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by: Dr. Jens-Uwe Voss

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Abstract: Toxicological basic data for the derivation of EU-LCI values for five substances/-groups from building products

The subject of this report is the preparation of substance reports for the derivation of EU-LCI values for the substances and substance groups 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 (e.g., Voss et al., 2021).

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 (2021) 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. German Environment Agency, Berlin, Germany. Online: https://www.umweltbundesamt.de/sites/default/files/medien/479/publikationen/texte_125-2021_toxicological_basic_data_for_the_derivation_of_eu-lci_values.pdf

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

Gegenstand des Berichts ist die Erstellung von Stoffberichten für die Ableitung von EU-LCI-Werten für die im Titel genannten Stoffe und Stoffgruppen. 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 (siehe etwa Voss et al., 2021).

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

2EHMA	2-Ethylhexyl methacrylate
ACGIH	American Conference of Governmental Industrial Hygienists
AgBB	Ausschuss zur gesundheitlichen Bewertung von Bauprodukten (Committee for Health-related Evaluation of Building Products)
AGÖF	Arbeitsgemeinschaft Ökologischer Forschungsinstitute (Association of Ecological Research Institutes)
AGW	Arbeitsplatzgrenzwert (Occupational Exposure Limit)
BMA	n-Butyl methacrylate
Bp.	Boiling point
CAS	Chemical abstract service
CLP	Classification, labelling and packaging
CNS	Central nervous system
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation)
DNEL	Derived no effect level
ECHA	European Chemicals Agency
EMA	Ethyl methacrylate
EU	European Union
F	Female(s)
GD	Gestation day
GLP	Good laboratory practice
iBMA	Isobutyl methacrylate
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)
MMA	Methyl methacrylate
Mp	Melting Point
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
o-, m-, p-	Ortho-, meta-, para-
OECD	Organization for economic cooperation and development

2EHMA	2-Ethylhexyl methacrylate
OEL	Occupational exposure limit
PND	Postnatal day
POD	Point of Departure
RAC	Committee for Risk Assessment
RD50	Concentration which elicits a respiratory rate decrease of 50 %
REACH	Registration, evaluation, authorization and restriction of chemicals
SCOEL	Scientific Committee on Occupational Exposure Limits
TLV	Threshold limit value

Summary

Substance profile and EU-LCI value for "other alkylbenzenes"

EU-LCI values have been derived for a number of alkyl benzenes. "Other alkylbenzenes" refers thus to a group of alkylbenzenes for which up to now no EU-LCI values have been derived. A search in bibliographic databases, portals and on websites of relevant organisations showed that the toxicological data basis for most of the alkylbenzenes with no EU-LCI value yet is very limited. At the same time, most of these alkylbenzenes are little used in building or consumer products and are rarely if ever detected in indoor air except for ethyltoluenes and isopropyltoluenes. While the toxicological database is very limited for ethyltoluenes, data are available for 1-isopropyl-4-methylbenzene (p-isopropyltoluene, p-cymene), the most frequently detected alkylbenzene in indoor air for which no EU-LCI has yet been derived.

Para-cymene is a naturally occurring compound belonging to the large group of terpenes and is widespread in plants. The substance is also an industrial product used in consumers products, and it is included in emission test chamber measurements of volatile organic compounds (VOC) from building materials and products.

The odour of isolated p-cymene has been described as wood- and citrus-like, but also as fuel-like. Concentrations of p-cymene in indoor are typically below 1 µg/m³ with maximum values below 100 µg/m³.

Data from animal studies indicate that p-cymene is about equally well absorbed after oral or inhalation exposure. Once absorbed and distributed, p-cymene is oxidised to a number of metabolites which are excreted in urine, mainly p-isopropylbenzoic acid or its glycine conjugate p-isopropylhippuric acid.

The acute toxicity of p-cymene is low. Central nervous system effects were described after inhalation of high concentrations (≥ 1100 mg/m³) in humans. Sensory irritation was noted after short-term (few seconds) exposure of humans to high concentrations (probably in the order of about 5000 mg/m³). Sensory irritation was also reported in animals at about 9700 mg/m³ in acute toxicity studies with several hours of exposure.

