by aldehyde dehydrogenase with the formation of alkoxyalkanoic acids (ECETOC, 2005; OECD SIDS, 2003). This pathway requires a primary hydroxyl (OH) group. In case of 3MB, this would lead to the formation of 3-methoxybutanoic acid. This pathway is important in case of methoxy- and ethoxyethanol since the derived methoxy- and ethoxyacetic acids are embryotoxic/teratogenic at concentrations lower than those leading to maternal toxicity. However, studies on structure-activity relationships indicate that the embryotoxicic/teratogenic effect becomes much less in propylene glycol ethers: In case of 2-methoxy-propan-1-ol, the derived 2-methoxypropanoic acid is much less potent and not selectively toxic to the foetus (Carney et al., 2003).

[2] Wilhelm-Klauditz-Institut, Material Analysis and Indoor Chemistry. Unpublished data, 2009 (personal communication)

2.5 Health effects

2.5.1 Acute toxicity, sensory irritation and local effects

The acute oral toxicity of 3MB is low (LD50 in a limit test with rats > 2000 mg/kg bw, LD50 in mice about 3000 mg/kg bw). In older studies, inhalation exposure of cats, rabbits and guinea pigs to 3MB saturated air (about 6200 mg/m^3) for 1 h and 6 h led to slight irritation of mucous membranes and to drowsiness in one cat after 6 h. No symptoms were observed in guinea pigs and rabbits (ECHA Dissemination, 2019).

3MB was not irritating to the skin in a guideline study with rabbits. In two studies with rabbits on eye irritation, 3MB was slightly irritating to the eyes (slight to moderate conjunctival redness, slight chemosis, discharge, slight corneal opacity and iritis, resolving within 3 days). Data on a skin sensitisation potential of 3MB are not available (ECHA Dissemination, 2019).

2.5.2 Repeated dose toxicity

In a combined oral dose toxicity and reproductive developmental toxicity study (OECD guideline 422) Sprague-Dawley rats (12 M + 12 F in mating groups, 10 F in control and high-dose group as non-mating females) were exposed to 0, 100, 300, and 1000 mg/(kg bw x d) 3MB by gavage. The administration volume was 5.0 mL/kg bw. Males were treated 14 days prior to mating and 28 days after mating (42 days); females were treated 14 days prior to mating and throughout pregnancy until PND4. In addition, the reversibility of effects was examined in some animals in the 0 and 1000 mg/kg groups (5 M + 5 non-mating F) by administering the drug for 42 days followed by a 14-day recovery period (BOZO Research Center, 2017).

There were no deaths from test substance administration. Drooling was observed in males and females at 1000 mg/(kg bw x d). There were no histopathological abnormalities in salivary glands, gastrointestinal tract, central nervous system or any other systemic organs in this study. However, as the test substance was moderately irritating to the eyes of the rabbits in another study (see chapter 2.5.1), drooling may be due to the irritation of the solution administered. In urinalysis, the pH was lowered in the 300 mg/(kg bw x d) and above group in males and in the 1000 mg/(kg bw x d) group in females. However, no abnormality was observed in the histopathological examination of the kidney and liver, and there were no changes in glucose, lipid, or cholesterol in the blood. Haematology and blood chemistry tests showed high platelet counts and inorganic phosphorus concentrations in males of the 1000 mg/(kg bw x d) group, high basophil counts and percentages in females of the crossed group, and low basophil percentages in females of the non-crossed group at the end of the treatment period, respectively. At the end of the recovery period, lower values for the number and percentage of monocytes, higher values for the lymphocyte percentage and A/G ratio, and lower values for the number and percentage of neutrophils were significantly higher in males and females of the 1000 mg/(kg bw x d) group, respectively. However, the extent of these changes was small and within the background values of the institution. At the end of the dosing period, there was a significantly higher absolute and relative weight of the kidneys in males in the 1000 mg/(kg bw x d) group and females in the non-cross group, a significantly lower or lower trend in the relative weight of the pituitary gland in males in the 300 mg/(kg bw x d) and above group, and a higher absolute and relative weight of the liver in females in the 1000 mg/(kg bw x d) group in the cross group. At the end of the recovery period, high absolute and relative weights of the thymus gland were observed in females in the 1000 mg/(kg bw x d) group, but there were no findings in the histopathological examination results of any of the organs at the end of the administration of the test substance, which may have been influenced by the test substance. Of these, the significantly lower or lower trend in pituitary relative weight observed in males of the 300 mg/(kg bw x d)

and above group was not considered to be an effect of the test substance administration, because there was no change in absolute weight, but only in relative weight. Other functional tests, grip strength, spontaneous locomotion, body weight, food intake, autopsy and histopathological results were not affected by the test substance administration. In conclusion, repeated oral administration of 3MB under the conditions of this study resulted in general toxicological changes that may have been caused by the test substance (drooling, slight changes of clinical chemistry and haematology parameters). The authors of the study concluded that the NOAEL for repeated dose toxicity of the test substance was 300 mg/(kg bw x d) for both males and females (BOZO Research Center, 2017).

Read-across: A study on rats exposed to **3-methoxybutyl acetate** via oral gavage for 28 days gave a NOAEL of 300 mg/(kg bw x d) and a LOAEL of 1000 mg/(kg bw x d) based on abnormal respiration. In this study, no effects on the functional observational battery (FOB) parameters examined for neurotoxicity were observed at doses up to 1000 mg/(kg bw x d) (US EPA, 2020).

Furthermore, data are available from studies with repeated exposure of rats to **3-methoxy-3-methylbutan-1-ol** (3MMB). This substance differs from 3MB by the presence of an additional 3-methyl group and is a methyl ether of a glycol with a tertiary OH-group.

In a subacute inhalation study, Sprague-Dawley rats (10 M/group) were exposed whole-body to 0, 100, 300, or 500 ppm 3MMB 4h/day, 5d/week for a total of 20 exposures. At 100 and 500 ppm, the serum transaminase (GOT) activity and absolute and relative kidney weights of the experimental groups were significantly higher than those of control group. However, no abnormal histopathological findings were noted in the liver. Regarding the kidney there was no significant difference between each experimental group and control group in each functional examination and no toxicological relevant change was noted in histopathological examinations (ECHA Dissemination, 2020).

A subacute oral toxicity study was conducted with Sprague-Dawley rats (5M + 5F/group). The animals were treated with 0, 15, 60, 250, and 1000 mg/(kg bw x d) 3MMB by gavage for 28 days. Subsequently, animals were kept for a post-exposure period of 14 days. Significant increase in relative kidney weight were noted in males at 250 mg/(kg bw x d) and in males and females at 1000 mg/(kg bw x d). A significant increase was also observed in relative liver weight in males and females at 1000 mg/(kg bw x d); the effect was decreased at the end of the post-exposure period. No histopathological changes caused by administration of the test substance were noted (ECHA Dissemination, 2020).

In a subchronic toxicity study (following OECD guideline 408) Sprague-Dawley rats (10 M + 10 F/group) were exposed by gavage to 0, 50, 250, and 1000 mg/(kg bw x d) 3MMB for 90 days. An increase of inflammatory cell foci was observed in the liver of medium and high dose females. However, in the absence of necrosis, Kupffer's cell proliferation, apoptosis, fibrosis, alteration in liver function and no significant increase in alanine aminotransferase (ALAT) or aspartate-aminotransferase (ASAT), this finding was deemed to be of a non-adverse nature. Statistically significantly alterations compared to the control were observed at the highest dose in haematological parameters (in males: higher mean lymphocyte and lower mean neutrophil counts, in females: lower mean reticulocyte counts and a higher mean prothrombin time value) and in clinical chemical parameters (females: higher mean glucose and mean potassium levels). The differences between the highest dose groups and the controls were only marginal, but statistically significant and indicate a toxicological response to the test item. Based on these results, the LOAEL for the systemic toxicity is 1000 mg/(kg bw x d) and the NOAEL is 250 mg/(kg bw x d) (ECHA Dissemination, 2020).

2.5.3 Genotoxicity and carcinogenicity

Genotoxicity

No mutagenicity of 3MB was observed *in vitro* in the absence or presence of exogenous metabolic activation system in a bacterial assay (Ames test with *Salmonella typhimurium* strains TA100, TA1535, TA1537, TA1538, TA98) when tested at non-cytotoxic concentrations and in a mammalian cell line (TK-assay with L5178Y mouse lymphoma cells) tested up to recommended limit concentrations. Furthermore, 3MB did not induce an increase in chromosome aberrations in the absence and presence of S9-mix in human lymphocytes (ECHA Dissemination, 2019).

Read-across: **3-methoxybutyl acetate** was (with and without metabolic activation) not mutagenic in a bacterial mutation assay (Ames test) and did not induce chromosomal aberrations in Chinese hamster lung (CHL) fibroblasts (US EPA, 2020).

Carcinogenicity

Carcinogenicity studies with 3MB (or with 3MMB) are not available.

Read-across: Applying expert scientific judgement based on the reasonably available information and weight of the scientific evidence, US EPA concluded that the lack of structural alerts in the parent chemical substance and negative genotoxicity results provide sufficient information to indicate that **3-methoxybutyl acetate** is unlikely to be carcinogenic or mutagenic (US EPA, 2020).

2.5.4 Toxicity to reproduction

In a combined oral dose toxicity and reproductive developmental toxicity study (OECD guideline 422) Sprague-Dawley rats were exposed via oral gavage to 3MB (see above). Males were treated 14 days prior to mating and 28 days after mating; females were treated 14 days prior to mating and throughout pregnancy until postnatal day 4. No reproductive effects (mating, fertility, and oestrus cycle) were observed at up to the highest dose tested, resulting in a NOAEL of 1000 mg/(kg bw x d) (BOZO Research Center, 2017; US EPA, 2020).

Read-across: In a developmental toxicity study with rats exposed via oral gavage to **3-methoxybutyl acetate** during GD7-16, no maternal or foetal toxicity was observed at 1000 mg/(kg bw x d), the only dose tested (ECHA Dissemination, 2019; US EPA, 2020).

In a reproduction/developmental toxicity screening test (OECD guideline 421) with **3MMB**, Sprague-Dawley rats (12 M + 12 F/group) were given 3MMB by gavage at 0, 8, 40, 200 or 1000 mg/(kg bw x d). Males were dosed for 47 days and females were dosed from day 14 before mating to day 4 of lactation throughout the mating and pregnancy period. In males, increases in absolute and relative weights of the kidney were observed at ≥ 200 mg/(kg bw x d). In females, relative weight of the liver and kidney was increased at 1000 mg/(kg bw x d). No effects of 3MMB were detected on developmental parameters, and no malformation was found at any dose (ECHA Dissemination, 2020).

In a developmental toxicity study, Sprague-Dawley rats (25 f/group) received 3MMB by gavage at 0, 250, 500 or 2000 mg/(kg bw x d) on GD6-15. Decreased motor activity, excess salivation, ataxia, muscle flaccidity, and loss of righting reflex at 2000 mg/(kg bw x d) and decreases in body weight gains and food consumption at ≥ 250 mg/(kg bw x d) were observed in dams. Foetal body weights were decreased at 2000 mg/(kg bw x d). No increases in embryonic/foetal deaths and foetal malformations were detected. Increases in skeletal variations and delayed ossification were found at the highest dose. The NOAELs were considered to be less than 250 mg/(kg bw x d) for maternal toxicity and 500 mg/(kg bw x d) for developmental toxicity,

indicating that developmental toxicity only occurs at doses already leading to maternal toxicity (ECHA Dissemination, 2020).

2.5.5 Odour perception

3-Methoxybutan-1-ol has a mild odour (ECHA Dissemination, 2019); however, odour threshold data are not available.

2.6 Evaluation

2.6.1 Existing regulations and classifications

There is no harmonised classification for 3MB (ECHA C&L Inventory, 2021).

Table 8: Guide values for 3MB (for explanation, see text)

Guide value Parameter/ Organisation	AgBB
Name (reference period)	NIK value (2011)
Value (mg/m³)	0.5
Organ/critical effect	
Species	
Basis	
Adjusted for continuous exposure	
Extrapolation factors Time LOAEC to NOAEC Interspecies Intraspecies Other Total	 100 x 2 200
Remarks	The derivation is based on a provisional OEL of 108 mg/m³ and a similar proposed workplace limit goal of 83 mg/m³, using an extrapolation of 100 and an additional factor of 2 to account for the poor data base.

Existing guide values for 3MB in air are summarised in Table 8. A NIK-value derived in 2011 is based on OELs (no details available). No DNEL for workers or the general population were derived in the registration dossier for 3MB (ECHA Dissemination, 2019).

2.6.2 Derivation of an EU-LCI value

The data basis for 3MB is limited. Additional data are available from studies with structurally related glycol ethers.

No data are available on the toxicity of 3MB in humans.

The acute oral toxicity of 3MB is low. In older studies, inhalation exposure of cats to 3MB saturated air (about 6200 mg/m^3) for 6 h led to slight irritation of mucous membranes and CNS effects. No symptoms were observed in guinea pigs and rabbits. 3MB is not irritating to the skin and slightly irritating to the eyes (ECHA Dissemination, 2019).

In a combined oral dose toxicity and reproductive developmental toxicity study (OECD guideline 422) with exposure of Sprague-Dawley rats by gavage, drooling was observed after application of 1000 mg/(kg bw x d). As other studies (see chapter 2.5.1) have shown that 3MB is slightly irritating to the eyes (as pure liquid) and to mucous membranes at vapour high concentrations, this effect may have been caused by the local irritant effect of the concentrated solution. Haematology and blood chemistry tests showed some slight changes of several parameters at 1000 mg/(kg bw x d). The authors of the study concluded that the NOAEL for repeated dose toxicity of the test substance was 300 mg/(kg bw x d) for both males and females (BOZO Research Center, 2017).

Furthermore, read-across data are available from studies with repeated exposure of rats to **3-methoxy-3-methylbutan-1-ol** (3MMB). This substance differs from 3MB by the presence of an additional 3-methyl group and is a methyl ether of a glycol with a tertiary OH-group. In a subacute inhalation study with 3MMB, no local or toxicological relevant systemic changes were observed in Sprague-Dawley rats after whole-body exposure with up to 500 ppm 3MMB 4h/day, 5d/week for a total of 20 exposures. A subchronic oral toxicity study in rats with 3MMB provided a NOAEL of 250 mg/(kg bw x d) and a LOAEL for systemic toxicity of 1000 mg/(kg bw x d), based on slight changes in haematological and clinical chemical parameters (ECHA Dissemination, 2020).

3MB and its acetate ester were not genotoxic in *in vitro* bacteria and mammalian cells (ECHA Dissemination, 2019; US EPA, 2020).

Carcinogenicity studies with 3MB are not available. Applying expert scientific judgement based on the reasonably available information and weight of the scientific evidence, US EPA concluded that the lack of structural alerts in the parent chemical substance and negative genotoxicity results provide sufficient information to indicate that **3-methoxybutyl acetate** is unlikely to be carcinogenic or mutagenic (US EPA, 2020). This conclusion can be adopted to 3MB, as glycol esters in general are rapidly hydrolysed *in vivo* to the corresponding glycol (OECD SIDS, 2003), in this case to 3MB.

No reproductive toxicity of 3MB was observed in rats in the combined oral dose toxicity and reproductive developmental toxicity study (see above) up to 1000 mg/(kg bw x d), the highest concentration tested (BOZO Research Center, 2017; US EPA, 2020). No developmental toxicity was observed in rats in a study after oral exposure to 1000 mg **3-methoxybutyl acetate**/(kg bw x d) during GD7-16 (ECHA Dissemination, 2019; US EPA, 2020). Also, a reproduction/developmental toxicity screening test with **3MMB** revealed no evidence of developmental toxicity or teratogenicity at doses up to 1000 mg/(kg bw x d) (ECHA Dissemination, 2020). In a developmental toxicity study with 3MMB, skeletal variations and delayed ossification were found at 2000 mg/(kg bw x d), the highest dose which already caused maternal toxicity (ECHA Dissemination, 2020). It is concluded that the available data do not provide evidence for reproductive toxicity effects of 3MB (or its read-across compounds).

The NOAEL of 300 mg/(kg bw x d) obtained in the combined oral dose toxicity and reproductive developmental toxicity study with rats summarised above is considered a suitable key study for the derivation of an EU-LCI value for 3MB. The full report of the study is available, although only in Japanese, but an official translation in English is available provided by the US EPA, and tables of results and other study measurements are available in English in the Appendix of the original report (BOZO Research Center, 2017).

As glycol ethers in general are nearly completely absorbed after oral or inhalation uptake, no factor is considered necessary to account for different relative absorption rates for both pathways. The following assessment factors (EC, 2013; ECHA, 2012) are used for the derivation:

- Route-to-route extrapolation (rats): 1.15 m^3 (kg bw x d)
- Adjusted study length factor (subchronic exposure study): 2
- Allometric scaling: already included in route-to-route extrapolation
- Interspecies extrapolation (systemic effects): 2.5
- Intraspecies extrapolation (interindividual variability, general population): 10
- Quality of whole database (limited data base, limited read-across): 3

Total assessment factor: 172.5 m^3 (kg bw x d). This leads to a concentration of 300 mg/(kg bw x d) : 172.5 m^3 (kg bw x d) = 1.739 mg/m^3.

A read-across with data from an oral subchronic toxicity study with the structurally related 3MMB provides support for the conclusion that the proposed EU-LCI does not underestimate the systemic toxicity of 3MB. In the study with 3MMB, a NOAEC of 250 mg/(kg bw x d) was obtained (see chapter 1.5.2). Using the standard extrapolation factors as above, but without a "quality of data base" factor, leads to a value of 250 mg/(kg bw x d) : 57.5 m^3 (kg bw x d) = 4.348 mg/m^3 or, with a "quality of data base" factor of 3, to a value of 1.449 mg/m^3. Taking into account the molar mass ratio of 3MB : 3MMB of 104.15 : 118.17 = 0.88 leads to a concentration of 1.275 mg 3MB/m^3. This value is in the same range as that one obtained on the basis of the NOAEC from the study with 3MB used for the derivation of the proposed EU-LCI.

It must me noted that the choice of the doses used in the two studies affects this comparison. In the study with 3MB, doses were 0, 100, 300 (NOAEC), and 1000 mg/(kg bw x d), whereas in the study with 3MMB, the doses were 0, 50, 250 (NOAEC), and 1000 mg/(kg bw x d). Thus, the differences in the NOAEC introduce a factor of 300 : 250 = 1.2 which merely reflects differences in the experimental design but not necessarily in the toxicity of the two substances. Assuming the same numerical value for the NOAEC in both studies would lead to a "read-across" value of 1.2 x 1.275 mg/m^3 = 1530 mg/m^3 for 3MB[3].

No suitable data are available regarding local effects of 3MB in the respiratory tract after repeated inhalation exposure. No or at most slight respiratory irritation was reported in an older study during or after acute inhalation exposure of various species against air saturated with 3MB-vapour (about 6200 mg/m^3) for 1 h and 6 h (ECHA Dissemination, 2019). The proposed EU-LCI is about 3600fold lower than this concentration.

Moreover, no respiratory tract effects or signs of irritation were reported in a subacute inhalation study in which rats were exposed against vapours of the structurally-related 3MMB (see chapter 2.5.2). Considering 500 ppm, the highest concentration used in that study, as a NOAEC for local effects, and taking into account the following standard assessment factors (EC, 2013; ECHA, 2012):

- Adjustment for continuous exposure (4 h/d, 5 d/week): 8.4
- Adjusted study length factor (subacute exposure): 6

[3] Such differences merely related to the experimental design leading to different NOAEC could principally be reduced by benchmark calculations which take into account information about the dose-response relationship. However, the available data for the studies with 3MB and 3MMB are insufficient for benchmark calculations.

- Interspecies extrapolation: allometry: 1 (inhalation exposure), remaining differences: 2.5
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 1260. This leads to a concentration of 500 ppm: 1260 = 0.397 ppm. Performing a read-across to 3MB, this corresponds to a concentration 0.397 x 4.29 = 1.703 mg/m^3, a value similar to the proposed EU-LCI value for 3MB.

It is concluded that the described comparisons support the derived proposed EU-LCI value for 3MB.

An EU-LCI value for 3MB of 1700 µg/m^3 is proposed.

Since no odour threshold is available for 3MB, no conclusions can be drawn regarding olfactory perception of 3MB at the proposed EU-LCI.

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B Appendix

B.1 Fact and data sheet for 3-methoxy-1-butanol

Table 9: Data collection sheet for 3-methoxy-1-butanol

Compound	3-Methoxy-1-butanol	Data collection sheet
Nº CAS 2517-43-3 1 ppm = 4.29 mg/m³ at 23 °C	**EU-Classification: -** **CLP,** harmonised classification: none	
Organisation name	AgBB	Reach registrants
Risk value name	NIK ('Lowest Concentration of Interest')	DNEL
Risk value (mg/m³)	0.5	not derived
Reference period	Chronic (general population)	
Risk value (mg/m³) Short term (15 min)	-	
Year	2011	2019
Key study		
Study type		
Species		
Duration of exposure in key study		
Critical effect		
Critical dose value		
Adjusted critical dose		
Single assessment factors	100 x UF_d 2 = 200	
Other effects		
Remarks	The derivation is based on a provisional OEL of 108 mg/m³and a similar proposed workplace limit goal of 83 mg/m³, using an extrapolation of 100 and an additional factor of 2 to account for the poor data base.	No hazard identified

AgBB = Ausschuss zur gesundheitlichen Bewertung von Bauprodukten
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study UF_D data deficiencies.

Table 10: Fact sheet for 3-methoxy-1-butanol

Compound	**3-Methoxy-1-butanol C5H12O2**		**Fact sheet**
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	1700
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2021
General information			
CLP-Index No.	4	INDEX	-
EC-No.	5	EINECS	219-741-8
CAS-No.	6	Chemical Abstract Service number	2517-43-3
Harmonised CLP classification	7	Human health risk related classification	-
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	104.15 1 ppm = 4.29 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	BOZO Research Center (2017)
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	Rat, Sprague-Dawley (10-12 M, 10-12 F/dose)
Route / type of study	12	Inhalation, oral feed, etc.	Oral (gavage)
Study length	13	Days, subchronic, chronic, etc.	42 d
Exposure duration	14	h/d, d/w	Daily
Critical endpoint	15	Effect (s), site of	Clinical chemistry and haematology
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEL
POD value	17	[mg/m³] or ppm or [mg/kg_{BW}×d]	300 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	2
Route-to-route extrapolation factor	21	-	1.15 m³/(kg bw x d) (assuming identical resorption rates for oral and inhalation exposure)

Compound	3-Methoxy-1-butanol C5H12O2		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		1
Other adjustment factors Quality of database	26	Quality of database	3
Results			
Summary of assessment factors	27	Total Assessment Factor	1.15 m³/(kg bw x d) x 150
POD/TAF	28	Calculated value [µg/m³ and ppb]	1739 µg/m³ (405 ppb)
Molar adjustment factor	29		
Rounded value	30	[µg/m³]	1700
Additional comments	31		
Rationale selection	32		

Data compilation and evaluation for 3-methoxy-1-butanol (3MB) is based on a project funded by the German Environment Agency (Voss et al., 2021).

Rationale for critical effects

The data basis for 3MB is limited. Additional data are available from studies with structurally related glycol ethers.

No data are available on the toxicity of 3MB in humans.

Toxicokinetic data for 3MB are not available. Glycol ethers in general are known to be well absorbed orally, after inhalation and via the skin. Once absorbed, glycol ethers are readily distributed through the body (ECETOC, 2005). The metabolism of glycol ethers follows two main oxidative pathways. One pathway involves oxidation by microsomal cytochrome P450 monooxygenases at the ether bond via O-dealkylation (OECD SIDS, 2003). In case of 3MB, this will lead to production of the corresponding glycol, i.e., 1,3-butanediol. This glycol is oxidised in the body by alcohol and aldehyde dehydrogenase with the formation of 3-hydroxybutanoic acid and 3-oxobutanoic acid (acetoacetic acid). Both of these are known as “ketone bodies”, represent normal products in the intermediary metabolism (derived from acetyl-CoA in fatty acid catabolism) and may be used as substrates in oxidative metabolism for ATP-generation. The other pathway of glycol ether metabolism involves oxidation of the unchanged compound by alcohol dehydrogenase and further oxidation by aldehyde dehydrogenase with the formation of

alkoxyalkanoic acids (ECETOC, 2005; OECD SIDS, 2003). This pathway requires a primary hydroxyl (OH) group. In case of 3MB, this would lead to the formation of 3-methoxybutanoic acid. This pathway is important in case of methoxy- and ethoxyethanol since the derived methoxy- and ethoxyacetic acids are embryotoxic/teratogenic at concentrations lower than those leading to maternal toxicity. However, studies on structure-activity relationships indicate that the embryotoxic/teratogenic effect becomes much less in propylene glycol ethers: In case of 2-methoxy-propan-1-ol, the derived 2-methoxypropanoic acid is much less potent and not selectively toxic to the foetus (Carney et al., 2003).

The acute toxicity of 3MB is low. Inhalation exposure of cats to 3MB saturated air (about 6200 mg 3MB/m^3) for 6 h led to slight irritation of mucous membranes and CNS effects. No symptoms were observed in guinea pigs and rabbits. 3MB is not irritating to the skin and slightly irritating to the eyes (ECHA Dissemination, 2019).

In a combined oral dose toxicity and reproductive developmental toxicity study (OECD guideline 422) Sprague-Dawley rats (12 M + 12 F in mating groups, 10 F in control and high-dose group as non-mating females) were exposed to 0, 100, 300, and 1000 mg/(kg bw x d) 3MB by gavage. The administration volume was 5.0 mL/kg bw. Males were treated 14 days prior to mating and 28 days after mating (42 days); females were treated 14 days prior to mating and throughout pregnancy until PND4. In addition, the reversibility of effects was examined in some animals (5 M + 5 non-mating F) in the 0 and 1000 mg/kg groups by administering the drug for 42 days followed by a 14-day recovery period. Drooling was observed after application of 1000 mg/(kg bw x d). As other studies have shown that 3MB is slightly irritating to the eyes (as pure liquid) and to mucous membranes at vapour high concentrations, this effect may have been caused by the local irritant effect of the concentrated solution. Haematology and blood chemistry tests showed some slight changes of several parameters, especially at 1000 mg/(kg bw x d). The authors of the study concluded that the NOAEL for repeated dose toxicity of the test substance was 300 mg/(kg bw x d) for both males and females. The full report of the study is available only in Japanese, but an official translation in English is available provided by the US EPA, and tables of results and other study measurements are available in English in the Appendix of the original report (BOZO Research Center, 2017).

Furthermore, read-across data are available from studies with repeated exposure of rats to 3 methoxy-3 methylbutan-1-ol (3MMB). This substance differs from 3MB by the presence of an additional 3 methyl group and is a methyl ether of a glycol with a tertiary OH-group. In a subacute inhalation study with 3MMB, no local or toxicological relevant systemic changes were observed in Sprague-Dawley rats after whole-body exposure with up to 500 ppm 3MMB 4h/day, 5d/week for a total of 20 exposures. A subchronic oral toxicity study in rats with 3MMB provided a NOAEL of 250 mg/(kg bw x d) and a LOAEL for systemic toxicity of 1000 mg/(kg bw x d), based on slight changes in haematological and clinical chemical parameters (ECHA Dissemination, 2020).

3MB and its acetate ester were not genotoxic in *in vitro* bacteria and mammalian cells (ECHA Dissemination, 2019; US EPA, 2020). Carcinogenicity studies with 3MB are not available. Applying expert scientific judgement based on the reasonably available information and weight of the scientific evidence, US EPA concluded that the lack of structural alerts in the parent chemical substance and negative genotoxicity results provide sufficient information to indicate that 3-methoxybutyl acetate is unlikely to be carcinogenic or mutagenic (US EPA, 2020). This conclusion can be adopted to 3MB, as glycol esters in general are rapidly hydrolysed in vivo to the corresponding glycol (OECD SIDS, 2003), in this case to 3MB.

No reproductive toxicity of 3MB was observed in rats in the combined oral dose toxicity and reproductive developmental toxicity study (see above) up to 1000 mg/(kg bw x d), the highest concentration tested (BOZO Research Center, 2017; US EPA, 2020). No developmental toxicity was observed in rats in a study after oral exposure to 1000 mg 3-methoxybutyl acetate/(kg bw x d) during GD7-16 (ECHA Dissemination, 2019; US EPA, 2020). Also, a reproduction/developmental toxicity screening test with 3MMB revealed no evidence of developmental toxicity or teratogenicity at doses up to 1000 mg/(kg bw x d) (ECHA Dissemination, 2020). In a developmental toxicity study with 3MMB, skeletal variations and delayed ossification were found at 2000 mg/(kg bw x d), the highest dose tested which already caused maternal toxicity (ECHA Dissemination, 2020). It is concluded that the available data do not provide evidence for reproductive toxicity effects of 3MB (or its read-across compounds).

Rationale for starting point

The NOAEL of 300 mg/(kg bw x d) obtained in the subchronic oral toxicity with 3MB in rats is used as POD for the derivation of an EU-LCI value (Bozo Research Center, 2017).

Rationale for assessment factors

- Route-to-route extrapolation factor (rat to human, assuming identical resorption rates for oral and inhalation exposure, as generally for other glycol ethers as well): 1.15 m^3/(kg bw x d)
- Adjusted study length factor (subchronic exposure): 2
- Allometric scaling (rat to human): already included in route-to-route extrapolation
- Interspecies extrapolation, remaining differences: 2.5
- Intraspecies differences: 10
- Quality of whole database (limited data base, limited read-across): 3

Total extrapolation factor: 150 x 1.15 m^3/kg bw x d, leading to a value of 300 mg/(kg bw x d) : (150 x 1.15) = 1739 µg/m^3 for 3MB.

A read-across with data from an oral subchronic toxicity study with the structurally related 3MMB provides support for the conclusion that the proposed EU-LCI does not underestimate the systemic toxicity of 3MB. In the study with 3MMB, a NOAEC of 250 mg/(kg bw x d) was obtained. Using the standard assessment factors as above leads to a value of 1.449 mg/m^3. Taking into account the molar mass ratio of 3MB : 3MMB of 104.15 : 118.17 = 0.88 leads to a concentration of 1.275 mg 3MB/m^3. This value is in the same range as that one obtained on the basis of the NOAEC from the study with 3MB used for the derivation of the proposed EU-LCI.

No suitable data are available regarding local effects of 3MB in the respiratory tract after repeated inhalation exposure. No or at most slight respiratory irritation was reported in an older study during or after acute inhalation exposure of various species against air saturated with 3MB-vapour (about 6200 mg/m^3) for 6 h (ECHA Dissemination, 2019). The proposed EU-LCI is about 3600fold lower than this concentration.

Moreover, no respiratory tract effects or signs of irritation were reported in a subacute inhalation study in which rats were exposed against vapours of the structurally-related 3MMB. Considering 500 ppm, the highest concentration used in that study, as a NOAEC for local effects, and taking into account the following standard assessment factors:

- Adjustment for continuous exposure (4 h/d, 5 d/week): 8.4
- Adjusted study length factor (subacute exposure): 6
- Interspecies extrapolation, remaining differences: 2.5
- Intraspecies extrapolation (interindividual variability, general population): 10

leads to a concentration of 500 ppm: 1260 = 0.397 ppm. This corresponds to a mass-based concentration of 0.397 x 4.29 = 1.703 mg 3MB/m^3, similar to the proposed EU-LCI value for 3MB.

It is concluded that the described comparisons support the derivation of the proposed EU-LCI value for 3MB.

An EU-LCI value for 3-methoxy-butan-1-ol (3MB) of 1700 µg/m^3 is proposed.

No odour threshold is available for 3MB, and no conclusions can be drawn regarding olfactory perception of 3MB at the proposed EU-LCI.

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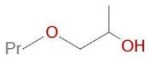
3 Toxicological evaluation of 1,2-propylene glycol n-propyl ether as basis for the derivation of an EU-LCI value

3.1 Substance identification

Substance identification data and physicochemical properties of 1,2-propylene glycol n-propyl ether (1-propoxypropan-2-ol, PGnPE) are shown in Table 11 and Table 12.

No natural sources of PGnPE are known. PGnPE is registered according to REACH in a total tonnage band of 1000 – 10000 tonnes/a. The technical product (DOWANOL PnP) consists mainly of 1-propoxypropan-2-ol (α-isomer, > 95 %, mostly > 99 %) with 2-propoxypropan-1-ol (ß-isomer) as a minor component. All available data refer to the technical mixture (ECETOC, 2005b; ECHA Dissemination, 2021; OECD SIDS, 2003b); no toxicity data are available for the individual isomers or for individual enantiomers.

Table 11: Substance identification of 1-propoxypropan-2-ol (ECHA Dissemination, 2021)

CAS-No. EU-No. CLP-Index-No.	Systematic name, common name	Sum formula	Structural formula
1569-01-3* 216-372-4 -	1-propoxypropan-2-ol, propylene glycol n-propyl ether, Propasol solvent P	$C_6H_{14}O_2$	

*For 1-propoxy-2-propanol. CAS No. 30136-13-1 for the isomer mixture of 1-propoxy-2-propanol and 2-propxy-1-propanol

3.2 Substance properties and uses

Table 12: Substance identification of 1-propoxypropan-2-ol (propylene glycol n-propyl ether) (ECHA Dissemination, 2021)

Molar mass (g/mol)	Melting point (° C)	Boiling point (° C)	Vapour pressure (Pa) (at 25 °C)	Conversion 1 ppm = x mg/m³ (23 °C)	log pow	Solubility in water (g/L)
118.2	< -70	149	3.8 hPa at 25 °C	4.87	0.621 at 20 °C	Completely miscible ≤ 32 °C

PGnPE is a water-miscible liquid with a mild ether-like odour. The substance is used in coatings and inks and as an ingredient in cleaning products for auto, commercial, industrial and home use.

3.3 Exposure

The general population may be exposed by breathing in vapours or direct skin contact, e.g., with consumer cleaning products. PGnPE was also detected in volatiles given off of adhesive removers (PubChem, 2021).

3.3.1 Indoor air

The above mentioned uses suggest that PGnPE may occur in indoor air. However, very few measurements of PGnPE concentrations seem to be available in homes, schools or offices.

In a case-control investigation on children with asthma and allergy and healthy controls, air samples were collected in the sleeping room of the children in altogether 381 homes. PGnPE could be detected in one room at a concentration of 1.55 µg/m^3 and at a concentration of 8.91 µg/m^3 in another (Choi et al., 2010). In an evaluation of altogether 1897 complaint-caused measurements performed in 1866 rooms of 714 public buildings in Germany, PGnPE could be detected in 6 cases (0.3 % of samples > LoD, no further details reported). The median value was 6 µg/m^3, while the 95th percentile and the maximum value were reported to be 23 µg/m^3 (Petzold, 2015).

3.3.2 Other sources

There are no substance-specific data available.

3.4 Toxicokinetics

Substance-specific studies with PGnPE are not available.

Propylene glycol ethers as a class are known to be rapidly absorbed and distributed throughout the body when introduced by inhalation or exposure (OECD SIDS, 2003b). Glycol ethers may also be well absorbed via the skin, even in the vapour state. Once absorbed, glycol ethers are readily distributed through the body (ECETOC, 2005a).

Propylene glycol ethers may be conjugated at the OH-group with glucuronide or sulphate and excreted as conjugates via the kidneys into the urine. However, the main pathway in the metabolism of propylene glycol ethers involves oxidation. Propylene glycol ethers esterified at the primary hydroxy group such as PGnPE are secondary alcohols (sec-alkoxypropanols) which cannot be oxidised by alcohol dehydrogenase to alkoxypropionic acids. Such alkoxypropanols are oxidised by microsomal cytochrome P450 monooxygenases at the ether bond with subsequent O-dealkylation by hydrolysis. In case of PGnPE this leads to oxidation products of the corresponding glycol, i.e., propan-1,2-diol (1,2-propylene glycol), and propan-1-ol. These two products may finally enter the intermediary metabolism via the citric acid cycle and may be completely metabolised to CO_2 and water (ECETOC, 2005a; OECD SIDS, 2003b).

Read across: A metabolism study is available with 1-^{14}C-labelled 1-methoxy-propan-2-ol (2-propylene glycol 1-methyl ether, 2PG1ME). After oral gavage of 2PG1ME to F344 rats, 10 to 20 % was eliminated within 2 days in urine, main as the glucuronide or sulphate conjugates with smaller amounts of propan-1,2-diol and 2PG1ME. At the same time, 50 to 60 % was eliminated in the expired air as carbon dioxide. Only a small amount of radioactivity (about 6 %) was recovered in the body after two days, mainly in bone and liver (ECETOC, 2005b; Miller et al., 1983).

3.5 Health effects

No data from studies on humans with PGnPE are available.

3.5.1 Acute toxicity, sensory irritation and local effects

No mortality was observed in any of the acute inhalation studies in which F344 and Sprague-Dawley rats were exposed up to 8 h against vapour concentrations up to the maximum attainable concentration at room temperature (1725 ppm = 8400 mg/m^3). During exposure to

saturated vapour, F344 rats appeared to be slightly lethargic indicating a slight sedative effect due to CNS-depression. In a 6h study with Sprague-Dawley rats, blepharospasm, conjunctivitis, drying of the cornea, ataxia and loss of righting reflexes were evident during or following exposure. Recovery was apparent after one day.

8 h exposure of an unspecified strain of rats against an atmosphere saturated with vapour of PGnPE led to clinical signs with poor coordination and anaesthesia. All animals recovered after 18 hours (ECETOC, 2005b; ECHA Dissemination, 2021).

The acute oral and dermal toxicity of PGnPE is also low (oral and dermal LD50 > 2000 mg/kg bw in studies with rats or rabbits, respectively). Following dermal application of liquid PGnPE to the skin of rabbits, not only local dermal irritation effects (erythema, oedema, necrosis, ulceration) were observed but also systemic toxicity with effects on the CNS (comatose appearance, dilated pupils, unsteady gait, sluggishness and prostration) which may be lethal, indicating that - as known from other glycol ethers - PGnPE may be absorbed through the skin (ECHA Dissemination, 2021).

Studies on skin irritation of PGnPE in rabbits showed minor to moderate erythema, minor oedema and desquamation. The effects were reversible within 14 days; it was concluded that PGnPE does not fulfil the criteria for EU-classification as a skin irritant (ECHA Dissemination, 2021).

PGnPE is an eye-irritant. In a study with rabbits (comparable to OECD guideline 405), the instillation of 0.1 ml PGnPE into the eyes resulted in minor diffuse corneal injury (opacity), iritis, and moderate to severe conjunctival irritation in all six treated animals. After 7 days, five rabbits exhibited a normal appearance, but one animal developed corneal vascularization which persisted through 21 days. Instillation of 0.01 or 0.005 ml led to similar but less pronounced effects which completely healed within 7 days (ECHA Dissemination, 2021).

PGnPE showed no skin sensitising potential in a LLNA assay (following OECD guideline 429) with female mice (ECHA Dissemination, 2021).

3.5.2 Repeated dose toxicity

No studies with repeated oral or dermal exposure of animals to PGnPE are available.

Subacute “whole body” inhalation toxicity studies were carried with rats, rabbits, and guinea pigs.