Neurotoxicity could not be demonstrated in the only available study with repeated inhalation exposure of rats with up to 250 ppm (about 1230 mg/m³) for four weeks.

A combined repeat dose and reproductive/developmental toxicity screening test (OECD TG 422) with oral exposure of rats for at least 35 days revealed toxic effects on the testes and sperm of male animals with lower organ weight, germ cell depletion/degeneration, depletion and/or sperm retention, along with correlative changes in the epididymis. A NOAEL for P0 males of 50 mg/(kg bw x d) was identified in this study.

Studies with substances structurally related to p-cymene indicate that the metabolism of p-cymene seems to play a critical role in the observed testicular and sperm toxicity. The effect on spermatogenesis appears to be linked to the formation of the metabolite p-isopropylbenzoic acid (p-iPBA). This metabolite could only be detected in rat hepatocytes, but not in rabbit and human hepatocytes. Additional studies indicate that the formation of this metabolite is related to the toxic effects on rat testes and sperm development and that humans, like rabbits, are unlikely to be vulnerable to p-iPBA hepatic and testicular toxicity.

Para-cymene was not genotoxic in *in vitro* in assays. *In vivo* genotoxicity or carcinogenicity studies are not available. The available data on genotoxicity and the metabolism of p-cymene do not provide evidence for concern regarding carcinogenic effects of p-cymene.

In the combined repeat dose and reproductive/developmental toxicity screening test described above, treatment-related effects were observed at ≥ 100 mg/(kg bw x d) on male fertility and on litters at 100 mg/(kg bw x d). No litters were delivered at 200 mg/(kg bw x d). The NOAEL for the P0 males and for the F1 offspring was 50 mg/(kg bw x d).

The NOAEL of 50 mg/(kg bw x d) for testes and sperm cell toxicity obtained in the oral Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test with rats is used as the POD for the derivation of an EU-LCI.

The results of the metabolism studies with p-cymene in animals indicate that oral absorption of p-cymene is as high or slightly higher than absorption by inhalation. 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 derivation:

- Route-to-route extrapolation: 1.15 m^3/(kg bw x d)
- Differences in absorption: 1
- Adjusted study length factor: 2
- Interspecies differences: 1.0 (metabolism studies indicate that rats are the most sensitive species and humans are less sensitive)
- Intraspecies differences: 10,

leading to a value of 50 mg/(kg bw x d) : (1.15 x 20) = 2174 µg/m^3 (rounded value: 2200 µg/m^3).

An EU-LCI value of 2200 µg/m^3 is proposed for p-cymene.

A median odour threshold of 43.2 µg/m^3 air has been reported for p-cymene (Schreiner et al. 2020). Consequently, olfactory perception must be expected at the proposed EU-LCI value.

The isopropyl side chain in para-position seems to be a prerequisite for the specific toxicity of p-cymene (1-isopropyl-toluene). Therefore, read-across to ortho- and meta-cymene and also 3- and 4-ethyltoluene, which lack this structural feature is not recommended.

Substance profile and EU-LCI value for C17–C22 aliphatic hydrocarbons

The n-alkanes C17, C18, C19, C20, C21 and C22 are waxy solids with melting points between 22 and 44 °C.

No human data relevant for the assessment are available.

Systemic availability of inhaled hydrocarbons is decreased at higher carbon number (> C12). For C17–C22 aliphatic hydrocarbons the amount of substance available as vapour is very limited due to the low vapour pressure of the substances.

The acute toxicity of saturated aliphatic hydrocarbons used in the read-across approach in the disseminated REACH registration dossiers is very low. The substances are not skin- or eye irritating and do not show a sensitising or sensory irritation potential.