In one study, F344 rats (10 M + 10 F/group) were exposed against, 0, 500, 1000, or 2000 ppm PGnPE for 6 h/day, 5 d/week for 9 days over an 11-day period. No mortalities from exposure to PGnPE were observed. Effects seen in both sexes at 2000 ppm were ataxia and prostration during the first two exposure days, losses in mean body weight over the study, and beginning by the 5th exposure day, corneal injury. Increases in liver and kidney weight occurred in both males and females, and an increase in urine volume in males was accompanied by a decrease in urine osmolality. No histopathology was seen in liver or kidney. Males and females of the 1000 ppm groups did show histological evidence of corneal lesions. Males also showed increases in liver and kidney weight. At 500 ppm there was histological evidence of corneal injury and, in males, increased relative kidney weight (ECETOC, 2005b; ECHA Dissemination, 2021).

In a further study, F344 and Sprague-Dawley rats (15 - 30 M + 15 - 30 F/group) were exposed to 0, 5, 50, or 100 ppm PGnPE for 6 h/day, 5 d/week for 9 days over an 11-day period. 10 animals/strain and group were kept for an additional 4-week recovery period. No toxic effects associated with exposure to PGnPE were observed. Observations of the eyes indicated a high incidence of corneal dystrophy in both rat strains in all groups; however, no apparent ocular

alteration was produced from the chemical exposure (ECETOC, 2005b; ECHA Dissemination, 2021).

A similar study with an exposure schedule as described above was also conducted with male F344 rats, Sprague-Dawley rats, Hartley guinea pigs, and New Zealand White rabbits (n=6/group). Exposure concentrations were 0, 100, 500, and 2000 ppm. Interim sacrifices of F344 rats were conducted and some F-344 rats were maintained for a 4-week recovery period. The purpose of this study was to further characterise and evaluate the ocular toxicity in F344 rats and to determine the potential ocular toxicity in another rat strain and in other species. The study also served as the dose-finding study for the subsequent subchronic inhalation toxicity study (see below). Exposure to 2000 ppm produced mortality in 3 of 6 rabbits. Ocular irritation, eye lesions, and central nervous system depression (ataxia, prostration, and narcosis) were also observed at this concentration in both strains of rats and in rabbits. F-344 rats were the most sensitive species for eye lesions, and developed conjunctivitis, keratitis, and corneal opacities. Histologically, the eyes of the 2000 ppm-exposed F-344 rats showed necrosis of the corneal epithelium, stromal mineralization and fibrosis, and corneal vascularization. In this study, the severity of these lesions was related to both the number of exposures and the exposure concentration. Furthermore, these ocular lesions persisted throughout a 4-week recovery period. Eye lesions were also observed but to a lesser extent at 500 ppm and at 100 ppm (ECHA Dissemination, 2021).

Mechanistic investigations indicated that the observed ocular changes were linked to a high incidence of corneal dystrophy, i.e., the presence of diffuse corneal crystals, in the rats used in the above-mentioned studies. Excluding animals with this spontaneous lesion prior to first exposure resulted in a NOAEC of ≥ 600 ppm (the highest concentration tested) in both F344 and Sprague-Dawley rats (ECETOC, 2005b).

In a subchronic inhalation toxicity study following OECD guideline 413, Sprague-Dawley and F344 rats (each 20 M + 20 F/group) were exposed “whole body” on 6 h/day, 5 d/week for 14 weeks to nominal vapour concentrations of 0, 30, 100, or 300 ppm PGnPE (analytical concentrations: 0, 30, 101, 304 ppm). Half the animals of each strain and group were kept for an additional 3-month recovery period. There were no exposure-related clinical signs during the study. The eyes of the animals did not show any exposure-related alterations (i.e., corneal alterations were observed in exposed and controls animals without exposure-related differences). Body weight gains were reported to be consistently lower for the female F-344 rats at 300 ppm during exposure but not during the recovery period (It is also reported that the body weight gain for the 300 ppm group females was 84 % of that of controls at the end of the last full week of exposure. No individual data or a table of the weight gains is provided in the available description of the study). Female F-344 rats of the 100 ppm group had decreased body weight gains for the first two weeks of the exposure regimen but not later on. No additional exposure-related differences in body weights or food and water consumptions were observed. Urine analyses were also normal. Female F-344 rats had a slight decrease in total leukocyte count (300 and 30 ppm groups) associated with a decrease in lymphocytes (300 ppm group); however, these hematologic effects were absent at the end of the recovery period and did not show a clear dose response. No exposure-related gross lesions were identified at necropsy, and organ weights of PGnPE-exposed animals were normal. Furthermore, there were no microscopic histological lesions attributable to exposure. As the decreased body weight gain was only observed in one sex of one strain and as it was reversible during the recovery period, it was considered as not adverse and a NOAEC of 300 ppm was established from this study (ECHA Dissemination, 2021).

3.5.3 Genotoxicity and carcinogenicity

Genotoxicity

No mutagenicity of PGnPE was observed *in vitro* in OECD-guideline studies in assays with bacteria (Ames test with strains TA1535, 1537, 98 and 100 of *Salmonella typhimurium* and test with *Escherichia coli* WP2 uvr A) and with mammalian cells (HGPRT assay in CHO cells), both in the absence or the presence of exogenous metabolic activation system (S9 mix from rat liver). Furthermore, no chromosomal aberrations were induced in mammalian cells (rat lymphocytes) in the absence or presence of S9 mix (ECHA Dissemination, 2021).

In vivo genetic toxicity data for PGnPE are not available.

Read-across: No genotoxicity was observed *in vivo* with two structurally related propylene glycol ethers: Dipropylene glycol n-butyl ether (DPGnBE) was not clastogenic in a micronucleus test in male and female CD-1 mice at doses up to 2500 mg/kg bw, the highest tested dose, already causing lethality in both sexes (ECHA Dissemination, 2019; OECD SIDS, 2003b). Also, propylene glycol methyl ether (PGME) at doses up to 6000 mg/kg bw administered to mice did not increase the frequency of micronuclei in polychromatic erythrocytes harvested from bone marrow (OECD SIDS, 2003b).

Carcinogenicity

Carcinogenicity studies with PGnPE are not available.

Read across: No evidence of carcinogenicity was observed in a two-year carcinogenicity study (according to OECD guideline 453) with inhalation exposure of F344 rats (50 M + 50 F/group) to PGME up to the highest concentration tested (3000 ppm) (OECD SIDS, 2003b). Generally, glycol ethers are not regarded as to reveal a carcinogenic potential for humans (Ad-hoc AG, 2013; ECETOC, 2005a; OECD SIDS, 2003a; OECD SIDS, 2003b).

3.5.4 Toxicity to reproduction

Fertility

No reproductive toxicity study with PGnPE is available.

Read-across:

A two-generation reproductive toxicity study (according to OECD guideline) 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 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 3000 ppm PGME P1 and P2 males and females was evidenced primarily as an increased incidence of sedation for several weeks early in the exposure regimen and significant decreases in body weights. Decreased 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 noted among P1 and P2 adult females exposed to 3000 ppm PGME included lengthened oestrous cycles, decreased fertility, decreased ovary weights and an increased incidence of histologic ovarian atrophy. The effects on fertility, oestrous cyclicity and ovarian weight/histology appeared to be interrelated and associated with the significant decreases in 3000 ppm PGME

female body weights and general toxicity/nutritional stress throughout the test period. No treatment-related differences in sperm counts 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 histopathologic 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 (NOEL) 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 (Carney et al., 1999; OECD SIDS, 2003b).

In a combined repeated dose and reproductive/developmental toxicity study (OECD TG 421), 12 F Sprague-Dawley rats/group received **dipropylene glycol mono propyl ether** (DPGnPE, isomer ratio: DPnP-2,2 = 83.86 %, DPnP-2,1 = 3.76 %, DPnP-1,1 = 0.58 %, and DPnP-1,2 = 11.80 %) by gavage at doses of 0, 100, 300 and 1000 mg/(kg bw x d) during pre-mating (two weeks), mating (two weeks), gestation (three weeks), and early lactation (four days). Males of the same group size were treated with the doses mentioned for two weeks prior to breeding and continuing through breeding (two weeks) up until necropsy (test day 29). No effects were noted at 300 or 100 mg/(kg bw x d). At the highest dose, treatment-related parental effects in males and females were observed as increases in the incidence of hepatocellular hypertrophy and corresponding increases in absolute and relative liver weights. In addition, absolute and relative kidney weights were increased in males and females. At 1000 mg/(kg bw x d) a slight, treatment-related increase in post implantation loss, along with a corresponding slight increase in gestation survival and very slight decrease in litter size was also observed. Based on these results, the NOEL for parental and reproductive toxicity was 300 mg/(kg bw x d) (ECHA Dissemination, 2021).

Developmental toxicity

In a developmental toxicity study (equivalent or similar to OECD Guideline 414), pregnant Sprague-Dawley rats (25 F/group) were exposed 6 h/day by inhalation to 0, 100, 750, and 1500 ppm PGnPE on GD 6 - 15. Maternal toxicity was observed at 1500 ppm. Effects included eye irritation, significant reductions in body weight gain early in the exposure period (days 6 – 9), and reduced food consumption during the exposure period. In a single dam at 1500 ppm, corneal opacity was observed and confirmed by histological evaluation. Gestational parameters were unaffected by exposure. Also, foetal body weights per litter were equivalent across exposure groups. There were no treatment-related changes in the incidence of external, visceral or skeletal malformations. Poorly ossified hindlimb phalanges were observed in litters of the 1500 ppm group. In conclusion, inhalation exposure to PGnPE vapour during organogenesis led to slight maternal and developmental toxicity at 1500 ppm (NOAEC 750 ppm) (ECHA Dissemination, 2021).

In a similar (OECD Guideline 414) study with New Zealand White Rabbits, 22 pregnant females/group were exposed by inhalation against 0, 100, 750, 1nd 1500 ppm PGnPE on GD 6 - 18. Maternal toxicity was evident at 1500 ppm (27.3 % mortality, reduction in weight gain and food and water consumption during the exposure period, and reduction in weight during and subsequent to exposures). Gestational parameters exhibited no significant changes, including number of corpora lutea, total implantations, nonviable or viable implantations per litter, sex ratio, pre- or post-implantation loss, and foetal body weights (total, males or females) per litter.

Also, there were no significant changes in the incidence of external, visceral or skeletal malformations or variations. In conclusion, exposure to PGnPE vapour during organogenesis in rabbits led to pronounced maternal toxicity at 1500 ppm but no exposure-related developmental toxicity at any exposure concentration. The NOAEC for maternal toxicity was 750 ppm and the NOAEC for developmental toxicity 1500 ppm, the highest concentration tested (ECHA Dissemination, 2021).

3.5.5 Odour perception

Data on odour thresholds of PGnPE are not available.

3.6 Evaluation

3.6.1 Existing regulations and classifications

There is no harmonised classification for PGnPE (ECHA C&L Inventory, 2021).

Existing guide values for PGnPE in air are summarised in Table 13.

The NIK value of the German AgBB is based on the great similarity in structure and active profile between EGPE (ethylene glycol n-propyl ether) and EGBE (ethylene glycol n-butyl ether). It was thus considered acceptable to adopt the NIK value for PGBE (propylene glycol n-butyl ether) for PGnPE (AGBB, 2018).

In the registration dossier for PGnPE, a DNEL of 38 mg/m^3 for the protection of the general population via inhalation route has been derived on the basis of a NOAEC of 300 ppm (1474 mg/m^3) obtained in a subchronic inhalation toxicity study with rats. Adjusting for continuous exposure (6 h/24 h, 5 d/ 7 d) lead to a NAEC of 263 mg/m^3. Based on a comparison of NOEC for different glycol ethers, the registrant considered that a factor of 1 would be sufficient to account for toxicodynamic differences. Based on an analysis of the RepDose database to derive assessment factors for extrapolating a NOEL from a shorter to a longer term study (Batke et al., 2011), a factor of 1.4 was considered sufficient as time extrapolation factor. Furthermore, an intraspecies factor of 5 was used based on an ECETOC evaluation report to address the intraspecies variability. With a total extrapolation factor of 7, a DNEL of 38 mg/m^3 was derived (ECHA Dissemination, 2021).

The German Ad-hoc Working Group on Indoor Guidelines has evaluated the toxicity of glycol ethers and glycol esters and derived substance-specific guide values for substances with sufficient data. No substance-specific value was derived by the working group for DPGnBE or dipropylene glycol t-butyl ether (DPGtBE). A default guide value I of 0.005 ppm was recommended for glycol ethers and glycol esters with insufficient data basis (Ad-hoc AG, 2013). This recommendation was based on a statistical analysis of the available data of all glycol ethers, not taking into account substance-specific structural criteria for individual compounds. In case of PGnPE, the recommended guide value I of 0.005 ppm corresponds to a mass-based concentration of 24 µg/m^3.

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

Guide value Parameter/ Organisation	AgBB	ECHA Dissemination (2021)	ECHA Dissemination (2021)
Name (reference period)	NIK value (2011)	DNEL (chronic, general population)	DNEL (chronic, workers)
Value (mg/m³)	1.4 (read-across from PGBE)	38	263
Organ/critical effect			
Species		rat	rat
Basis		NOAEC: 1474 mg/m³ (300 ppm)	NOAEC: 1474 mg/m³ (300 ppm)
Adjusted for continuous exposure		1474 mg/m³ x 5/7 x 6/24 = 263 mg/m³	1474 mg/m³ x 6/8 = 1105.5 mg/m³
Extrapolation factors Time LOAEC to NOAEC Interspecies Intraspecies Total		 1.4 - 1 5 7	 1.4 - 1 3 4.2
Remarks	Based on the great similarity in structure and active profile between EGPE (ethylene glycol n-propyl ether) and EGBE (ethylene glycol n-butyl ether) it was considered acceptable to adopt the NIK value for PGBE (propylene glycol n-butyl ether) for PGnPE		

3.6.2 Derivation of an EU-LCI value

The data basis for PGnPE is limited. Additional data are available from studies with structurally related propylene glycol ethers.

No data are available on the toxicity of PGnPE in humans.

In animals, acute symptoms of PGnPE toxicity include depressant effects on the CNS at high inhalation concentrations or dermal or oral doses, and local irritation of the skin and, especially, the eyes after contact with liquid PGnPE (ECHA Dissemination, 2021).

Data from studies with repeated oral or dermal exposure are not available.

Subacute inhalation toxicity studies with rats, guinea pigs and rabbits revealed CNS-depression with narcosis (followed by death in some of the rabbits) during or shortly after the exposure to 2000 ppm (9740 mg/m^3). Exposure to PGnPE also led to increased liver and kidney weights, probably as an adaptive response, but no histopathological lesions were noted in these or other organs. Especially in F344 rats, ocular lesions with corneal damage were observed after exposure to PGnPE vapour. In further studies, these lesions were observed in both control and PGnPE-exposed groups of F344 and Sprague-Dawley rats (ECETOC, 2005b; ECHA Dissemination, 2021). Mechanistic investigations indicated that the observed ocular changes were linked to a

high incidence of corneal dystrophy in the rats used in the above-mentioned studies. Excluding animals with this spontaneous lesion prior to first exposure resulted in a NOAEC of ≥ 600 ppm (the highest concentration tested) in subacute inhalation studies with F344 and Sprague-Dawley rats (ECETOC, 2005b).

In a subchronic toxicity study (following OECD guideline 413) with "whole body exposure" of Sprague-Dawley and F344 rats, the eyes of the animals did not show any exposure-related alterations. No clinical signs or concentration-dependent effects of PGnPE on haematology, clinical chemistry, urine analysis, organ weights or histopathology were observed. Only in female, but not in male F344 or in female and male Sprague-Dawley rats body weight gain was consistently lower at 300 ppm during exposure but not during the 4-week recovery period. As the decreased body weight gain was only observed in one sex of one strain and as it was reversible during the recovery period, it was considered as not adverse and a NOAEC of 300 ppm (1461 mg/m^3) was established from this study (ECHA Dissemination, 2021).

In this subchronic inhalation study, the nominal vapour concentration of PGnPE was nearly identical to the analytically confirmed exposure concentration. No evidence of aerosol formation was reported which could have led to an additional exposure of the animals via deposition of aerosol and subsequent oral exposure by fur licking. In an acute inhalation toxicity study, the maximum attainable vapour concentration at room temperature was reported to be 1725 ppm (8400 mg/m^3) (see chapter 3.5.1). Therefore, it is unlikely that a significant aerosol formation has to be expected at 300 ppm (1461 mg/m^3), the NOAEC obtained in the subchronic inhalation toxicity study with rats.

No subchronic inhalation studies are available with a second animal species. However, subacute toxicity studies with inhalation exposure of rats, guinea pigs and rabbits (see chapter 3.5.2) and also developmental toxicity studies with inhalation exposure of rats and rabbits (see chapter 3.5.4) provided no evidence for species-specific differences in the toxicity of PGnPE. Moreover, no substantial species differences have been observed in general in studies with various propylene glycol ethers (ECETOC, 2005a; OECD SIDS, 2003b).

In vitro studies provided no evidence for genotoxic effects of PGnPE in bacteria and mammalian cells (ECHA Dissemination, 2021). *In vivo* studies with PGnPE are not available, but no genotoxicity (induction of micronuclei) was observed in studies with mice with the two structurally related propylene glycol ethers dipropylene glycol n-butyl ether (DPGnBE) and propylene glycol methyl ether (PGME) (ECHA Dissemination, 2021; OECD SIDS, 2003b).

Carcinogenicity studies with PGnPE are not available. The available data from genotoxicity studies *in vitro* and from repeated dose toxicity studies with PGnPE do not provide evidence for concern regarding carcinogenic effects of the substance. Also, glycol n-alkyl ethers in general are not regarded as to reveal a carcinogenic potential for humans (Ad-hoc AG, 2013; ECETOC, 2005a; OECD SIDS, 2003b).

Studies regarding effects of PGnPE on fertility are not available. PGnPE had no effects on reproductive organs in male and female rats in the subchronic inhalation study with rats mentioned above. Read-across using data from a two-generation reproductive toxicity study in rats with PGME provided no evidence for a specific reproduction toxicity of this propylene glycol ether. Observed effects on reproductive parameters or organs in females appeared to be interrelated and associated with systemic toxicity, and neonatal effects were considered secondary to maternal toxicity. The no-observed-effect-level (NOEL) for fertility and reproductive effects in this two-generation inhalation reproduction study was 1000 ppm (Carney et al., 1999; OECD SIDS, 2003b). In a combined oral repeated dose and reproductive/developmental toxicity study with dipropylene glycol mono propyl ether

(DPGnPE), the NOEL for parental and reproductive toxicity was 300 mg/(kg bw x d). At 1000 mg/(kg bw x d) systemic effects (hepatocellular hypertrophy, increased kidney weight) and reproductive effects (post implantation loss, decrease in litter size) were noted (ECHA Dissemination, 2021). It is concluded that the limited data base for PGnPE and the data from read-across provide no evidence for effects on fertility at concentrations or doses which do not also cause general systemic toxicity.

In a developmental toxicity study with rats, slight maternal toxicity (eye irritation, reduced weight gain) and a slight delayed ossification in foetuses but no embryotoxicity or teratogenicity were noted at 1500 ppm PGnPE (7305 mg/m^3). Maternal toxicity was more pronounced in a similar developmental toxicity study in rabbits, including mortality of dams at 1500 ppm; however, no developmental toxicity was observed up to 1500 ppm, the highest concentration tested. No effects were noted in both species at 750 ppm (3653 mg/m^3) (ECHA Dissemination, 2021). It is concluded that the available data provide no concern for developmental toxicity of PGnPE.

The subchronic inhalation toxicity study with rats summarised above is considered a suitable key study for the derivation of an EU-LCI value for PGnPE. The study is described in sufficient detail in the REACH registration dossier (ECHA Dissemination, 2021) and the ECETOC report (ECETOC, 2005b). The NOAEC of 300 ppm (1461 mg/m^3 at 23 °C) from that study is used as POD for the calculation.