No repeated inhalation studies with the relevant substances are available. Data from two 90-day inhalation studies with hydrocarbons C11-14 NIC (Normal, Iso- and Cyclic alkanes), < 2% aromatics and C10-12 I (Iso alkanes), <2% aromatics are available for a read-across approach. In both studies with rats the respective NOAEC is reported as the highest concentration tested (6000 mg/m^3 and 10400 mg/m^3). In male animals, kidney effects in all dose groups were observed which were

consistent with the picture of alpha2u-globulin nephropathy, a species-specific effect in male rats with no relevance to humans. In addition, liver weight was increased in the mid and high exposure group in males and in the high exposure group in females. The changes in liver weight were not accompanied by histological changes and are considered as an adaptive response. These liver effects in the mid and high exposure groups (at 3000 and 6000 mg/m³) may be considered the most relevant effects and the basis for the derivation of a potential EU-LCI value (POD: 1500 mg/m³).

The substances did not show a genotoxic or carcinogenic potential nor is there a concern for reproductive or developmental toxicity.

Saturated aliphatic hydrocarbons C17-C22 are compounds with saturated vapour concentrations below 5 mg/m³. A hypothetical EU-LCI value of 30 mg/m³ (1500 mg/m³ : 2 (adjustment for study length) : 2.5 (interspecies differences) : 10 (interspecies differences)) could be derived based on increased liver weight in inhalation studies with read-across substances that have shorter chain length and are therefore more volatile. However, vapour exposure to saturated aliphatic hydrocarbons C17-C22 is not considered relevant.

In a different approach the saturated vapour concentration of the C17-C22 saturated aliphatic hydrocarbons (0.02 – 4.5 mg/m³ at 25 °C) could be used as an EU-LCI value. Since this approach is not described in the methodological report on EU-LCI values (EC, 2013), currently no EU-LCI value is suggested for saturated aliphatic hydrocarbons C17-C22.

Substance profile and EU-LCI value for 3-carene

3-Carene is an unsaturated monoterpene hydrocarbon. The substance has a sweet and pungent odour with woody character. The compound is chiral, both forms and the racemate are widespread in nature, e. g. in essential oils and in turpentine oils.

3- Carene may be emitted from wooden construction materials or furniture, together with other monoterpenes, but also from cleaning agents, air refreshers, laundry products, paints or varnishes. Concentrations of 3-carene in indoor are mostly in the order of several µg/m³. However, very high maximum levels exceeding 1000 µg/m³ (up to 8200 µg/m³) are also reported, probably from complaint-related measurements.

Studies with controlled exposure of humans against 3-carene revealed that 70 % of 3-carene were taken up in the lungs. In a metabolism study with oral intake of 3-carene in humans, the cumulative excretion of metabolites within 24 h after in urine accounted for 28 % of the applied oral dose.

The acute toxicity of 3-carene is low. In an inhalation study with rats, death was observed at 5070 mg/m³ after 4-hour exposure but not at 1050 mg/m³. Short-term (30 min) exposure above 1400 ppm (7800 mg/m³) caused slight sedation or drowsiness but no death in mice. Liquid 3-carene causes only mild and temporary irritation of eyes and skin. However, oxidised 3-carene is a skin sensitiser.

Data from human studies indicate that high concentrations of 3-carene in air may cause sensory irritation. Sensory irritating effects were noted by volunteers exposed to 450 mg/m³ 3-carene for two hours. In animal studies, an RD50 for sensory irritation of 1345 ppm (7532 mg/m³) was obtained for (+)-3-carene in a study with mice.

After repeated exposure of humans against a mixture of 280 mg/m³ α-pinene, 30 mg/m³ ß-pinene and 140 mg/m³ 3-carene (overall terpene concentrations 450 mg/m³) three hours/day on four days within two weeks, the bronchoalveolar lavage revealed signs of a weak acute alveolar reaction.

In a subchronic oral (feeding) toxicity study following OECD guideline 408, reduced grip strength was observed in female rats after oral exposure to (+)-carene at concentrations of 12000 ppm (752

mg/(kg bw x d)) , but not at 4500 ppm (about 282 mg/(kg bw x d)). The effects on grip strength were outside the background control range and were only partially reversible within the four-week recovery period.

3-carene was not genotoxic in *in vitro* in assays with bacteria and mammalian cells. *In vivo* data are not available nor are carcinogenicity studies. The available data on genotoxicity and from repeated dose toxicity studies do not provide evidence for concern regarding carcinogenic effects of 3-carene.

A pre-study for an extended one-generation reproductive toxicity study in rats revealed no effects on reproductive performance up to the highest dose of 12000 ppm 3-carene in food (between 639 and 1622 mg/(kg bw x d)). Food intake was lower at ≥ 6000 ppm (314 to 841 mg/(kg bw x d)), probably due to reduced palatability. In a prenatal developmental toxicity study, pregnant rats showed a lower weight gain and food intake at 350 mg/(kg bw x d). In a pre-study, pre-implantation losses seemed to be increased at 600 mg/(kg bw x d). No developmental toxicity was observed at 300 and 450 mg/(kg bw x d).

The NOAEL of 282 mg/(kg bw x d) obtained in the subchronic oral (feeding) toxicity study with (+) 3 carene in rats is used as POD for the derivation of an EU-LCI value. The results of toxicokinetic studies with 3-carene in humans indicate that pulmonary uptake by inhalation is about 70 %. Oral uptake may be lower (28 %) as indicated by recovery of metabolites in urine. Thus, the default factor of two to account for differences in absorption after oral or inhalation exposure will be considered, and the following assessment factors are used:

- Route-to-route extrapolation factor: 1.15 m^3/(kg bw x d) (default factor for rats)
- Default factor in case of oral-to-inhalation extrapolation: 2
- 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 282 mg/(kg bw x d) : (1.15 x 2 x 50) = 2452 µg/m^3 for (+)-3-carene.

The proposed EU-LCI value for 3-carene value is based on a NOAEL for systemic effects observed in a study with oral exposure of rats. Signs of irritation of mucous membranes (eyes and nose) have been noted in humans in a short-term inhalation study with 3-carene at 450 mg /m^3, i.e., at an 180fold higher concentration, indicating that sensory irritation is unlikely at the proposed EU-LCI value.

It should be noted that conventional analytical methods normally applied for the detection of 3-carene in air do not differentiate between both enantiomers, (+)- and (-)-3-carene. Consequently, the value is proposed for (the sum of both isomers of) 3-carene without specification of the enantiomer.

An EU-LCI value of 2500 µg/m^3 is proposed for 3-carene.

Odour perception cannot be excluded at the proposed EU-LCI value for 3-carene.

Substance profile and EU-LCI value for C4-C13 saturated n- and iso-alcohols

"Other C_4-C_{13} n- and iso-alcohols" within the context of this project refers to primary aliphatic straight or branched (but non-cyclic) alcohols of the specified number of carbon atoms. Since the

toxicological data base for C_4- and C_5-alkanols is currently evaluated separately by the EU-LCI working group it was agreed to restrict this evaluation to "C_6-C_{13} n-and iso-alkanols". This group contains a great many of compounds of which only a few are produced and used as individual substances or in technical mixtures. The composition of commercial products depends on the route to manufacture and the related feedstocks. Most of the alcohols have linear carbon chains but certain manufacturing processes create branched structures. The technical products contain linear saturated primary non-branched aliphatic alcohols (n-alkanols) with an even number of carbon atoms, while the so-called technical "essentially linear alcohols" are saturated primary alcohols and their saturated mono-branched primary alcohol isomers of corresponding chain length.

Linear aliphatic alcohols are of a low order of toxicity. The lower members cause local irritation at the site of first contact and induce signs of CNS depression and respiratory effects when administered at very high dose levels as a bolus dose. In a combined repeated dose and reproductive/ developmental toxicity screening test with gavage administration of 3,5,5-trimethyl-1-hexanol to rats, a NOAEL of 12 mg/(kg bw x d) was obtained for systemic toxicity and fertility in females. Developmental toxicity of straight- or branched-chain alcohols was not expressed in studies with inhalation exposure of animals. Effects were observed after oral administration, mostly at high doses, and typically at maternally toxic concentrations. The available data do not indicate that C_6-C_{22} linear and branched chain saturated primary alcohols have a genotoxic potential.