The following assessment factors are used (EC, 2013; ECHA, 2012):

- Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6
- Adjusted study length factor (subchronic exposure study): 2
- Interspecies extrapolation: allometry: 1 (inhalation exposure), remaining differences: 2.5
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 280. This leads to a concentration of 1461 mg/m^3: 280 = 5.218 mg/m^3.

An EU-LCI value for PGnPE of 5200 µg/m^3 is proposed.

Since no odour threshold is available for PGnPE, no conclusions can be drawn regarding olfactory perception of PGnPE at the proposed EU-LCI.

3.7 List of references

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C Appendix

C.1 Fact and data sheet for 1-propoxypropan-2-ol

Table 14: Data collection sheet for 1-propoxypropan-2-ol

Compound	1-Propoxypropan-2-ol	Data collection sheet
Nº CAS 1569-01-3 (mixture*: 3016-13-1) 1 ppm = 4.87 mg/m³ at 23 °C	**EU-Classification: -** **CLP,** harmonised classification: none	
Organisation name	AgBB	Reach registrants
Risk value name	NIK ('Lowest Concentration of Interest')	DNEL
Risk value (mg/m³)	1.4	38
Reference period	Chronic (general population)	Chronic (general population)
Risk value (mg/m³) Short term (15 min)	-	not derived (no hazard identified)
Year	2011	2020
Key study	Read across: (see below)	Study report from 1990 reported as key study for repeated dose inhalation
Study type		Inhalation study (vapour)
Species		Rat, Sprague-Dawley + F344 (each 20 M + 20 F/conc.)
Duration of exposure in key study		14 weeks
Critical effect		No adverse effect observed up to the highest concentration
Critical dose value		NOAEC: 300 ppm
Adjusted critical dose		6/24 x 5/7

Compound	1-Propoxypropan-2-ol	Data collection sheet
Single assessment factors		UF_S 1.4, UF_A 1, UF_H 5 = 7
Other effects		
Remarks	Read-across was performed: Based on the great similarity in structure and active profile between EGPE (ethylene glycol n-propyl ether) and EGBE (ethylene glycol n-butyl ether) it was considered acceptable to adopt the NIK value for PGBE (propylene glycol n-butyl ether) for PGnPE (propylene glycol n-propyl ether.	

*: Isomer mixture of 1-propoxy-2-propanol and 2-propxy-1-propanol
AgBB = Ausschuss zur gesundheitlichen Bewertung von Bauprodukten
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study UF_D data deficiencies.

Table 15: Fact sheet 1-propoxypropan-2-ol

Compound	**1-Propoxypropan-2-ol C6H14O2**		**Fact sheet**
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	5200
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2021
General information			
CLP-Index No.	4	INDEX	-
EC-No.	5	EINECS	216-372-4
CAS-No.	6	Chemical Abstract Service number	1569-01-3 (mixture: 30136-13-1)
Harmonised CLP classification	7	Human health risk related classification	-
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	118.2 1 ppm = 4.87 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	ECHA (2021) Subchronic inhalation toxicity study (vapour) with rats, OECD guideline 413
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	Rat, Sprague-Dawley + F344 (each 20 M + 20 F /conc.)
Route / type of study	12	Inhalation, oral feed, etc.	Inhalation (vapour)
Study length	13	Days, subchronic, chronic, etc.	14 weeks
Exposure duration	14	h/d, d/w	Daily, 6 h/d, 5 d/week
Critical endpoint	15	Effect (s), site of	No adverse effect observed up to the highest concentration
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEC
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	300 ppm (1461 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

Compound	1-Propoxypropan-2-ol C6H14O2		Fact sheet
Route-to-route extrapolation factor	21	-	1
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		1
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]	5218 µg/m³ (1071 ppb)
Molar adjustment factor	29		-
Rounded value	30	[µg/m³]	5200
Additional comments	31		
Rationale selection	32		

Data compilation and evaluation for 1-propoxypropan-2-ol is based on a project funded by the German Environment Agency (Voss et al., 2021).

Rationale for critical effects

No human data are available for the derivation of an EU-LCI value for 1-propoxypropan-2-ol (propylene glycol n-propyl ether, PGnPE).

Toxicokinetic data for PGnPE are not available. Propylene glycol ethers in general are known to be rapidly absorbed and distributed throughout the body when introduced by inhalation or exposure (OECD SIDS, 2003b). Once absorbed, glycol ethers are readily distributed through the body (ECETOC, 2005a). Propylene glycol ethers may be conjugated at the OH-group and excreted as conjugates via the kidneys into the urine. However, the main pathway in the metabolism of propylene glycol ethers involves oxidation. In case of PGnPE this leads to oxidation products of the corresponding glycol, i.e., propan-1,2-diol (1,2-propylene glycol), and propan-1-ol. These two products may finally enter the intermediary metabolism via the citric acid cycle and may be completely metabolised to CO_2 and water (ECETOC, 2005a; OECD SIDS, 2003b).

The acute oral and dermal toxicity of PGnPE is low (oral and dermal LD50 > 2000 mg/kg bw in studies with rats or rabbits, respectively). Following dermal application of liquid PGnPE to the skin of rabbits, not only local dermal irritation effects were observed but also systemic toxicity with effects on the CNS, indicating that - as known from other glycols - PGnPE may be absorbed through the skin. No mortality was observed in any of the acute inhalation studies in rats at saturated vapour concentrations up to the maximum attainable concentration at room temperature (1725 ppm = 8400 mg/m^3) (ECHA Dissemination, 2021).

No studies with repeated oral or dermal exposure of animals to PGnPE are available.

Subacute inhalation toxicity studies with rats, guinea pigs and rabbits revealed CNS-depression with narcosis (followed by death in some of the rabbits) during or shortly after the exposure to 2000 ppm (9740 mg/m^3). Exposure to PGnPE also led to increased liver and kidney weights, probably as an adaptive response, but no histopathological lesions were observed in these or other organs. Especially in F344 rats, ocular lesions with corneal damage were observed after exposure to PGnPE vapour. In further studies, these lesions were observed in both control and PGnPE-exposed groups of F344 and Sprague-Dawley rats (ECETOC, 2005b; ECHA Dissemination, 2021). Mechanistic investigations indicated that the observed ocular changes were linked to a high incidence of corneal dystrophy in the rats used in the above-mentioned studies. Excluding animals with this spontaneous lesion prior to first exposure resulted in a NOAEC of ≥ 600 ppm (the highest concentration tested) in subacute inhalation studies with F344 and Sprague-Dawley rats (ECETOC, 2005b).

In a subchronic inhalation toxicity study following OECD guideline 413, Sprague-Dawley and F344 rats (each 20 M + 20 F/group) were exposed “whole body” to 0, 30, 100, or 300 ppm PGnPE vapour on 6 h/day, 5 d/week for 14 weeks. Half the animals of each strain and group were kept for an additional 3 -month recovery period. There were no exposure-related clinical signs during the study. The eyes of the animals did not show any exposure-related alterations. Body weight gain for the female F-344 rats at 300 ppm was 84 % of the weight gain in controls during exposure but was not different during the recovery period. No additional exposure-related differences in body weights or food and water consumptions were observed. Urine analyses were also normal. Female F-344 rats had a slight decrease in total leukocyte count (300 and 30 ppm groups) associated with a decrease in lymphocytes (300 ppm group); however, these hematologic effects did not show a clear-dose response and were absent at the end of the recovery period. No exposure-related gross lesions were identified at necropsy, and organ weights of PGnPE-exposed animals were normal. Furthermore, there were no microscopic histological lesions attributable to exposure. As the decreased body weight gain was only observed in one sex of one strain and as it was reversible during the recovery period, it was considered as not adverse and a NOAEC of 300 ppm was established from this study (ECHA Dissemination, 2021).

In vitro studies provided no evidence for genotoxic effects of PGnPE in bacteria and mammalian cells (ECHA Dissemination, 2021). In vivo studies with PGnPE are not available, but no genotoxicity (induction of micronuclei) was observed in studies with mice with the two structurally related propylene glycol ethers dipropylene glycol n-butyl ether (DPGnBE) and propylene glycol methyl ether (PGME) (ECHA Dissemination, 2021; OECD SIDS, 2003b).

Carcinogenicity studies with PGnPE are not available. The available data from genotoxicity studies in vitro and from repeated dose toxicity studies with PGnPE do not provide evidence for concern regarding carcinogenic effects of the substance. Also, glycol n-alkyl ethers in general are not regarded as to reveal a carcinogenic potential for humans (Ad-hoc AG, 2013; ECETOC, 2005a; OECD SIDS, 2003b).

Studies regarding effects of PGnPE on fertility are not available. PGnPE had no effects on reproductive organs in male and female rats in the subchronic inhalation study with rats mentioned above. Read-across using data from a two-generation reproductive toxicity study in rats with propylene glycol methyl ether (PGME) (Carney et al., 1999; OECD SIDS, 2003b) and a combined oral repeated dose and reproductive/developmental toxicity study with dipropylene glycol mono propyl ether (DPGnPE) (ECHA Dissemination, 2021; OECD SIDS, 2003a) provide no evidence for effects on fertility at concentrations or doses in the absence of general systemic toxicity. In a developmental toxicity study with rats, slight maternal toxicity (eye irritation, reduced weight gain) and a slight delayed ossification in foetuses but no embryotoxicity or teratogenicity were noted at 1500 ppm (7305 mg/m^3). Maternal toxicity was more pronounced in a similar developmental toxicity study rabbits, including mortality of dams at 1500 ppm; however, no developmental toxicity was observed up to 1500 ppm PGnPE, the highest concentration tested. No effects were noted in both species at 750 ppm (3653 mg/m^3) (ECHA Dissemination, 2021). It is concluded that the available data provide no concern for developmental toxicity of PGnPE.

Rationale for starting point

The derivation of the EU-LCI is based on data from a guideline study with subchronic inhalation exposure of rats. A NOAEC of 300 ppm (1461 mg/m^3, the highest concentration tested) was obtained for local and systemic effects in a subchronic inhalation toxicity study with two different strains of rats. This NOAEC is used as the POD for the derivation of an EU-LCI value for PGnPE.

Rationale for assessment factors

The following default factors are used (EC, 2013):

- Factor for adjustment for exposure duration: 5.6
- Adjusted study length factor: 2 (subchronic exposure)
- Allometric scaling (rat to human): 1
- Interspecies differences, remaining differences: 2.5
- Intraspecies differences: 10

Total extrapolation factor: 280, leading to a value of 300 ppm : 280 = 1.071 ppm.

1 ppm = 4.87 mg/m^3, leading to a value of 5218 µg/m^3.

An EU LCI value of 5200 µg/m^3 is proposed for 1-propoxypropan-2-ol (propylene glycol n-propyl ether, PGnPE).

Since no odour threshold is available for PGnPE, no conclusions can be drawn regarding olfactory perception of PGnPE at the proposed EU-LCI.

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4 Toxicological evaluation of methyl formate as basis for the derivation of an EU-LCI value

4.1 Substance identification

Substance identification data and physicochemical properties of methyl formate are shown in Table 16 and Table 17.

Table 16: Substance identification of methyl formate (ECHA Dissemination, 2020)

CAS-No. EU-No. CLP-Index-No.	Systematic name, common names	Summary formula	Structural formula
107-31-3 203-481-7 607-014-00-1	methyl formate; methyl methanoate; formic acid, methyl ester; methanoic acid methyl ester	$C_2H_4O_2$	

4.2 Substance properties and uses

Methyl formate is a clear colourless liquid with a pleasant characteristic odour (ECHA Dissemination, 2020). About 100000 - 100000000 tonnes of methyl formate are manufactured and/or imported into the European Economic Area annually (ECHA Dissemination, 2020).

A major proportion of methyl formate is produced as an intermediate during the production of formic acid and methanol (NLM, 2021; OECD, 2008). Methyl formate is also employed in organic syntheses (e.g., production of dimethylformamide or high purity carbon monoxide) (OECD, 2008). It is used as a solvent for fats, oils, fatty acids, cellulose ester, and acrylic resins (OECD, 2008). In 2008 it was reported that methyl formate was used in the production of foundry moulds (OECD, 2008). Formerly, it was used as a high-boiling refrigerant for house appliances (NLM, 2021; OECD, 2008). Furthermore, it can be used for crop protection as a fumigant and larvicide for food and tobacco crops (ACGIH, 2001; NLM, 2021; OECD, 2008; SCOEL, 2004).

Table 17: Physicochemical properties of methyl formate (ECHA Dissemination, 2020; NLM, 2021; OECD, 2008)

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa) (at 25°C)	Density (g/cm³, relative)	log Pow (at 25 °C)	Solubility in water (g/l) (at 20°C)
60.05	-99.8	31.5	780.9	0.97	-0.21	240

4.3 Exposure

4.3.1 Indoor air

Regarding the occurrence of methyl formate in indoor air only limited data is available.

Air quality monitoring was conducted at the end of construction and during the early occupation at a college. On five construction days hourly measurements of three contaminants (methyl formate, ethanol, and carbon monoxide) were taken. In one representative 24-hour

measurement, which is depicted as a diagram in the publication, measured methyl formate concentrations were approx. between 0.5 and 0.7 ppm during a workday. Additionally, single measurements of indoor air were taken at 1 p.m. each workday and analysed for contaminants as combined total amounts, which were averaged over periods (construction, ventilation testing, a two-week air-out (ventilation with fresh air to remove contaminants) , furniture move-in, initial student use, and two weeks after total occupation). Methyl formate was one contaminant that was monitored together with four other contaminants (propane, carbon monoxide, ethyl alcohol, and 3-pentanone) in a sum parameter. During construction the highest concentration (5.22 ppm) of the sum parameter occurred, which decreased continuously (air out: 1.90 ppm) until furniture was moved in (3.14 ppm), and staff and students used the college (3.28 and 3.66 ppm). However, the authors of the study do not regard the small amount differences as significant because detection limits overlapped. Unfortunately, individual contamination concentrations are not available for methyl formate (Valicenti and Wenger, 1997).

In chamber experiments, in which 58 materials were tested for their chemical emissions, three novel brands of building materials (e.g., one medium density fibreboard and two oriented strand board flooring materials) emitted methyl formate. Air samples of the chambers drawn after 24 hours determined peak concentrations in the range of 0.09 to 0.13 µg/m^3 for methyl formate. After 24 hours a reduction in emission was observed. Environment and Climate Change Canada concluded in its screening assessment from 2017 that by a ventilation system in place these low emissions of methyl formate would be rapidly eliminated from the indoor air and thus the emission from building materials although they might *"pose a risk of transient, low-level inhalation exposure"* are considered to be low for humans (Health Canada, 2017).

4.3.2 Other sources

Methyl formate occurs as an aroma flavour in apples and as a volatile constituent in brewed, roasted, and dried coffee (NLM, 2021; OECD, 2008; SCOEL, 2004). Additionally, it was detected in volatiles of chicken, beef, and pork flavour (NLM, 2021; OECD, 2008). As additional sources of methyl formate release, cigarette smoke and gasoline exhaust were identified (NLM, 2021; OECD, 2008; SCOEL, 2004).

4.4 Toxicokinetics

Systemic effects observed after inhalation and dermal exposure show that the substance is absorbed well via these exposure routes. Absorption via the oral route is also expected.

After absorption methyl formate is rapidly and almost completely (97%; no further details given) cleaved by esterases via an enzymatic hydrolytic reaction to methanol and formic acid (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019b; OECD, 2008). The metabolite methanol is oxidized via formaldehyde to formic acid (formate). Oxidation of formate by the saturable tetrahydrofolate system leads to carbon dioxide, which is exhaled (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019b). One mole methyl formate leads to the release of two moles of formate.

Methanol is eliminated more efficiently by primates (48 mg/(kg bw x h)) when compared to rats (30 mg/(kg bw x h)) (Greim and MAK Commission, 2003). Accumulation of formate can occur in primates in comparison to rats due to lower levels of tetrahydrofolate (50-75%), which results in a more rapid saturation of the tetrahydrofolate system. Therefore, the blood of primates may contain higher concentrations of formate, which can cause acidosis earlier in primates than in rodents (Hartwig and MAK Commission, 2019b). In volunteers no accumulation of formate concentration in blood was observed after an exposure to 200 ppm methanol vapours for six

hours. A slight increase in formate blood concentration was only observed after an exposure to 400 ppm methanol for eight hours (Hartwig and MAK Commission, 2019a).

A toxicokinetic model was established based on available data from volunteers and workers exposed to methyl formate via inhalation (dermal route was not excluded) and the urinary excretion of methanol and formate. It was predicted that an exposure over eight hours to 50 ppm methyl formate at an elevated respiratory volume results in an excretion of approx. 4.5 mg methanol/l in urine. Excretion of formate is three times higher than the background level, however the model seems to be overpredicting these results (Hartwig and MAK Commission, 2019b).

The fatal case report of a 19-month old child, which was exposed to a liniment containing methyl formate, methanol, and formate dermally under occlusive conditions on the head, indicate that methyl formate is absorbed well via this route.

Based on the physicochemical parameters for a saturated aqueous solution of methyl formate and using three different model calculations, fluxes of 188, 469, and 1185 µg/cm^2 x h were reported. The dermal exposure of a skin area of 2000 cm^2 for one hour would lead to absorbed amounts of 376, 938, and 2370 mg, respectively (Hartwig and MAK Commission, 2019b).

4.5 Health effects

4.5.1 Acute toxicity, sensory irritation and local effects

In the literature, it is reported that in humans the exposure via inhalation to 1500 ppm methyl formate vapours for one minute led to the recognition of the typical agreeable and pleasant odour without causing any signs of irritation or toxicity (Greim and MAK Commission, 2003).

In a blind study, 20 volunteers were exposed to 100 ppm methyl formate for eight hours at rest in inhalation chambers and sensory and neurobehavioural tests were performed, which were compared to 20 unexposed controls. The median concentrations of methanol in urine were determined before (2.0 mg/l (range: < 1–3.3 mg/l)) and after exposure (3.3 mg/l (range: 2.1–6.4 mg/l)). In case of formate, the median concentration in urine was 13.9 mg/g creatinine (range: 8.0–35.2 mg/g creatinine) before and 33.0 mg/g creatinine (range: 10.5–55.7 mg/g creatinine) after exposure. Of the investigated 20 parameters only two were different: subjective fatigue and electromyography in a neck muscle. A multi-variance analysis was conducted and showed that the influence of time on fatigue was more important than exposure. In the end the authors of the study concluded that exposure to methyl formate only slightly increased the subjects' tiredness without having an influence on the performance of the neurobehavioural tests (Greim and MAK Commission, 2003; Hartwig and MAK Commission, 2019b; Sethre et al., 2000a; Sethre et al., 1998a).

The application of a liniment containing methyl formate, methanol, and formate on the head of a 19-month old child under a bathing cap resulted in collapse, cyanosis, slowed breathing, non-responding reflexes, and respiratory arrest after 20 minutes. Except for a blood congestion in the small as well as in the large blood circulation, no further findings were seen during autopsy. Based on an alkaline hydrolysis, which was performed on the brain and liver, the methyl formate content was calculated to be 97.2 mg in the liver and 246.5 mg in the brain (ECHA Dissemination, 2020; Greim and MAK Commission, 2003).

A RD50 concentration (concentration which elicits a respiratory rate decrease of 50%) of 1109 ppm for irritation of the upper respiratory tract (extrapolated RD0 of 184 ppm) was calculated in mice exposed to 200-1168 ppm methyl formate. Pulmonary irritation was not

observed. For humans it was estimated that concentrations of 30-100 ppm methyl formate are not causing local irritating effects. But irritating effects on the olfactory epithelium can also be caused by methyl formate's metabolites methanol and formate which can be released directly in the nasal tissue via cleavage of esterases (Hartwig and MAK Commission, 2019b; OECD, 2008).