Evaluation of the available data for this group of substances shows that sensory irritation as observed in humans and in animal studies represents the critical endpoint for the derivation of health-based LCI values. Sensory irritation of C_6 – C_{13} alkanols in humans and laboratory animals increases with increasing chain length.

For the derivation of an EU-LCI value for C_6-C_{13} n- and iso-alkanols read-across from 2-ethylhexan-1-ol is performed and an EU-LCI value of 300 µg/m³ is proposed for this group of substances[1].

This represents a "conservative approach". Inspection of the reported NOAEC/NOAEL derived for other substances of this group indicates that an EU-LCI value of 300 µg/m³ based on sensory irritation will also cover other adverse effects observed in studies with C_6-C_{13} n- and iso-alcohols.

No molar adjustment is recommended. Adjustment to lower members of this group (C_6 and C_7 alcohols) would lead to a lower mass-based value, which is not supported by the available data. The database for alcohols with a higher number of carbon atoms than 2-ethyl-1-hexanol is limited, but indicates that the derived value seems appropriate.

As far as data were available, the C_6-C_{13} n- and iso alcohols show very low odour thresholds. The lowest reported values for the individual compounds are in the range 5 µg/m³ for 1-decanol to 73 µg/m³ for 2-ethyl-1-hexanol. Therefore, olfactory perception must be expected at the proposed EU-LCI value.

Substance profile and EU-LCI value for "other methacrylates"

Methacrylate esters form a group with a common methacrylate moiety in all representatives and an alkyl chain differing in the number of carbon atoms and, in higher members (starting at C_3), possible branching of this chain. "Other methacrylates" refers to all esters of methacrylic acid other than methyl methacrylate for which an EU-LCI value was already derived.

[1] Note: The derivation of the EU-LCI value for 2-ethyl-1-hexanol is currently under re-evaluation. In case that the EU-LCI value will be changed, the rationale presented here for the group of C_6-C_{13} n- and isoalkanols should be reviewed and modified if necessary.

Compared to methyl methacrylate, the database for toxicological effects of other methacrylates is much more limited. A category approach is justified for this group of “other methacrylates” due to trends observed in toxicokinetics and toxicity.

In case of methyl methacrylate (MMA), a concentration-dependent increase in the incidence and severity of olfactory epithelial lesions was observed in a chronic inhalation study with rats. Similar lesions of the olfactory epithelium as produced by MMA were also observed following inhalation exposure of rats to aliphatic esters of other saturated and unsaturated carboxylic acids with saturated alkanols. The lesion is associated with the formation of the carboxylic acid by hydrolysis of the corresponding ester, which, after exceeding the specific buffer capacity of the cells, leads to acidification and consequently cytotoxic damage. Ethyl methacrylate (EMA) also produces olfactory lesions comparable to MMA following acute exposure. Alkyl methacrylate esters with longer alkyl chains than EMA do not elicit a toxic response after acute exposure. However, similar olfactory epithelial lesions were observed after repeated (subacute) inhalation of rats with n-butyl methacrylate (MBA). No sufficient corresponding data are available for other alkyl methacrylates.

For the derivation of an EU-LCI value for ethyl methacrylate, it is suggested to perform the read-across from methyl methacrylate. An EU-LCI value of 850 µg/m³ is proposed for ethyl methacrylate. A similar read-across can be performed for n- and isopropyl methacrylate, and an EU-LCI value of 950 µg/m³ may be proposed for n- and isopropyl methacrylate.

In a subacute inhalation study (6 h/d, 5 d/week for 4 weeks) with rats, n-butyl methacrylate (BMA) caused degeneration of the olfactory epithelium of the nasal cavity ≥ 952 ppm (≥ 5626 mg/m³). The NOAEC of 310 ppm (1832 mg/m³) is used as the POD for the derivation of the EU-LCI. The following adjustment factors are used:

- Adjustment for exposure duration: 5.6
- Study length (subacute to chronic): 6
- Interspecies differences: 2.5
- Intraspecies differences: 10

Total assessment factor: 840,

leading to a calculated value of 2181 µg/m³ (rounded value: 2200 µg/m³).

An EU-LCI value of 2200 µg/m³ is proposed for n-butyl methacrylate. The same value can be adopted for the other butyl isomer methacrylates.

For 2-ethylhexyl methacrylate, no suitable inhalation toxicity is available for the proposal of an EU-LCI value. In a subchronic oral toxicity study with rats, systemic toxicity (effects on weight gain, blood chemical parameters, increased relative organ weights of liver and kidney) were observed at 360 mg/(kg bw x d). The NOAEL of 120 mg/(kg bw x d) obtained in this toxicity study is used as the POD for the derivation of the EU-LCI. The following adjustment factors are used:

- Route-to-route extrapolation factor: 1.15 m³/(kg bw x d)
- Differences in absorption: 1 (assuming similar absorption by oral and inhalation 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 calculated value of 120 mg/(kg bw x d) : (1.15 x 2 x 25) = 2087 µg/m³ (rounded value: 2100 µg/m³).

An EU-LCI value of 2100 µg/m³ is proposed for 2-ethylhexyl methacrylate.

No odour thresholds were available for any of the alkyl methacrylates. No conclusions can be drawn regarding olfactory perception at the proposed EU-LCI.

Zusammenfassung

Stoffprofil und EU-LCI-Wert für „andere Alkylbenzole“

EU-LCI-Werte wurden für eine Reihe von Alkylbenzole abgeleitet. "Andere Alkylbenzole" bezieht sich somit auf eine Gruppe von Alkylbenzolen, für die bisher keine EU-LCI-Werte abgeleitet wurden. Eine Recherche in bibliografischen Datenbanken, Portalen und auf Websites relevanter Organisationen ergab, dass die toxikologischen Datenbasis für die meisten Alkylbenzole, für die es noch keinen EU-LCI-Wert gibt, sehr begrenzt ist. Zudem werden die meisten dieser Alkylbenzole kaum in Bau- oder Konsumgütern verwendet und mit Ausnahme von Ethyltoluolen und Isopropyltoluolen nur selten oder gar nicht in der Innenraumluft nachgewiesen. Während die toxikologische Datenbasis für Ethyltoluole sehr begrenzt ist, sind Daten für 1-Isopropyl-4-methylbenzol (p-Isopropyltoluol, p-Cymol) verfügbar, das am häufigsten in der Innenraumluft nachgewiesene Alkylbenzol, für das noch kein EU-LCI abgeleitet wurde.

Para-Cymol ist eine natürlich vorkommende Verbindung, die zu der großen Gruppe der Terpene gehört und in Pflanzen weit verbreitet ist. Die Substanz wird industriell produziert, in Konsumgütern verwendet und in Prüfkammermessungen flüchtiger organischer Verbindungen (VOC) aus Baumaterialien und Produkten erfasst.

Der Geruch von isoliertem p-Cymol wurde als holz- und zitrusähnlich, aber auch als kraftstoffähnlich beschrieben. Die Konzentrationen von p-Cymol in Innenräumen liegen in der Regel unter 1 µg/m³ mit Höchstwerten unter 100 µg/m³.

Daten aus Tierversuchen deuten darauf hin, dass p-Cymol nach oraler oder inhalativer Exposition etwa gleich gut absorbiert wird. Nach der Absorption und Verteilung wird p-Cymol zu einer Reihe von Metaboliten oxidiert, die mit dem Urin ausgeschieden werden, hauptsächlich p-Isopropyl-benzoesäure oder ihr Glycin-Konjugat p-Isopropylhippursäure.