Acute toxicity after inhalation of methyl formate was investigated in various animal species. A LC50 value greater than 2085 ppm (5200 mg/m^3) was reported in rats exposed for 4 hours to methyl formate. The three-hour long exposure to 500 ppm methyl formate vapours led to sublethal lung oedema in mice (LC50: 3000 ppm). Guinea pigs exposed for five minutes to 1500 ppm and above showed signs of nasal irritancy, exposure for 3-10 minutes to 3500 ppm and above caused eye irritation, and exposure for 1-2 minutes to 10000 ppm and above led additionally to slow breathing, incoordination, narcosis, and death (Greim and MAK Commission, 2003).

In two studies (similar to OECD guideline 401) oral LD50 values of 1382-1500 mg/kg bw have been determined in rats (ECHA Dissemination, 2020; Greim and MAK Commission, 2003; OECD, 2008; SCOEL, 2004). In dermal toxicity studies (similar to OECD guideline 402), LD50 values of > 15689 mg/kg bw in rabbits and > 4000 mg/kg bw in rats were determined (ECHA Dissemination, 2020; Greim and MAK Commission, 2003; OECD, 2008; SCOEL, 2004).

Methyl formate was slightly irritating to the skin of rabbits (n=3) in a study similar to OECD guideline 404 (except prolonged exposure) after occlusive treatment for 24 hours. After eight days, erythema was still observed in 2 out of 3 rabbits (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019b; OECD, 2008).

In an eye irritation test in rabbits according to the US Federal Register guidelines, methyl formate did cause cornea opacity, iritis, as well as chemosis, and redness of the conjunctivae. The observed irritating effects were not reversible after eight days (ECHA Dissemination, 2020; Greim and MAK Commission, 2003; Hartwig and MAK Commission, 2019b; OECD, 2008).

A Buehler test in guinea pigs (according to OECD 406) did not reveal a dermal sensitising potential of methyl formate (ECHA Dissemination, 2020).

Acute inhalation studies showed that methyl formate causes signs of respiratory tract irritation (OECD, 2008).

4.5.2 Repeated dose toxicity

In the older literature there is one report about occupational exposure to vapours of a boiling solvent mixture containing 30% methyl formate and in unspecified amounts ethyl formate, methyl acetate, and ethyl acetate (details on exposure duration not given). Irritation of mucous membranes, visual disturbance (temporary blindness in one case), cardiovascular and central nervous symptoms such as shortness of breath, loss of memory, agitation, and depression were reported by ten exposed female workers. The reported symptoms were reversible after some time when exposure had stopped (ACGIH, 2001; ECHA Dissemination, 2020; Greim and MAK Commission, 2003).

In a workplace study, 21 foundry workers (23 respective controls) which were exposed to median concentrations of 47 ppm methyl formate (concurrent exposure to isopropyl alcohol, but concentration not given) or 68 ppm methyl formate (personal air sampling, range: 22-136 ppm) and 28 ppm isopropyl alcohol (personal air sampling, range: 6-73 ppm) performed neurobehavioural tests after their shifts. Lifetime exposure of workers to solvents were given in the range 1 week up to 26 years (Sethre et al., 1998b; Sethre, 1998). In urine the median methanol concentration of workers were < 1 mg/l (range: < 1–2.9 mg/l) before and 2.7 mg/l

(range: < 1–9.7 mg/l) after the shift. In case of formate, the median urine concentrations were 18.9 mg/g creatinine (range: 10.0–23.5 mg/g creatinine) before and 33.0 mg/g creatinine (range: 9.9–128.6 mg/g creatinine) after the shift. The methyl formate concentration in air correlates well with the methanol concentration in urine, which can be used for biomonitoring purposes. Exposure to methyl formate alone did not result in neurobehavioural effects in exposed workers. In three of 15 neurological behaviour tests, three workers with the highest exposure to methyl formate and isopropyl alcohol (maximum: 136 ppm methyl formate and 73 ppm isopropyl alcohol) performed worse than the workers exposed to low concentrations. The authors of the study attribute these effects to the exposure to isopropyl alcohol and not to methyl formate. In a follow-up examination of nine out of the 21 foundry workers the previous mentioned observations were not confirmed (Sethre et al., 2000b). The personal air sampling revealed a median concentration of 58 ppm methyl formate and maximum cumulative exposure of 150 ppm methyl formate and 375 ppm isopropyl alcohol. The only observation was that three workers with the highest levels of exposure performed poorer in the balance test. However, the author of the study attributed this effect to the normal group differences, which may occur due to the low number of subjects. Workers, who were exposed to higher concentrations of isopropyl alcohol or had higher methanol concentrations in urine showed a reduction in fatigue. Taking all together these workplace studies did not observe an explicit neurobehavioural effect caused by methyl formate (up to 150 ppm) (Greim and MAK Commission, 2003; Hartwig and MAK Commission, 2019b).

In a short-term repeated inhalation toxicity study (similar to OECD guideline 412), Wistar rats (5 M + 5 F/group) were exposed via “whole body” to 0, 100, 500 or 1500 ppm methyl formate (0, 0.252, 1.237, 3.693 mg/l, concentrations analytically confirmed) for 6 h/d, 5 d/week, over 2 weeks. Neither clinical signs nor mortality were observed during the study. The terminal body weights of rats were markedly decreased (-14.3% in males, -9.3% in females) in the highest concentration group compared to controls. At 500 ppm and above histopathological alterations in the olfactory epithelium in the nose (multifocal degeneration, and necrosis) were observed, which increased concentration dependent. In the mid concentration group only one male and one female were affected. Additionally, squamous metaplasia and infiltration of inflammatory cells were seen in the respiratory tract of the mid concentration group (one male and two females). Organ weight changes of liver, lung, kidney, and spleen were altered in the highest concentration group. The derived NOAEC and LOAEC for local effects in the study were 100 and 500 ppm, respectively. Based on body weight and organ weight changes at the highest tested concentration, NOAEC and LOAEC for systemic effects of 500 and 1500 ppm were derived (Hartwig and MAK Commission, 2019b; OECD, 2008).

A subchronic inhalation toxicity study reported to be conducted according to OECD guideline 413 is only published in Korean language with an abstract in English. Sprague-Dawley rats were exposed to 0, 100, 400 or 1600 ppm methyl formate for 6 h/d, 5 d/week and 13 weeks. At 400 ppm and above, a concentration-dependent reduction in feed intake and body weight development was observed. In addition, females of the mid and high concentration group had increased relative organ weights of ovaries, adrenals, and brains, which were regarded as caused by the decreased body weights. A statistically significant increase of almost all investigated relative organ weights and alterations in haematological and blood parameters were seen in animals of the highest concentration group. Atrophy of the respiratory tract in the nose as well as degeneration, regeneration, and contraction of olfactory cells were reported (no further details provided). In the study a NOAEC and LOAEC for local effects of 400 and 1600 ppm were derived. Based on the observed effects on body weight development and organ weights, a NOAEC and LOAEC of 100 and 400 ppm were derived for systemic effects (Hartwig and MAK Commission, 2019b; Kim et al., 2010). In its evaluation from 2019, MAK states that the reduced

body weight development might be a secondary effect due to the decreased food consumption. Furthermore, the reported NOAEC for local effects is not contradicting to the NOAEC for local effects reported in the subacute study (see previous section) as only a few animals of the 500 ppm group in the subacute study were affected (Hartwig and MAK Commission, 2019b).

4.5.3 Genotoxicity and carcinogenicity

Genotoxicity

Methyl formate was not mutagenic in *in vitro* bacterial mutation assays (Ames test) with and without exogenous metabolic activation system (S9 mix from rat/hamster liver) in all tested strains of *Salmonella typhimurium* (TA97, TA98, TA100, TA1535, TA1537, TA1538) (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019b).

Methyl formate was not clastogenic *in vivo* in a micronucleus test in male ICR mice (n=6) at doses up to 1000 mg/kg bw, no clinical signs were observed (Hartwig and MAK Commission, 2019b).

Carcinogenicity

No data is available for this endpoint for methyl formate.

Data on methyl formate's metabolite methanol is used as read-across source. Formate is not further considered as humans are less susceptible for a significant accumulation of formate after exposure to methyl formate (see section 4.4) and no valid carcinogenicity or chronic study conducted with formate is available (Greim and MAK Commission, 1997; Greim and MAK Commission, 2003; Hartwig and MAK Commission, 2019b).

Read-across: methanol

A carcinogenicity study was conducted with methanol inhalation exposure of rats and mice. Up to the highest concentration tested (1000 ppm), no significant evidence of carcinogenicity was observed. An indication of an increase in proliferative changes in the alveolar epithelium of the lungs of male animals was observed in rats. A slight, but not statistically significant, increase in the incidence of adrenal pheochromocytomas was noticed in females exposed to 1000 ppm. The maximum tolerated dose was not achieved in both species; however methanol's metabolism was already saturated at the highest concentration of 1000 ppm (Greim and MAK Commission, 2003; Hartwig and MAK Commission, 2019a).

In a drinking study it is reported that methanol (no further details provided) led to increased incidences of animals bearing a tumour, "lympho-immunoblastic lymphomas" predominantly in the lungs of female rats, and carcinomas of the ear canal in male rats. However, a re-evaluation of a pathology working group from US EPA and NTP did not confirm the reported results (Hartwig and MAK Commission, 2019a).

4.5.4 Toxicity to reproduction

There are no studies available with exposure to methyl formate. Data on methyl formate's metabolite methanol is used as read-across source (for justification see section 4.5.3).

Fertility

Read-across: methanol

In a two-generation reproduction toxicity study (similar to OECD guideline 416) Sprague-Dawley rats (30 animals per sex and concentration group in F0 generation) were exposed via inhalation (whole-body) continuously to 0, 10, 100, or 1000 ppm methanol (0, 0.013, 0.13, or

1.3 mg/l, nominal concentration) for 19-20 h/d. No adverse effects were observed in the F0 generation. Methanol concentrations up to 1000 ppm did not result in adverse reproduction effects in the F0 or F1 generation (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019a). The 100 ppm concentration group showed no effects on reproduction or development in the parent animals as well as in the offspring (F1 and F2). At 1000 ppm decreased absolute and relative brain weights were observed in offspring of the F1 and F2 generations in either sex at an age of 8 and 16 weeks. However, neither histological findings nor significantly difference in neurobehavioural tests were seen. In male rats of the F1 and F2 generation exposed to the highest concentration descending of testes was observed 0.5 to 1 d earlier compared to controls. Additionally, males of the F2 generation had lower thymus and pituitary weights. Due to the long exposure of up to 20 hours daily, a prolonged steady-state blood level of methanol was reached, which was 76 mg/l and might be higher than a shorter exposure at the same exposure concentration. In conclusion the NOAEC was 1000 ppm (highest tested concentration) for F0 animals. For F1 and F2 animals the NOAEC was 100 ppm and the LOAEC 1000 ppm based on decreased brain weights and earlier descending testis (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019a; OECD, 2008).

No change in sex hormones was observed in male rats either exposed once for 6 hours to 5000 ppm methanol or for 6 h/d for seven days to 200 ppm (Hartwig and MAK Commission, 2019a). Testis weight was unchanged in rats exposed for 13 weeks to 200 ppm methanol and histopathological examinations of testes did not find any effects at 800 ppm (Hartwig and MAK Commission, 2019a).

Male mice treated with 1000 mg methanol/(kg bw x d) orally for five consecutive days showed a slight but not statistically significant increase in sperm abnormalities (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019a).

In a one-generation reproduction toxicity study in cynomolgus monkeys (n=12 per concentration group), which were exposed to 0, 200, 600, or 1800 ppm methanol vapour (0, 0.27, 0.8, 2.39 mg/l air, nominal concentration) via inhalation daily for 2.5 hours prior to, during breeding, and gestation (approx. 350 days), no overt signs of systemic toxicity were observed in parent animals of all concentration groups. Although complications occurred during gestation and were noted in the low and mid concentration group (e.g., vaginal bleeding and prolonged labour) these were not statistically significant and did not influence the reproductive performance. The duration of pregnancy was decreased (6 to 8 days) in all treated concentration groups compared to controls. However, this effect was not concentration dependent and no effects in offspring were seen, thus it cannot be solemnly related to methanol exposure. No mortalities nor malformations of offspring were observed. In the highest concentration group two out of seven female offspring aged 12 months had a ‘wasting syndrome’, which was characterised by growth retardation, malnutrition, and gastroenteritis. In two out of nine neurobehavioural tests in the offspring, dose-dependent effects were not clear (especially delayed sensorimotor development in males) (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019a; OECD, 2008). For maternal toxicity and fertility, a NOAEC of 1800 ppm was suggested by the MAK commission. The MAK commission (2019a) regarded the study as “only limited reliable” due to its small sampling size and short exposure duration of 2.5 hours daily, which did not result in a steady state. Thus, a NOAEC/LOAEC for developmental toxicity is not derived (Hartwig and MAK Commission, 2019a). However, the findings in monkeys can be used to support the results obtained in rodent studies.

Development

There are no studies available with exposure to methyl formate. Data on methyl formate's metabolite methanol is used as read-across source (for justification see section 4.5.3).

Read-across: methanol

The prenatal developmental toxicity of methanol was studied (similar to OECD guideline 414) in rats (number of animals per sex and dose not provided) exposed via inhalation at concentrations of 5000 or 10000 ppm (6.65 or 13.3 mg/l) for 7 h/d on GD 1-19. An additional group was exposed to 20000 ppm methanol (26.6 mg/l) on GD 7-15. No maternal toxicity was observed at 10000 ppm, but foetal body weight was reduced. In the highest concentration group unsteady gait of dams and malformations occurred (extra cervical ribs, defects on cardiovascular system and urinary tract, encephalocele, and exencephaly). In dams methanol concentration in blood was 1580 mg/l at 5000 ppm and 2040 mg/l at 10000 ppm. As no adverse effects were observed at the lowest concentration the derived NOAEC for developmental effects was 5000 ppm and thus the LOAEC 10000 ppm. For maternal toxicity, a NOAEC of 10000 and a LOAEC of 20000 ppm were derived (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019a; OECD, 2008).

In a similar study, rats were continuously exposed to 0, 200, 1000, and 5000 ppm methanol (0.27, 1.33, and 6.65 mg/l, approx. 22.7 h/d) from GD 7-17. Maternal toxicity was observed in the highest concentration group. Additionally, a reduction in the number of living foetuses, decreased foetal body weight at PND 4, and skeletal and visceral malformations were seen in this group. The postnatal development of these offspring was delayed (e.g., breakthrough of incisors and eye lid opening). The descent of testes was premature in male offspring. A decrease in absolute and relative brain, thyroid, thymus, and testis weights and an increase in absolute and relative pituitary gland weight were noted in males at the age of 8 weeks. In female offspring only the absolute brain weights were lower. No treatment-related changes were found in histological examinations in both sexes. For maternal and developmental toxicity, a NOAEC of 1000 ppm and a LOAEC of 5000 ppm were derived (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019a; OECD, 2008).

Mice (number of animals per sex and concentration vary from 6 (15000 ppm) to 70 (controls)) were exposed to 0, 1000, 2000, 5000, 7500, 10000 or 15000 ppm methanol (1.33, 2.66, 6.65, 9.97, 13.3, 19.94 mg/l, nominal concentrations) from GD 6-15. No maternal toxicity was observed up to the highest tested concentration. No adverse effects were observed in offspring of the lowest concentration. At 2000 ppm offspring had a higher incidence for an extra cervical rib and at 5000 ppm and above teratogenic effects (cleft palate, exencephaly, defects of the sternum and internal organs) were noted. An increase in embryo or foetal death occurred at 7500 ppm and above. At 10000 ppm and above foetal body weight was reduced. In the highest tested concentration almost complete resorption of foetuses were observed. The measured methanol concentration in blood of the dams was 97, 537, and 1650 mg/l at 1000, 2000, and 5000 ppm, respectively. For maternal toxicity, a NOAEC of 15000 ppm was derived. Due to the observed effects at higher concentrations, a NOAEC of 1000 ppm and a LOAEC of 2000 ppm were derived for developmental effects (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019a; OECD, 2008). Mice are more susceptible to methanol exposure than rats. An explanation might be the accumulation of methanol in blood, which can be caused by the higher respiration and resorption rate of mice than rats. The teratogenic effects observed in mice were associated with methanol itself and not caused by its metabolite formate (Hartwig and MAK Commission, 2019a).

4.5.5 Odour perception

The odour of methyl formate is reported to be characteristic, but pleasant or agreeable (Hartwig and MAK Commission, 2019b; NLM, 2021). In a study from 2003, an odour threshold of 130 ppm equal to 321 mg/m^3 at 23°C was measured for methyl formate by applying the triangle odour bag method (Nagata, 2003). In the literature, a broader range for the odour threshold of methyl formate is given ranging from 600 to 2000 ppm (1500 to 5000 mg/m^3) (Hartwig and MAK Commission, 2019b; SCOEL, 2004).

4.6 Evaluation

4.6.1 Existing regulations and classifications

In its harmonised classification methyl formate is classified for flammable liquid category 1 (H224), acute toxicity category 4 * (H302 and H332, * = minimum classification), eye irritation category 2 (H319), and specific target organ toxicity - single exposure (H 335) (ECHA C&L Inventory, 2020).

Existing guide values for methyl formate in air are summarised in Table 18.

A NIK (Lowest Concentration of Interest) value was neither derived for methyl formate nor its metabolites methanol and formate (AgBB, 2018).

In the registration dossier for methyl formate, a DNEL of 14.29 mg/m^3 for the protection of the general population via inhalation route has been reported. The dose descriptor used was the worker-DNEL long-term for the inhalation route (see below) which was corrected for the differences in duration of exposure between worker and consumer (24h per day, 7 days per week) and the intraspecies difference (ECHA Dissemination, 2020).

Table 18: Guide values for methyl formate in air (for explanation, see text)

Guide value Parameter/ Organisation	SCOEL (2004)	MAK commission (2019)	ECHA Dissemination (2020)	ECHA Dissemination (2020)
Name (reference period)	Indicative occupation exposure limit value (2004)	MAK value (2019)	DNEL (chronic, general population)	DNEL (chronic, workers)
Value (mg/m³)	125 (50 ppm)	120 (50 ppm)	14.29	120 (50 ppm)
Organ/critical effect	Effects on CNS	Effects on CNS, degeneration of olfactory epithelium (rat)	Effects on the CNS, degeneration of olfactory epithelium (rat)	Effects CNS, degeneration of olfactory epithelium (rat)
Species	human/rat	human/rat	human	human
Basis	NOAEC: 250 mg/m³ (100 ppm)	NOAEC: 250 mg/m³ (100 ppm)	DNEL (chronic, workers)	NOAEC: 250 mg/m³ (100 ppm)
Adjusted for cont. exposure	-	-	-	-
Extrapolation factors				
Time	-	-	4.2	-
LOAEC to NOAEC	-	-	-	-
Interspecies	-	-	-	-
Intraspecies	-	-	2 (general population)	-
Other#	2 (workers)#	2 (workers)#		2 (workers)*
Total	2	2	8.4	2
Remarks			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 10 for consumers).	The guide value corresponds to the derived occupational exposure limit value by SCOEL and the German MAK commission.

#: MAK/SCOEL apply an assessment factor of 2, which considers that the systemic effect from a study with volunteers at rest needs to be extrapolated to the increased respiratory minute volume at the workplace

*: for this assessment factor no further details are provided

A DNEL of 120 mg/m^3 for workers is reported in the registration dossier for methyl formate on the ECHA website. The German MAK commission set the same value as MAK-value in 2019. SCOEL published an indicative occupational exposure limit value of 125 mg/m^3 in 2004. In Germany, an OEL value of 120 mg/m^3 (50 ppm) based on the substance evaluation by the MAK commission is in force (AGS, 2021). The basis for the limit value derived by the MAK commission are a volunteer study supported by workplace studies (also exposure to isopropyl alcohol) and data from repeated exposure via inhalation in rats. A single exposure of volunteers to 100 ppm (250 mg/m^3) methyl formate for eight hours at rest resulted in subjective tiredness, but no adverse effects were observed in neurobehavioural tests. No adverse effects in neurobehavioural tests were noted in workers exposed up to 150 ppm methyl formate (co-exposure to isopropyl alcohol). Therefore, SCOEL and the MAK commission derived a NOAEC of 100 ppm (250 mg/m^3) based on central nervous effects. As the volunteer study was conducted on subjects which were not physically active an intraspecies factor of 2 was applied in order to compensate for the higher respiratory rate (10 m^3/8 h) of workers. Thus, the derived MAK value and the indicative occupational limit value derived by SCOEL were 50 ppm (120 or 125 mg/m^3, respectively). This limit value is further supported by the subchronic inhalation study in rats (see section 4.5.2) reporting a NOAEC of 400 ppm for local effects. Based on this NOAEC a limit value for local toxicity of 50 ppm could be derived by applying a factor of 6 (3 for interspecies differences and 2 for an increase of the effect after prolonged exposure as observed effects on the respiratory tract did not occur after subacute exposure) and considering the preferred value approach. In its evaluation from 2019, the MAK commission states that the systemic effects observed in the subchronic rat study (reduced body weight development) might be a secondary effect due to the decreased food consumption (Hartwig and MAK Commission, 2019b). For systemic toxicity, the derived limit value would be below 50 ppm based on a NOAEC of 100 ppm and the application of a factor of 4 (2 for interspecies differences and 2 for an increase of the effect after prolonged exposure).

However, as the rat inhalation study is based on a worst-case approach it is not in contradiction to the derived MAK value of 50 ppm based on a study in volunteers and supported by two studies from workplaces (Hartwig and MAK Commission, 2019b).

4.6.2 Derivation of an EU-LCI value

The data basis for methyl formate is limited. However, additional data is available from several studies with methyl formate's metabolite methanol.

Methyl formate can be absorbed via the inhalation, dermal, and oral route. Irritation of the olfactory epithelium was observed in animal studies after acute and repeated exposure either caused by methyl formate or by its metabolites.

Data from inhalation studies in humans and animals showed that the most critical effects of methyl formate are its systemic effect on the central nervous system as well as impairments to the olfactory and respiratory epithelium of rats (Hartwig and MAK Commission, 2019b). After a single exposure to 100 ppm in volunteers, subjective tiredness was observed, but neurobehavioural tests were unobtrusive. Workplace studies in which exposures to median concentrations of 47 or 58 ppm methyl formate (maximum: up to 150 ppm) occurred showed no explicit effects caused by methyl formate exposure (Sethre et al., 2000b; Sethre et al., 1998b). A subchronic study in rats exposed to concentrations up to 1600 ppm methyl formate supported these finding and derived a NOAEC of 400 ppm for local effects on the respiratory tract in the nose and a NOAEC of 100 ppm for systemic effects (Kim et al., 2010). In a subacute inhalation study in rats the reported NOAEC for local effects was 100 ppm but only one animal per sex of the 500 ppm group were affected. Thus, the MAK commission in its evaluation from 2019

concluded that the NOAEC for local effects reported in the subchronic study is not contradicting to the NOAEC for local effects reported in the subacute study (Hartwig and MAK Commission, 2019b).The authors of this evaluation agree with the conclusion by the MAK commission as only a few animals were affected at 500 ppm in the subacute toxicity study.

In vitro genotoxicity studies conducted with methyl formate in prokaryotes were negative. Also, an *in vivo* micronucleus assay in mice was clearly negative, indicating that methyl formate is not clastogenic.

Data on carcinogenic effects of methyl formate are not available. A read-across with a carcinogenicity study in rats with methanol provided no evidence for a carcinogenic activity of this compound.

Neither fertility/reproduction nor developmental toxicity studies are available for methyl formate. Read-across using data from a two-generation reproduction toxicity study and investigation of sperm morphology in rats and a one-generation reproduction toxicity study in monkey with methanol provided no evidence for reproduction toxicity (see section 4.5.4).

Teratogenic and embryotoxic effects of methanol were observed at high concentrations in mice (≥ 2000 ppm, exposure GD 6-15) and in rats (≥ 5000 ppm, exposure GD 1-19). The derived NOAECs for prenatal developmental toxicity were 1000 ppm methanol in mice and 5000 ppm methanol in rats, which corresponds to methanol blood concentrations of 97 mg/l in mice and 1580 mg/l in rats. In comparison, an 8-hour long exposure to 800 ppm methanol led in humans (at rest) to blood concentration of 30 mg/l. According to Hartwig and MAK Commission (2019a) an exposure concentration of 1000 ppm methanol would correspond to 37 mg/l (at rest) and approx. 75 mg/l (in activity). The MAK commission concluded in its evaluation on methanol from 2019 that the space between methanol blood concentrations leading to developmental toxicity and the limit value for methanol (100 ppm) are sufficient (Hartwig and MAK Commission, 2019a). Additionally, the formate concentration did not increase when volunteers were exposed to 200 ppm methanol for six hours. However, a slight increase in formate blood concentration in humans was only observed after an exposure to 400 ppm methanol for eight hours. Therefore, the MAK commission also regards the limit value of 50 ppm methyl formate as safe. As outlined in section 4.4, the metabolism of methanol in humans is dependent on tetrahydrofolate. The limit value also sufficiently protects against developmental effects caused by methanol during folate deficient pregnancies (Hartwig and MAK Commission, 2019a).

As a starting point for the derivation of an EU-LCI value, the NOAEC of 100 ppm (250 mg/m^3) determined in a volunteer study and supported by workplace studies is regarded as appropriate.

The following assessment factors are used:

- Adjustment for continuous exposure (8 h/d, 5 d/week): 4.2
- Adjusted study length factor: 2
- Interspecies extrapolation: not required
- Intraspecies extrapolation (interindividual variability, general population): 10

In a conservative approach, an assessment factor of 2 was applied for study length to consider that a few of the foundry workers have not been exposed chronically. No factor was used for interspecies differences.

Total assessment factor: 84 leading to a value of 250 mg/m^3 : 84 = 2.976 mg/m^3 (2976 µg/m^3, 1.204 ppm) for methyl formate (rounded to 3000 µg/m^3).

If the subchronic inhalation study in rats with a NOAEC for local effects of 400 ppm is used as a POD, the following assessment factors need to be considered: 5.6 for continuous exposure (6 h/d, 5 d/w), 2 for adjustment of study length, 2.5 for interspecies differences (allometric scaling not performed since route of exposure is inhalation), and 10 for intraspecies differences. By applying the total assessment factor of 280, a value of 400 ppm: 280 = 1.428 ppm (3530 µg/m^3) is calculated for methyl formate, which is in the same range as the proposed EU-LCI value.

The proposed EU-LCI value is also supported by a value derived for ethyl formate, which is the closest homologue compound within the chemical class 'carboxylic acid esters' and an adequate data base. For ethyl formate, a value according to the standards of deriving an EU-LCI value was calculated to be 3571 µg/m^3 and was based on nasal irritation (olfactory damage and squamous metaplasia) and systemic effects on the central nervous system and body weights. Taking into account the molar mass of methyl formate (60.05 g/mol) and of ethyl formate (74.08 g/mol), the value for ethyl formate corresponds to an EU-LCI value of 2895 µg/m^3 (rounded to 2900 µg/m^3) for methyl formate on a molar basis. This value is in the same range as the proposed EU-LCI value for methyl formate based on the derived OEL/MAK value.

An EU-LCI value of (rounded) 3000 µg/m^3 is proposed for methyl formate.

The proposed EU-LCI value is below the odour threshold of 321 mg/m^3 reported by Nagata (Nagata, 2003).

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D Appendix

D.1 Fact and data sheet for methyl formate

Table 19: Data collection sheet for methyl formate

Compound	Methyl formate	Data collection sheet	
Nº CAS 107-31-3) 1 ppm = 2.47 mg/m³ at 23 °C	**EU-Classification: -** **CLP,** harmonised classification: Flam. Liq. 1 (H224), Acute Tox. 4 * (H302 and H332), Eye Irrit. 2 (H319), STOT SE (H335); *minimum classification		
Organisation name	MAK commission	SCOEL	REACH registrants
Risk value name	MAK value	Indicative OEL	DNEL
Risk value (mg/m³)	120	125	14.29
Reference period	Acute (general population), subchronic (rat)	Acute (general population), subchronic (rat)	Chronic (general population)
Risk value (mg/m³) Short term (15 min)	250	250	-
Year	2019	2004	2020
Key study	Study reports from Sethre et al. (1998a; 1998b; 2000a; 2000b) mentioned by MAK (2003) and (2019)	Study reports from Sethre et al. (1998a; 1998b; 2000a; 2000b) mentioned by SCOEL (2004)	Derived OEL/MAK value
Study type	Volunteer study (human)	Volunteer study (human)	Volunteer study (human)
Species	Human	Human	Human
Duration of exposure in key study	8 h	8 h	8 h
Critical effect	Effects on CNS (subjective tiredness)	Effects on CNS (subjective tiredness)	Effects on CNS (subjective tiredness)
Critical dose value	NOAEC: 250 mg/m³ (100 ppm)	NOAEC: 250 mg/m³ (100 ppm)	DNEL (chronic, workers): 120 mg/m³ (based on a NOAEC: 250 mg/m³ (100 ppm))
Adjusted critical dose	-	-	-

Compound	Methyl formate	Data collection sheet	
Single assessment factors	UF_H 2 = 2	UF_H 2 = 2	UF_H 2 x UF_T 4.2 = 8.4
Other effects			
Remarks	Derived MAK value is supported by workplace studies in humans and a subchronic inhalation study in rats.	Derived OEL value is supported by workplace studies in humans and a subchronic inhalation study in rats.	

OEL occupation exposure limit; UF_H Intraspecies variability; UF_T time extrapolation

Table 20: Fact sheet methyl formate

Compound		Methyl formate C2H4O2	Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	3000
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2021
General information			
CLP-Index No.	4	INDEX	607-014-00-1
EC-No.	5	EINECS	203-481-7
CAS-No.	6	Chemical Abstract Service number	107-31-3
Harmonised CLP classification	7	Human health risk related classification	Acute Tox. 4 * (H302 and H332), Eye Irrit. 2 (H319), STOT SE (H335) * minimum classification
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	60.05 1 ppm = 2.471 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	Volunteer study and workplace studies by Sethre et al. (1998a; 1998b; 2000a; 2000b) mentioned by Greim (2003) and Hartwig (2019)
Read across compound	10	Where applicable	-
Species	11	Rat, human, etc.	Human
Route / type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic, etc.	Acute/subchronic
Exposure duration	14	h/d, d/w	8 h, 5 d/w
Critical endpoint	15	Effect (s), site of	Central nervous system
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEC
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	250 mg/m³ (100 ppm)
Assessment factors (AF)			
Adjustment for exposure duration	19	Study exposure h/d, d/w	4.2
Study length	20	sa→sc→c	2

Compound	Methyl formate C2H4O2		Fact sheet
Route-to-route extrapolation factor	21	-	1
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	1
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		1
Other adjustment factors Quality of database	26	Quality of database	1
Results			
Summary of assessment factors	27	Total Assessment Factor	84
POD/TAF	28	Calculated value [µg/m³ and ppb]	2976 µg/m³ (1204 ppb)
Molar adjustment factor	29		-
Rounded value	30	[µg/m³]	3000
Additional comments	31		
Rationale selection	32		

Data compilation and evaluation for methyl formate is based on a project funded by the German Environment Agency (Voss et al., 2021).

Rationale for critical effects and starting point

The data base for methyl formate is limited. No data regarding carcinogenicity and fertility/reproduction or developmental toxicity of methyl formate were available. Thus, when necessary and available, data for methyl formate's metabolite methanol was reported as read-across.

As shown in inhalation studies in humans and animals, the most critical effects of methyl formate are its systemic effect on the central nervous system as well as impairments to the olfactory and respiratory epithelium (Hartwig and MAK commission, 2019). Single exposure to 100 ppm methyl formate resulted in subjective tiredness in volunteers, but no significant effect was seen in neurobehavioural tests (Sethre et al., 1998a; Sethre et al., 2000a). Workplace studies in which exposures to median concentrations of 47 or 58 ppm methyl formate (maximum: up to 150 ppm) occurred showed no explicit effects caused by methyl formate exposure (Sethre et al.,

1998b; Sethre et al., 2000b). A subchronic study in rats exposed to concentrations up to 1600 ppm methyl formate supported these finding and derived a NOAEC of 400 ppm for local effects on the respiratory tract in the nose (Kim et al., 2010). In 2019, the MAK commission derived a limit value of 120 mg/m³ (50 ppm), which is also the OEL value in force in Germany, based on the previous mentioned data base. The derived MAK/OEL limit value is also protecting against developmental effects caused by methanol during pregnancies.

As a starting point for the derivation of an EU-LCI value, the NOAEC of 100 ppm (250 mg/m³) determined in a volunteer study and supported by workplace studies is regarded as appropriate.

Rationale for assessment factors

- Adjustment for continuous exposure (8 h/d, 5 d/w): 4.2
- Adjustment for study length: 2
- Intraspecies extrapolation (interindividual variability, general population): 10

In a conservative approach, an assessment factor of 2 was applied for study length to consider that a few of the foundry workers have not been exposed chronically. No factor was used for interspecies differences.

Total assessment factor: 84 leading to a value of 250 mg/m³ : 84 = 2.976 mg/m³ (2976 µg/m³, 1.204 ppm) for methyl formate.

If the subchronic inhalation study in rats with a NOAEC for local effects of 400 ppm is used as a POD the following assessment factors need to be considered: 5.6 for continuous exposure (6 h/d, 5 d/w), 2 for adjustment of study length, 2.5 for interspecies differences (allometric scaling not performed since route of exposure is inhalation), and 10 for intraspecies differences. By applying the total assessment factor of 280, a value of 400 ppm : 280 = 1.428 ppm (3530 µg/m³) is calculated for methyl formate, which is in the same range as the proposed EU-LCI value.

The proposed EU-LCI value is also supported by a value derived for ethyl formate, which is the closest homologue compound within the chemical class 'carboxylic acid esters' and an adequate data base. For ethyl formate, a value according to the standards of deriving an EU-LCI value was calculated to be 3571 µg/m³ and was based on nasal irritation (olfactory damage and squamous metaplasia) and systemic effects on the central nervous system and body weights. Taking into account the molar mass of methyl formate (60.05 g/mol) and of ethyl formate (74.08 g/mol), the value for ethyl formate corresponds to an EU-LCI value of 2895 µg/m³ (rounded 2900 µg/m³) for methyl formate on a molar basis. This value is in the same range as the proposed EU-LCI value for methyl formate based on the derived OEL/MAK value.

An EU-LCI value of (rounded) 3000 µg/m³ is proposed for methyl formate.

The proposed EU-LCI value is below the odour threshold of 321 mg/m³ reported by Nagata (Nagata, 2003).

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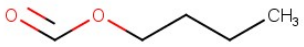
5 Toxicological evaluation of butyl formate as basis for the derivation of an EU-LCI value

5.1 Substance identification

Substance identification data and physicochemical properties of butyl formate are shown in Table 21 and Table 22.

Butyl formate is a colourless to pale yellow liquid with a characteristic odour (FAO, 2021; NLM, 2021b).

Table 21: Substance identification of butyl formate (ECHA Dissemination, 2020)

CAS-No. EU-No. CLP-Index-No.	Systematic name, common names	Summary formula	Structural formula
592-84-7 209-772-5 607-017-00-8	butyl formate; butyl methanoate; formic acid, butyl ester;	$C_5H_{10}O_2$	

5.2 Substance properties and uses

Butyl formate belongs to the class of formate esters and can be obtained by condensation of formic acid with butan-1-ol (NLM, 2021b). It is miscible with alcohol, ether, and most organic solvents, but only poorly soluble in water (NLM, 2021b; Ortelt, 2020). Butyl formate is used mainly as a flavouring agent and to a lesser degree as a solvent or fragrance (NLM, 2021b). No data on the production volume of this substance could be identified in the available literature.

Table 22: Physicochemical properties butyl formate (NLM, 2021b)

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa) (at 25°C)	Density (g/cm³, relative)	log Pow (at 25 °C)	Solubility in water (g/l) (at 20°C)
102.13	-91.50	106.10	29.00	0.92	1.32	7.50

5.3 Exposure

5.3.1 Indoor air

Few data are available regarding the occurrence of butyl formate in indoor air (see Table 23). Butyl formate could be detected in approx. 30% of all samples (n=818) from offices, homes, and (pre)schools in Germany. The measured concentrations were low as indicated by a mean of 0.5 µg/m^3 (UBA, 2008). According to another evaluation based on 2847 measurements, concentrations exceeding 1.0 µg/m^3 may be considered as “conspicuous value” (corresponding to the 90th percentile of measured concentrations) (AGÖF, 2013).

Table 23: Data on the occurrence of butyl formate in indoor air from homes, schools, children day care centres and offices

Rooms	N	LoD (µg/m³)	N > LoD	Median (µg/m³)	P95 (µg/m³)	Maximum (µg/m³)	Source
Offices, homes, (pre)-schools, Germany	818	0.4 – 5.0 (mean: 1.0)	241	0.5	4.0	52	(UBA, 2008)
Indoor air (not further specified), Germany	2847	not reported		< 1	1.0*		(AGÖF, 2013)

* given as P90 value

5.3.2 Other sources

The substance naturally occurs in apples, strawberries, blackcurrant, sherry, and Parmesan cheese (NLM, 2021b).

5.4 Toxicokinetics

Absorption of butyl formate via the oral or inhalation route are expected. Systemic effects observed after exposure via inhalation show that the substance is absorbed via this route. However, no reliable quantitative data are available (NLM, 2021b).

Further data on absorption, distribution, excretion, and metabolism of butyl formate are not available.

Read-across: methyl formate

Systemic effects observed after inhalation, dermal or oral exposure show that methyl formate is absorbed via these pathways. After absorption methyl formate is almost completely (97%; no further details given) and rapidly cleaved by esterases via an enzymatic hydrolytic reaction to methanol and formic acid (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019b; OECD, 2008). The metabolite methanol is oxidised via formaldehyde to formic acid (formate). Oxidation of formate by the saturable tetrahydrofolate system leads to carbon dioxide, which is exhaled (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019b). Thus, one mole methyl formate leads to the release of two moles of formate.

Methanol is eliminated more efficiently by primates (48 mg/(kg bw x h)) when compared to rats (30 mg/(kg bw x h)) (Greim and MAK Commission, 2003). Accumulation of formate can occur in primates in comparison to rats due to lower levels of tetrahydrofolate (50-75%), which results in a more rapid saturation of the tetrahydrofolate system. Therefore, the blood of primates may contain higher concentrations of formate which can cause acidosis in primates earlier than in rodents (Greim and MAK Commission, 2003). No accumulation of formate concentration in blood was observed in volunteers after an exposure for six hours to 200 ppm methanol vapours. A slight increase in formate blood concentration was only observed after an exposure to 400 ppm methanol for eight hours (Hartwig and MAK Commission, 2019a).

A toxicokinetic model based on available data on volunteers and workers predicts that an exposure over eight hours to 50 ppm methyl formate at an elevated respiratory volume results in an excretion of approx. 4.5 mg methanol/l in urine. Excretion of formate is three times higher

than the background level, however the model seems to be overpredicting these results (Hartwig and MAK Commission, 2019b).

Read-across: ethyl formate

Ethyl formate can be absorbed via inhalation, ingestion, and to a lesser extent by the dermal route (ECHA Dissemination, 2020). Enzymatic hydrolysis of ethyl formate leads to the formation of formate and ethanol. As mentioned above, formate is metabolised via the saturable tetrahydrofolate system to carbon dioxide and finally exhaled. In the liver, degradation of ethanol takes place via alcohol dehydrogenase to form acetate aldehyde, which is oxidised by aldehyde dehydrogenase to acetic acid. Acetic acid is either oxidised to carbon dioxide and exhaled or included in the tricarboxylic acid cycle (ECHA Dissemination, 2020; Greim and MAK Commission, 1997b).