Die akute Toxizität von p-Cymol ist gering. Auswirkungen auf das Zentralnervensystem wurden nach Einatmen hoher Konzentrationen (≥ 1100 mg/m³) beim Menschen beschrieben. Sensorische Reizung wurde nach kurzzeitiger (wenige Sekunden dauernder) Einwirkung hoher Konzentrationen (wahrscheinlich in der Größenordnung von etwa 5000 mg/m³) beim Menschen festgestellt. Auch bei Tieren wurde in Studien zur akuten Toxizität bei mehrstündiger Exposition eine sensorische Reizung bei etwa 9700 mg/m³ festgestellt.

Neurotoxizität konnte in der einzigen verfügbaren Studie mit wiederholter Inhalationsexposition bei Ratten nach Exposition mit bis zu 250 ppm (etwa 1230 mg/m³) über vier Wochen nicht nachgewiesen werden.

Ein kombinierter Screening-Test auf Toxizität bei wiederholter Verabreichung sowie Reproduktions-/Entwicklungstoxizität (OECD TG 422) mit oraler Exposition von Ratten über einen Zeitraum von mindestens 35 Tagen ergab toxische Wirkungen auf Hoden und Spermien männlicher Tiere mit geringerem Organgewicht, Verminderung/Degeneration von Keimzellen, Verminderung und/oder Retention von Spermien sowie damit verbundenen Veränderungen der Nebenhoden. In dieser Studie wurde ein NOAEL für P0-Männchen von 50 mg/(kg KG x d) ermittelt.

Studien mit Substanzen, die strukturell mit p-Cymol verwandt sind, deuten darauf hin, dass der Metabolismus von p-Cymol eine entscheidende Rolle bei der beobachteten Hoden- und Spermientoxizität spielen dürfte. Die Wirkung auf die Spermatogenese scheint mit der Bildung des Metaboliten p-Isopropylbenzoesäure (p-iPBA) verbunden zu sein. Dieser Metabolit konnte nur in Rattenhepatozyten, nicht aber in Kaninchen- und menschlichen Hepatozyten nachgewiesen werden. Weitere Studien deuten darauf hin, dass die Bildung dieses Metaboliten mit den toxischen Wirkungen auf die Hoden und die Spermienentwicklung von Ratten zusammenhängt und dass der Mensch, ebenso wie Kaninchen, wahrscheinlich nicht oder sehr viel weniger als Ratten empfindlich hinsichtlich der Leber- und Hodentoxizität von p-iPBA ist.

Para-Cymol war in *In-vitro*-Tests nicht genotoxisch. *In-vivo*-Studien zur Genotoxizität oder Karzinogenität sind nicht verfügbar. Die verfügbaren Daten zur Genotoxizität und zum Metabolismus von p-Cymol geben keinen Anlass zur Besorgnis hinsichtlich einer karzinogenen Wirkung von p-Cymol.

In dem oben beschriebenen kombinierten Test wurden behandlungsbedingte Auswirkungen auf die männliche Fruchtbarkeit bei ≥ 100 mg/(kg Körpergewicht x Tag) und auf die Würfe bei 100 mg/(kg Körpergewicht x Tag) beobachtet. Bei 200 mg/(kg KG x d) konnten gar keine Würfe verzeichnet werden. Der NOAEL für die P0-Männchen und für die F1-Nachkommen betrug 50 mg/(kg KG x d).

Der NOAEL von 50 mg/(kg KG x d) für Hoden- und Spermientoxizität wird als POD für die Ableitung eines EU-LCI verwendet.

Die Ergebnisse der Metabolismusstudien mit p-Cymol bei Tieren deuten darauf hin, dass die orale Absorption von p-Cymol gleich hoch oder leicht höher ist als die Absorption durch Inhalation. Daher wird kein Faktor zur Berücksichtigung von Unterschieden in der Absorption nach oraler oder inhalativer Exposition berücksichtigt, und die folgenden Extrapolationsfaktoren (EC, 2013; ECHA, 2012) werden zur Ableitung herangezogen:

- Pfad-zu-Pfad-Extrapolation (Ratte): 1,15 m^3/(kg KG x d)
- Extrapolation von oraler zu inhalativer Aufnahme: 1
- Zeitextrapolation: 2
- Allometrisches Scaling: bereits in der Pfad-zu-Pfad-Übertragung berücksichtigt
- Interspeziesextrapolation (verbleibende Unterschiede): 1 (Stoffwechselstudien deuten darauf hin, dass Ratten die empfindlichste Spezies und Menschen weniger empfindlich sind)
- Intraspeziesextrapolation: 10.