5.5 Health effects

5.5.1 Acute toxicity, sensory irritation, and local effects

On direct contact to skin and eyes butyl formate is reported to cause pain, redness, and blurred vision (Bingham and Cohrssen, 2012). If inhaled butyl formate may lead to burning sensation, drowsiness, and sore throat (Bingham and Cohrssen, 2012). The reported lowest toxic concentration in humans after inhalation is 10418 ppm butyl formate.

Irritation of eyes, adverse effects on respiration tract and lung, as well as muscle contractions or spasms were observed (NLM, 2021a). Oral ingestion of the substance can result in abdominal pain and vomiting (Bingham and Cohrssen, 2012). An oral LD50 value of 2656 mg/kg bw has been reported without details for rabbits (NLM, 2021a). No further data were identified in the available literature.

Read-across: methyl formate

Exposure via inhalation to 1500 ppm methyl formate vapours for one minute did not cause any signs of irritation or toxicity in humans (Greim and MAK Commission, 2003). In a blind study, 20 volunteers were exposed to 100 ppm methyl formate for eight hours at rest in inhalation chambers. Of the 20 investigated parameters only subjective fatigue and electromyography in a neck muscle differed from controls (n=20). The authors of the study concluded that exposure to methyl formate only slightly increased the subjects' tiredness without having an influence on the performance of the neurobehavioural tests (Greim and MAK Commission, 2003; Hartwig and MAK Commission, 2019b; Sethre et al., 2000a; Sethre et al., 1998a).

The application of a liniment containing methyl formate, methanol, and formate on the head of a 19-month old child under a bathing cap resulted in collapse, cyanosis, slowed breathing, non-responding reflexes and respiratory arrest after 20 minutes. Based on an alkaline hydrolysis performed on the brain and liver the methyl formate content was calculated to be 97.2 mg in liver and 246.5 mg in brain (ECHA Dissemination, 2020; Greim and MAK Commission, 2003).

A RD50 concentration (concentration which elicits a respiratory rate decrease of 50%) of 1109 ppm for irritation of the upper respiratory tract (extrapolated R0 of 184 ppm) was calculated in mice exposed to 200-1168 ppm methyl formate. For humans it was estimated that concentrations of 30-100 ppm methyl formate are not causing local irritating effects. However, methyl formate's metabolites methanol and formate may cause irritation on the olfactory epithelium (Hartwig and MAK Commission, 2019b).

For acute toxicity of methyl formate in rats a LC50 value of > 2085 ppm (5200 mg/m^3, 4 h) after inhalation, a dermal LD50 value of > 4000 mg/kg bw, and an oral LD50 values of 1382-

1500 mg/kg bw were reported (ECHA Dissemination, 2020; Greim and MAK Commission, 2003; OECD, 2008; SCOEL, 2004).Methyl formate was slightly irritating to skin and caused eye irritation in animals but was not sensitising on skin (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019b; OECD, 2008).

Read-across: ethyl formate

In a study from 1931, volunteers were exposed to 330 ppm ethyl formate (presumably single exposure). Slight eye irritation and rapidly increasing nasal irritation were observed, which were still noticeable 4 hours after exposure. A higher concentration of ethyl formate (10500 ppm) caused moderate severe irritation of eyes and nose (no further details provided). After a short-term exposure to 200 ppm ethyl formate, no systemic effects are expected. No skin irritating effects were observed in volunteers occlusively exposed to 4% ethyl formate (Greim and MAK Commission, 1997b; Greim and MAK Commission, 2000).

In cats exposed to 10000 ppm ethyl formate for 75 minutes deep narcosis were observed, which resulted in death after 90 minutes. A 4-hour long exposure to 8000 ppm or 10000 ppm ethyl formate was lethal in rats or dogs (ACGIH, 2001a; Greim and MAK Commission, 1997b). In comparison to methyl formate it is reported that ethyl formate has a stronger narcotic effect (depression of central nervous system, which can cause death from circulatory and respiratory failure) without causing convulsions and coma, which are typical for lethal doses of methyl formate (ACGIH, 2001a).Oral LD50 values in a range from 1110 to 5600 mg/kg bw in animals are reported in the literature (ECHA Dissemination, 2020; Greim and MAK Commission, 1997b). A dermal LD50 value > 18000 mg/kg bw was determined in rabbits (Greim and MAK Commission, 1997b).

Ethyl formate was irritating to eyes but not to skin of animals (ECHA Dissemination, 2020; Greim and MAK Commission, 1997b).

Read-across: pentyl formate

The acute oral toxicity of pentyl formate in rats was determined to be > 2000 mg/kg bw. Dermal LD50 values of > 2000 mg/kg bw in rats and > 5000 mg/kg bw in rabbits were reported. The substance is irritating to skin and considered to cause eye irritation based on *in vitro* experiment. In a maximisation test, humans were exposed to 3% pentyl formate for 48 hours without causing any skin sensitising effects (ECHA Dissemination, 2020).

5.5.2 Repeated dose toxicity

There are no data available for effects following repeated exposure of humans or animals against butyl formate, except for the following general statement:

Prolonged or repeated dermal exposure to butyl formate can defat the skin and thus result in dryness or cracking of the skin (no further information provided) (IPCS, 2017).

Read-across: methyl formate

In the older literature a report for exposure to methyl formate at the workplace was found. After occupational exposure to vapours of a boiling solvent mixture containing 30% methyl formate and in unspecified amounts ethyl formate, methyl acetate, and ethyl acetate (details on exposure duration not given), ten exposed female workers reported the following reversible symptoms: irritation of mucous membranes, visual disturbance (temporary blindness in one case), cardiovascular, and central nervous symptoms (shortness of breath, loss of memory, agitation, and depression) (ACGIH, 2001b; ECHA Dissemination, 2020; Greim and MAK Commission, 2003).

In a workplace study, 21 foundry workers (23 respective controls) exposed to median concentrations of 47 ppm methyl formate (concurrent exposure to isopropyl alcohol, but concentration not given) or 68 ppm methyl formate (personal air sampling, range: 22-136 ppm) and 28 ppm isopropyl alcohol (personal air sampling, range: 6-73 ppm) performed neurobehavioural tests after their shifts. Lifetime exposure of workers to solvents were given in the range 1 week up to 26 years (Sethre et al., 1998b; Sethre, 1998). Biomonitoring of methanol in urine, which correlates well with the methyl formate concentration in air was conducted. The solemn exposure to methyl formate did not result in neurobehavioural effects in exposed workers. In three out of 15 conducted neurological behaviour tests three workers with the highest exposure to methyl formate and isopropyl alcohol (maximum: 136 ppm methyl formate and 73 ppm isopropyl alcohol) performed worse than the workers exposed to low concentrations. This is regarded by the authors of the study as an effect caused by isopropyl alcohol rather than methyl formate. In a follow-up examination of nine out of the 21 foundry workers the previous mentioned observations were not confirmed (Sethre et al., 2000b). The personal air sampling revealed median a concentration of 58 ppm methyl formate and maximum cumulative exposure of 150 ppm methyl formate and 375 ppm isopropyl alcohol. The only observation was that three workers with the highest levels of exposure performed poorer in the balance test. However, the author of the study attributed this effect to the normal group differences, which may occur due to the low number of subjects. Workers exposed to higher concentrations of isopropyl alcohol or who had higher methanol concentrations in urine showed a reduction in fatigue. Taking all together these workplace studies did not observe an explicit neurobehavioural effect caused by methyl formate (up to 150 ppm) (Greim and MAK Commission, 2003; Hartwig and MAK Commission, 2019b).

In a short-term repeated inhalation toxicity study (similar to OECD guideline 412), Wistar rats (5 M + 5 F/group) were exposed via “whole body” to 0, 100, 500 or 1500 ppm methyl formate (0, 0.252, 1.237, 3.693 mg/l, concentrations analytically confirmed) for 6 h/d, 5 d/week, over 2 weeks. Neither clinical signs nor mortality were observed during the study. The terminal body weights of rats were markedly decreased (-14.3% in males, -9.3% in females) in the highest concentration group compared to controls. At 500 ppm and above histopathological alterations in the olfactory epithelium in the nose (multifocal degeneration, and necrosis) were observed, which increased concentration dependent. In the mid concentration group only one male and one female were affected. Squamous metaplasia and infiltration of inflammatory cells were seen in the respiratory tract of the mid concentration group (one male and two females). Organ weight changes of liver, lung, kidney, and spleen were altered in the highest concentration group. The derived NOAEC and LOAEC for local effects in the study were 100 and 500 ppm, respectively. Based on body weight and organ weight changes at the highest tested concentration, NOAEC and LOAEC for systemic effects of 500 and 1500 ppm were derived (Hartwig and MAK Commission, 2019b; OECD, 2008).

A subchronic inhalation toxicity study reported to be conducted according to OECD guideline 413 is only published in Korean language with an abstract in English. Sprague-Dawley rats were exposed to 0, 100, 400 or 1600 ppm methyl formate for 6 h/d, 5 d/week and 13 weeks. At 400 ppm and above, a concentration-dependent reduction in feed intake and body weight development was observed. Females of the mid and high concentration group had increased relative organ weights of ovaries, adrenals, and brains, which were regarded as caused by the decreased body weights. A statistically significant increase of almost all investigated relative organ weights and alterations in haematological and blood parameters were seen in animals of the highest concentration groups. Atrophy of the respiratory tract in the nose as well as degeneration, regeneration, and contraction of olfactory cells (no further details provided) were observed. A NOAEC and LOAEC for local effects of 400 and 1600 ppm were derived in the study.

Based on the observed effects on body weight development and organ weights, a NOAEC and LOAEC of 100 and 400 ppm were derived for systemic effects (Hartwig and MAK Commission, 2019b; Kim et al., 2010). In its evaluation from 2019, MAK states that the reduced body weight development might be a secondary effect due to the decreased food consumption. Furthermore, the reported NOAEC for local effects is not contradicting to the NOAEC for local effects reported in the subacute study as only a few animals of the 500 ppm group were affected (Hartwig and MAK Commission, 2019b).

Read-across: ethyl formate

Group of rats (Sprague-Dawley, 10 M + 10 F/group) were exposed "whole body" 6 h/d, 5 d/week for 13 weeks to ethyl formate vapours at 0, 66, 330, and 1320 ppm. In rats, no lethality was observed. A decrease in locomotor activity was observed during exposure of animals at 1320 ppm, which was reversible after the end of exposure. A continuous reduction of body weight and food consumption was observed in both sexes at 1320 ppm from week 1 or 3 in comparison to controls. In female rats at 330 ppm as well as in male and female rats at 1320 ppm degeneration, squamous metaplasia of olfactory epithelium in nasopharyngeal tissue or both were observed. At 1320 ppm findings in haematological parameters (increase in haemoglobin and haematocrit in males and decrease in reticulocytes in females) or serum biochemistry (calcium and triglyceride levels decreased in males and females) were not regarded as adverse by the authors of the cited publication. At 1320 ppm in male and female rats an increase in absolute and relative adrenal weight and a decrease in absolute and relative thymus weight were observed. Histopathological examination of both organs could not identify any explanation for the weight changes. Additional observed organ weight changes at 1320 ppm were regarded as secondary to alterations in body weight and thus were not considered as adverse effects by the authors of the cited publication. A NOAEC of 330 ppm ethyl formate can be derived from this data (ECHA Dissemination, 2020; Lee and Kim, 2017).

In a subchronic oral toxicity study, Osborne-Mendel rats (10 M + F/group) were exposed to 1000, 2500, or 10000 ppm ethyl formate (100, 250, or 1000 mg/(kg bw x d)) via feed for 17 weeks. No adverse effects were observed and thus a NOAEL of 10000 ppm was derived. The MAK commission regarded the substance application via feed as not appropriate due to ethyl formate's volatility (Greim and MAK Commission, 1997b).

5.5.3 Genotoxicity and carcinogenicity

Genotoxicity

No data are available for this endpoint for butyl formate.

Read-across: methyl formate

Methyl formate showed no mutagenic activity in *in vitro* bacterial mutation assays (Ames test) with and without exogenous metabolic activation system (S9 mix from rat/hamster liver) (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019b).

Methyl formate was not clastogenic *in vivo* in a micronucleus test in male ICR mice (n=6) at doses up to 1000 mg/kg bw, no clinical signs were observed (Hartwig and MAK Commission, 2019b).

Read-across: ethyl formate

No studies were located for ethyl formate regarding *in vivo* genotoxic effects in humans or animals.

Ethyl formate was not mutagenic *in vitro* in several bacterial mutation assays with and without exogenous metabolic activation system. The substance did not induce mutations or chromosomal aberrations with and without metabolic activation in mammalian cells (ECHA Dissemination, 2020).

Carcinogenicity

No data are available for this endpoint for butyl formate, including the registration dossiers for the read-across substances methyl formate, ethyl formate, and pentyl formate.

Data on methyl formate's metabolite methanol is used as read-across source. Formate is not further considered as humans are less susceptible for a considerable accumulation of formate after exposure to methyl formate (see section 4.4) and no valid carcinogenicity or chronic study conducted with formate is available (Greim and MAK Commission, 1997a; Greim and MAK Commission, 2003; Hartwig and MAK Commission, 2019a).

Read-across: methanol

A carcinogenicity study was conducted with methanol inhalation exposure of rats and mice. No significant evidence of carcinogenicity was observed up to the highest concentration tested (1000 ppm). An indication of an increase in proliferative changes in the alveolar epithelium of the lungs of male animals was observed in rats. A slight, but not statistically significant, increase in the incidence of adrenal pheochromocytomas was noticed in females exposed to 1000 ppm. The maximum tolerated dose was not achieved in both species, however at the highest concentration of 1000 ppm methanol's metabolism was already saturated (Hartwig and MAK Commission, 2019a).

In a drinking study it is reported that methanol (no further details provided) led to increased incidences of animals bearing a tumour, "lympho-immunoblastic lymphomas" predominantly in the lungs of female rats, and carcinomas of the ear canal in male rats. However, a re-evaluation of a pathology working group from US EPA and NTP did not confirm the reported results (Hartwig and MAK Commission, 2019a).

5.5.4 Toxicity to reproduction

No data are available for this endpoint for butyl formate, including the registration dossiers for the read-across substances methyl formate, ethyl formate, and pentyl formate. Data on methyl formate's metabolite methanol is used as read-across source (for justification see section 5.5.3).

Fertility

Read-across: methanol

In a two-generation reproduction toxicity study (similar to OECD guideline 416) Sprague-Dawley rats (30 animals per sex and concentration group in F0 generation) were exposed via inhalation (whole-body) continuously to 0, 10, 100, or 1000 ppm methanol (0, 0.013, 0.13, or 1.3 mg/l, nominal concentration) for 19-20 h/d. No adverse effects were observed in the F0 generation. Methanol concentrations up to 1000 ppm did not result in adverse reproduction effects in the F0 or F1 generation (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019a). The 100 ppm concentration group showed no effects on reproduction or development in the parent animals as well as in the offspring (F1 and F2). At 1000 ppm decreased absolute and relative brain weights were observed in offspring of the F1 and F2 generations in either sex at an age of 8 and 16 weeks. However, neither histological findings nor significantly difference in neurobehavioural tests were seen. In male rats of the F1 and F2 generation exposed to the highest concentration descending of testes was observed 0.5 to 1 d earlier compared to controls.

Additionally, males of the F2 generation had lower thymus and pituitary weights. Due to the long exposure of up to 20 hours daily, a prolonged steady-state blood level of methanol was reached. This was 76 mg/l and might be higher than a shorter exposure at the same exposure concentration. In conclusion the NOAEC was 1000 ppm (highest tested concentration) for F0 animals. For F1 and F2 animals the NOAEC was 100 ppm and the LOAEC 1000 ppm based on decreased brain weights and earlier descending testis (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019a; OECD, 2008).

No change in sex hormones was observed in male rats either exposed once for 6 hours to 5000 ppm methanol or for 6 h/d for seven days to 200 ppm methanol (Hartwig and MAK Commission, 2019a). Testis weight was unchanged in rats exposed to 200 ppm methanol for 13 weeks and at 800 ppm histopathological examinations of testes did not find any effects (Hartwig and MAK Commission, 2019a).

Male mice treated with 1000 mg methanol/(kg bw x d) orally for five consecutive days showed a slight but not statistically significant increase in sperm abnormalities (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019a).

In a one-generation reproduction toxicity study in cynomolgus monkeys (n=12 per concentration group) exposed to 0, 200, 600, or 1800 ppm methanol vapour (0, 0.27, 0.8, 2.39 mg/l air, nominal concentration) via inhalation daily for 2.5 hours prior to, during breeding, and gestation (approx. 350 days), no overt signs of systemic toxicity were observed in parent animals of all concentration groups. Although complications occurred during gestation and were noted in the low and mid concentration group (e.g., vaginal bleeding and prolonged labour) these were not statistically significant and did not influence the reproductive performance. The duration of pregnancy was decreased (6 to 8 days) in all treated concentration groups compared to controls. However, this effect was not concentration dependent and no effects in offspring were seen, thus it cannot be solemnly related to methanol exposure. No mortalities nor malformations of offspring were observed. In the highest concentration group two out of seven female offspring aged 12 months had a ‘wasting syndrome’, which was characterised by growth retardation, malnutrition, and gastroenteritis. In two out of nine neurobehavioural tests in the offspring, dose-dependent effects were not clear (especially delayed sensorimotor development in males) (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019a; OECD, 2008). A NOAEC of 1800 ppm was suggested by the MAK commission for maternal toxicity and fertility. The MAK commission (2019a) regarded the study as “only limited reliable” due to its small sampling size and short exposure duration of 2.5 hours daily, which did not result in a steady state. Thus, a NOAEC/LOAEC for developmental toxicity is not derived (Hartwig and MAK Commission, 2019a). However, the findings in monkeys can be used to support the results obtained in rodent studies.

Development

There are no studies available with exposure to butyl formate. Data on methyl formate’s metabolite methanol is used as read-across source (for justification see section 5.5.3).

Read-across: methanol

The prenatal developmental toxicity of methanol was studied (similar to OECD guideline 414) in rats (number of animals per sex and dose not provided) exposed via inhalation at concentrations of 5000 or 10000 ppm (6.65 or 13.3 mg/l) for 7 h/d on GD 1-19. An additional group was exposed to 20000 ppm methanol (26.6 mg/l) on GD 7-15. No maternal toxicity was observed at 10000 ppm, but foetal body weight was reduced. In the highest concentration group unsteady gait of dams and malformations occurred (extra cervical ribs, defects on cardiovascular system and urinary tract, encephalocele, and exencephaly). Methanol concentration in blood of the

dams was 1580 mg/l at 5000 ppm and 2040 mg/l at 10000 ppm. As no adverse effects were observed at the lowest concentration the derived NOAEC for developmental effects was 5000 ppm and the LOAEC 10000 ppm. A NOAEC of 10000 and a LOAEC of 20000 ppm were derived for maternal toxicity (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019a; OECD, 2008).

In a similar study, rats were continuously exposed to 0, 200, 1000, and 5000 ppm methanol (0.27, 1.33, and 6.65 mg/l, approx. 22.7 h/d) from GD 7-17. Maternal toxicity was observed in the highest concentration group. A reduction in the number of living foetuses, decreased foetal body weight at PND 4, and skeletal and visceral malformations were seen in this group. The postnatal development of these offspring was delayed (e.g., breakthrough of incisors and eye lid opening). The descent of testes was premature in male offspring. A decrease in absolute and relative brain, thyroid, thymus, and testis weights and an increase in absolute and relative pituitary gland weight were noted in males at the age of 8 weeks. In female offspring only the absolute brain weights were lower. No treatment-related changes were found in histological examinations in both sexes. For maternal and developmental toxicity, a NOAEC of 1000 ppm and a LOAEC of 5000 ppm were derived (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019a; OECD, 2008).

Mice (number of animals per sex and concentration vary from 6 (15000 ppm) to 70 (controls)) were exposed to 0, 1000, 2000, 5000, 7500, 10000 or 15000 ppm methanol (1.33, 2.66, 6.65, 9.97, 13.3, 19.94 mg/l, nominal concentrations) from GD 6-15. No maternal toxicity was observed up to the highest tested concentration. No adverse effects were observed in offspring of the lowest concentration. At 2000 ppm offspring had a higher incidence for an extra cervical rib and at 5000 ppm and above teratogenic effects (cleft palate, exencephaly, defects of the sternum and internal organs) were noted. An increase in embryo or foetal death occurred at 7500 ppm and above. At 10000 ppm and above foetal body weight was reduced. In the highest tested concentration almost complete resorption of foetuses were observed. The measured methanol concentration in blood of dams was 97, 537, and 1650 mg/l at 1000, 2000, and 5000 ppm, respectively. For maternal toxicity, a NOAEC of 15000 ppm was derived. Due to the observed effects at higher concentrations, a NOAEC of 1000 ppm and a LOAEC of 2000 ppm were derived for developmental effects (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019a; OECD, 2008). Mice are more susceptible to methanol exposure than rats. An explanation might be the accumulation of methanol in blood, which can be caused by the higher respiration and resorption rate of mice than rats. The teratogenic effects observed in mice were associated with methanol itself and not caused by its metabolite formate (Hartwig and MAK Commission, 2019a).

5.5.5 Odour perception

The odour of butyl formate is reported to be fruity and plum-like (FAO, 2021; NLM, 2021b).

In a study from 2003, an odour threshold of 0.087 ppm equal to 0.37 mg/m^3 at 23°C was measured for butyl formate by applying the triangle odour bag method (Nagata, 2003).

5.6 Evaluation

5.6.1 Existing regulations and classifications

Butyl formate is classified for flammable liquid category 2 (H225), eye irritation category 2 (H319), and specific target organ toxicity - single exposure (H 335) (ECHA C&L Inventory, 2020).

A NIK (Lowest Concentration of Interest) value of 2000 µg/m³ is reported for butyl formate (AgBB, 2018). This value is based on the EU OEL/MAK value for methyl formate (120 mg/m³, read-across substance). The toxicologically critical endpoint for methyl formate, as well as for butyl formate, are their effect on the central nervous system and local irritation effects on olfactory or respiratory epithelium. For deriving the NIK value, molar adjustment from methyl formate to butyl formate was performed.

Further existing guide values for butyl formate in air are not available.

5.6.2 Derivation of an EU-LCI value

Only limited data are available on the possible toxicity of butyl formate. It is reported that butyl formate causes pain, redness, and additional blurred vision on direct contact with eyes and skin. Inhalation of toxic concentrations of 10418 ppm butyl formate caused adverse effects on respiratory tract and lung in humans. Additionally, burning sensation, drowsiness or sore throat may occur. Further data on the toxicity after repeated exposure, genotoxicity, carcinogenicity, fertility/reproduction or developmental toxicity of butyl formate are not available.

Additional data was obtained by read-across from studies with methyl formate, ethyl formate, and pentyl formate. All of the formates have the same critical effects (impairments to the olfactory and respiratory epithelium as well as systemic effect on the central nervous system) and thus read-across between the compounds is suitable.

From a subchronic inhalation study conducted with ethyl formate in rats a NOAEC of 330 ppm (1000 mg/m³) was derived based on observed nasal irritation (olfactory damage, squamous metaplasia) as well as systemic effects on central nervous system and body weight.

Methyl formate and ethyl formate were not mutagenic in *in vitro* assays and methyl formate was also not clastogenic in an *in vivo* micronucleus test in male mice (ECHA Dissemination, 2020; Hartwig and MAK Commission, 2019b).

For the read-across substances no data on carcinogenicity studies as well as on fertility/reproduction or developmental toxicity studies are available.

For methyl formate, its metabolites, methanol and formate, have to be considered for causing adverse effects on reproduction or pup development. In 2019, the MAK commission concluded that if the MAK value of 50 ppm methyl formate is complied with, no adverse effects will occur. This is supported by two observations in humans, in which the formate concentration did not increase in serum when volunteers were exposed to 200 ppm methanol for six hours and only a slight increase in formate concentration was observed after humans were exposed to 400 ppm formate for eight hours. In case of ethyl formate, ethanol and formate are the critical metabolites. In its evaluation from 1997, the MAK commission also considered the derived MAK value of 100 ppm ethyl formate as safe to protect against adverse effects on reproduction and pup development (Greim and MAK Commission, 1997b; Hartwig and MAK Commission, 2019b).

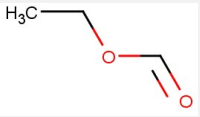
Due to the lack of inhalation toxicity data for butyl formate the inhalation data of the read-across substance ethyl formate is considered as suitable for the derivation of an EU-LCI value for butyl formate.

The rationale for read-across with ethyl formate are:

- Data poor compound: no adequate toxicological data for butyl formate; *de novo* derivation of EU-LCI for butyl formate is not possible.

- Read-across from ethyl formate: within the chemical class 'carboxylic acid esters', ethyl formate is the closest homologue compound with an adequate data base. Two additional CH2 groups in the aliphatic chain of ethyl formate are the only difference between the two substances.
- Toxicological critical endpoint for ethyl formate: nasal irritation (olfactory damage and squamous metaplasia) and systemic effects on the central nervous system and body weights.
- The key assumption underlying the read-across of the EU-LCI value from ethyl formate to butyl formate is that both compounds have the same critical endpoints (impairments to the olfactory and respiratory epithelium as well as systemic effect on the central nervous system) and this is caused by the common functional group (and not by the additional CH2 groups).

Table 24: Substance information of butyl formate and methyl formate for deriving an EU-LCI value (ECHA Dissemination, 2020; NLM, 2021b)

Compound	Structure	Molar mass [g/mol]	EU-LCI value
Butyl formate		102.13	(read-across to ethyl formate) *Rounded value: 4900 µg/m³*
Ethyl formate		74.08	proposed EU-LCI value according to the EU-LCI protocol: 3571 µg/m³

- No cut-off rule in place: difference in chain length between the two homologue compounds is no more than two CH2 groups per aliphatic chain
- When applying the proposed EU-LCI value for ethyl formate of 3571 µg/m³ and performing MW conversion at 23 °C and 1013 hPa: EU-LCI of butyl formate = 3571 µg/m³ x 1.379= 4924 µg/m³ is rounded to 4900 µg/m³.

For the calculation of an EU-LCI value for butyl formate, the proposed unrounded EU-LCI value for ethyl formate (3571 µg/m³) was used. By applying molar adjustment at 23 °C and 1013 hPa, the differences in molar masses of butyl formate and ethyl formate were considered, therefore the newly derived EU-LCI of butyl formate was multiplied by a factor of 1.379 and results in an EU-LCI value for butyl formate of 4924 µg/m³, which is rounded to 4900 µg/m³ (see Table 24).

The proposed EU-LCI value is supported by read-across from the EU-LCI value for methyl formate (proposal 2021). This read-across is suitable as both substances belong to the chemical class 'carboxylic acid esters'. The data base for methyl formate is adequate and a proposed EU-LCI value is available. Three additional CH2 groups in the aliphatic chain of butyl formate are the only difference between the two substances. The EU-LCI value of 3000 µg/m³ for methyl

formate is based on effects on central nervous system in humans observed after inhalation exposure with methyl formate. The derived EU-LCI value for methyl formate is also protective against systemic effects of methyl formate. Taking into account that the cut-off rule (difference in chain length between the two homologue compounds is larger than two CH2 groups per aliphatic chain) has to be applied, the molar mass of propyl formate (88.11 g/mol) and methyl formate (60.05 g/mol) are considered for performing the molar adjustment (factor: 1.467). The EU-LCI value for methyl formate corresponds to a value of 4401 µg/m^3 and rounded to 4400 µg/m^3 for butyl formate on a molar basis at 23 °C and 1013 hPa.

An EU-LCI value of (rounded) 4900 µg/m^3 is proposed for butyl formate.

An odour threshold of 0.37 mg/m^3 is reported for butyl formate in the literature. Thus, the fruity and plum-like odour may be noticed at the proposed EU-LCI.

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E Appendix

E.1 Fact and data sheet for butyl formate

Table 25: Data collection sheet for butyl formate

Compound	Butyl formate	Data collection sheet
Nº CAS 592-84-7) 1 ppm = 4.20 mg/m³ at 23 °C	**EU-Classification: -** **CLP,** harmonised classification: Flam. Liq. 2 (H225), Eye Irrit. 2 (H319), STOT SE (H335)	
Organisation name	AgBB	
Risk value name	NIK ('Lowest Concentration of Interest')	
Risk value (mg/m³)	2 (read-across to methyl formate)	
Reference period	Chronic (general population)	
Risk value (mg/m³) Short term (15 min)	-	
Year	2008 (read-across from methyl formate, derived MAK/OEL value in Germany)	
Key study	Study report from Sethre (1998) and (2000) mentioned by MAK (2003) and (2019)	
Study type	Volunteer study (human)	
Species	Human	
Duration of exposure in key study	8 h	
Critical effect	Effects on CNS (subjective tiredness)	
Critical dose value	MAK/OEL value: 120 mg/m³ for methyl formate based on NOAEC (methyl formate): 250 mg/m³	
Adjusted critical dose	-	
Single assessment factors	Default assessment factor: 100	
Other effects		
Remarks	Derived MAK value is supported by workplace studies in humans and a subchronic inhalation study in rats. Read-across was applied and methyl formate was used as test item instead of butyl formate. The derived NIK value for methyl formate was transformed into a NIK value for butyl formate by considering a molar adjustment.	

AgBB = Ausschuss zur gesundheitlichen Bewertung von Bauprodukten
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study UF_D data deficiencies.

Table 26: Fact sheet ethyl formate

Compound		**Ethyl formate C3H6O2**	**Fact sheet**
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	3600#
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	-
General information			
CLP-Index No.	4	INDEX	607-015-00-7
EC-No.	5	EINECS	203-721-0
CAS-No.	6	Chemical Abstract Service number	109-94-4
Harmonised CLP classification	7	Human health risk related classification	Acute Tox. 4 *(H302, H332, *= minimum classification), Eye Irrit. 2 (H319), STOT SE (H335)
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	74.08 1 ppm = 3.048 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	Lee and Kim (2017)
Read across compound	10	Where applicable	-
Species	11	Rat, human, etc.	Rat
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	Nasal irritation (olfactory damage, squamous metaplasia) and systemic effects on central nervous system
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEC
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	1000 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

Compound	Ethyl formate C3H6O2		Fact sheet
Route-to-route extrapolation factor	21	-	1
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)	2.5
	23b	Kinetic + dynamic	
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		1
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]	3571 µg/m³ (1172 ppb)
Molar adjustment factor	29		-
Rounded value	30	[µg/m³]	3600
Additional comments	31		
Rationale selection	32		

[#] Newly derived EU-LCI value according to the current EU-LCI concept (EC, 2013).

Rationale for derivation of EU-LCI

In a subchronic inhalation study in rats, which were exposed "whole body" 6 h/d, 5 d/week for 13 weeks to ethyl formate vapours at 0, 66, 330, and 1320 ppm (0, 200, 1000, and 4000 mg/m^3), observed treatment-related effects were nasal irritation (olfactory damage, squamous metaplasia) as well as systemic effects on central nervous system and body weight (Lee, 2017; ECHA Dissemination, 2020). The derived NOAEC from this subchronic inhalation study of 1000 mg/m^3 (330 ppm) was used as POD. As assessment factors 2.5 (remaining interspecies differences in inhalation studies), 10 (intraspecies variance), 2 (time extrapolation from subchronic to chronic), and 5.6 (adjustment for exposure duration) were applied (total 280). Thus, the proposal for a derived EU-LCI value for ethyl formate is 3571 µg/m^3 (rounded to 3600 µg/m^3).

References

EC, European Commission (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. http://publications.jrc.ec.europa.eu/repository/handle/JRC83683

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Table 27: Fact sheet butyl formate

Compound	**Butyl formate C5H10O2**		**Fact sheet**
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	4900
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2021
General information			
CLP-Index No.	4	INDEX	607-017-00-8
EC-No.	5	EINECS	209-772-5
CAS-No.	6	Chemical Abstract Service number	592-84-7
Harmonised CLP classification	7	Human health risk related classification	Eye Irrit. 2 (H319), STOT SE (H335)
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	102.13 1 ppm = 4.203 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	Ethyl formate
Species	11	Rat, human, etc.	
Route / type of study	12	Inhalation, oral feed, etc.	
Study length	13	Days, subchronic, chronic, etc.	
Exposure duration	14	h/d, d/w	
Critical endpoint	15	Effect (s), site of	
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	POD/TAF of ethyl formate: 3.571 mg/m³
Assessment factors (AF)			
Adjustment for exposure duration	19	Study exposure h/d, d/w	
Study length	20	sa→sc→c	
Route-to-route extrapolation factor	21	-	

Compound	Butyl formate C5H10O2		Fact sheet
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	
	22b	Severity of effect (R8 6d)	
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	
	23b	Kinetic + dynamic	
Intraspecies differences	24	Kinetic + dynamic General population	
AF (sensitive population)	25		
Other adjustment factors Quality of database	26	Quality of database	
Results			
Summary of assessment factors	27	Total Assessment Factor	
POD/TAF	28	Calculated value [µg/m³ and ppb]	4924 µg/m³ (1172 ppb)
Molar adjustment factor	29		1.379
Rounded value	30	[µg/m³]	4900
Additional comments	31		
Rationale selection	32		

Data compilation and evaluation for butyl formate is based on a project funded by the German Environment Agency (Voss et al., 2021).

Rationale for critical effects

The data base regarding the toxicity of butyl formate is very limited. Butyl formate is irritating to skin and eyes. Adverse effects on respiratory tract and lung were observed in humans after inhalation. Additionally, burning sensation, drowsiness or sore throat may occur. Toxicity studies with repeated exposure of humans or animals to butyl formate are not available. No data regarding genotoxicity, carcinogenicity, fertility/reproduction or developmental toxicity of butyl formate were identified.

Rationale for read-across

Due to the limited database on butyl formate, read-across needs to be performed in order to derive an EU-LCI value for butyl formate. Therefore, available data for shorter chained carboxylic acid esters (methyl and ethyl formate) as well as longer chained carboxylic acid esters (pentyl formate) were investigated. A read-across to these substances is warranted as they cause the same critical effects after exposure as butyl formate (impairments to the olfactory and respiratory epithelium as well as systemic effect on the central nervous system). A

subchronic inhalation study conducted with ethyl formate in rats was regarded as suitable for read-across.

In this study, groups of rats (Sprague-Dawley, 10 M + 10 F/group) were exposed "whole body" 6 h/d, 5 d/week for 13 weeks to ethyl formate vapours at 0, 66, 330, and 1320 ppm (0, 200, 1000, and 4000 mg/m^3). No lethality was observed. A decrease in locomotor activity was observed during exposure in animals exposed to 1320 ppm, which was reversible after the daily exposure ended. The authors of the study regarded this effect as treatment-related but not as adverse. A continuous reduction of body weight and food consumption was observed in both sexes at 1320 ppm from week 1 or 3 in comparison to controls. In male and female rats, degeneration, squamous metaplasia of olfactory epithelium in nasopharyngeal tissue or both were observed at 1320 ppm. An increase in absolute and relative adrenal weight and a decrease in absolute and relative thymus weight were observed in male and female rats at 1320 ppm. Histopathological examination of both organs could not identify any explanation for the weight changes. The authors of the study considered these effects to be treatment-related and secondary to stress. A NOAEC of 330 ppm (1000 mg/m^3) was derived based on nasal irritation (olfactory damage, squamous metaplasia) as well as systemic effects on central nervous system and body weight (Lee, 2017; ECHA Dissemination, 2020).

Read-across can also be performed using the newly proposed EU-LCI value of methyl formate (proposal 2021).

1) Read-across from methyl formate

The read-across from methyl formate is suitable as both substances belong to the chemical class 'carboxylic acid esters'. The data base for methyl formate is adequate and a proposed EU-LCI value is available. Three additional CH2 groups in the aliphatic chain of butyl formate are the only difference between the two substances.

The EU-LCI value of 3000 µg/m^3 for methyl formate is based on effects on central nervous system in humans observed after inhalation exposure with methyl formate. The derived EU-LCI value for methyl formate is also protective against systemic effects of methyl formate. Taking into account that the cut-off rule (difference in chain length between the two homologue compounds is larger than two CH2 groups per aliphatic chain) has to be applied, the molar mass of propyl formate (88.11 g/mol) and methyl formate (60.05 g/mol) are considered for performing the molar adjustment (factor: 1.467). The EU-LCI value for butyl formate corresponds to a value of 4401 µg/m^3 and rounded to 4400 µg/m^3 on a molar basis.

2) Read-across from ethyl formate:

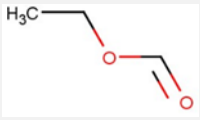
The NOAEC of 330 ppm (1000 mg/m^3) obtained in the subchronic inhalation toxicity study with ethyl formate in rats (Lee, 2017) is used as the POD for calculating a value according to the standards of deriving an EU-LCI value.

The applied default assessment factors were 5.6 for adjustment for exposure duration, 2 for study length (subchronic to chronic), 2.5 for interspecies differences and 10 for intraspecies differences, thus resulting in a total assessment factor of 280. The calculated corresponding EU-LCI value for ethyl formate was 3571 µg/m^3. This value is used for read-across to calculate the EU-LCI of butyl formate.

Rationale for read-across:

- Data poor compound: no adequate toxicological data for butyl formate; de novo derivation of EU-LCI for butyl formate is not possible.
- Read-across from ethyl formate: within the chemical class 'carboxylic acid esters', ethyl formate is the closest homologue compound with an adequate data base. Two additional CH2 groups in the aliphatic chain of ethyl formate are the only difference between the two substances.
- Toxicological critical endpoint for ethyl formate: nasal irritation (olfactory damage and squamous metaplasia) and systemic effects on the central nervous system and body weights.
- The key assumption underlying the read-across of the EU-LCI value from ethyl formate to butyl formate is that both compounds have the same critical endpoints (impairments to the olfactory and respiratory epithelium as well as systemic effect on the central nervous system) and this is caused by the common functional group (and not by the additional CH2 groups).

Table 28: Comparison of structure and molar mass of butyl and ethyl formate

Compound	Structure	Molar mass [g/mol]	EU-LCI value
Butyl formate		102.13	(Read-across to ethyl formate) Rounded value: 4900 µg/m³
Ethyl formate		74.08	proposed EU-LCI value according to the EU-LCI protocol: 3571 µg/m³

- No cut-off rule in place: difference in chain length between the two homologue compounds is no more than two CH2 groups per aliphatic chain
- When applying the proposed EU-LCI value for ethyl formate of 3571 µg/m3 and performing MW conversion at 23 °C and 1013 hPa: EU-LCI of butyl formate = 3571 µg/m^3 x 1.379= 4924 µg/m^3 rounded to 4900 µg/m^3.

For the derivation of an EU-LCI value for butyl formate, it is suggested to perform the read-across from ethyl formate and thus an EU-LCI value of 4900 µg/m^3 is proposed.

An odour threshold of 0.37 mg/m^3 is reported for butyl formate in the literature (Nagata, 2003). Thus, the fruity and plum-like odour may be noticed at the proposed EU-LCI value (NLM, 2021).

References

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NLM, U.S. National Library of Medicine, PubChem (2021): Butyl formate. https://pubchem.ncbi.nlm.nih.gov/compound/Butyl-formate (15.09.2020)

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