Daraus ergibt sich ein Wert von 50 mg/(kg KG x d) : (1,15 x 20) = 2174 µg/m^3 (gerundeter Wert: 2200 µg/m^3).

Für p-Cymol wird ein EU-LCI-Wert von 2200 µg/m^3 vorgeschlagen.

Für p-Cymol wurde eine mittlere Geruchsschwelle von 43,2 µg/m^3 Luft angegeben (Schreiner et al. 2020). Folglich muss bei dem vorgeschlagenen EU-LCI-Wert mit einer Geruchswahrnehmung gerechnet werden.

Die Isopropyl-Seitenkette in para-Position scheint eine Voraussetzung für die spezifische Toxizität von p-Cymol (1-Isopropyl-Toluol) zu sein. Daher wird ein Read-across auf ortho- und meta-Cymol sowie 3- und 4-Ethyltoluol, denen dieses Strukturmerkmal fehlt, nicht empfohlen.

Stoffprofil und EU-LCI-Wert für C17-C22-n-Alkane

Die n-Alkane C17, C18, C19, C20, C21 und C22 sind wachsartige Feststoffe mit Schmelzpunkten zwischen 22 und 44 °C.

Es liegen keine für die Bewertung relevanten Humandaten vor.

Die systemische Verfügbarkeit von inhalierten Kohlenwasserstoffen ist bei höheren Kohlenstoffzahlen (> C12) geringer. Bei aliphatischen C17-C22-Kohlenwasserstoffen ist die als Dampf verfügbare Stoffmenge aufgrund des niedrigen Dampfdrucks der Stoffe sehr begrenzt.

Die akute Toxizität der gesättigten aliphatischen Kohlenwasserstoffe, die im Rahmen des Read-Across-Ansatzes in den verfügbaren REACH-Registrierungsdossiers verwendet werden, ist sehr gering. Die Stoffe sind nicht haut- oder augenreizend und weisen kein sensibilisierendes oder sensorisches Reizungspotenzial auf.

Es liegen keine Inhalationsstudien mit wiederholter Exposition zu den betreffenden Stoffen vor. Daten aus zwei 90-Tage-Inhalationsstudien mit C11-14-Alanen NIC (Normale, Iso- und zyklische Alkane, < 2% Aromaten und C10-12 I (Iso-Alkane), <2% Aromaten) sind für einen Read-Across-Ansatz verfügbar. In beiden Studien mit Ratten wird die jeweilige NOAEC als die höchste getestete Konzentration angegeben (6000 mg/m³ und 10400 mg/m³). Bei männlichen Tieren wurden in allen Dosisgruppen Niereneffekte beobachtet, die mit dem Bild der Alpha-2u-Globulin-Nephropathie übereinstimmen, einer artspezifischen Wirkung bei männlichen Ratten, die für den Menschen nicht relevant ist. Darüber hinaus war das Lebergewicht in der mittleren und hohen Expositionsgruppe bei männlichen Tieren und in der hohen Expositionsgruppe bei weiblichen Tieren erhöht. Die Veränderungen des Lebergewichts wurden nicht von histologischen Veränderungen begleitet und werden als adaptive Reaktion betrachtet. Diese Lebereffekte in der mittleren und hohen Expositionsgruppe (bei 3000 und 6000 mg/m³) können als die relevantesten Effekte und als Grundlage für die Ableitung eines potenziellen EU-LCI-Wertes (POD: 1500 mg/m³) betrachtet werden.

Die Stoffe zeigten weder ein genotoxisches oder karzinogenes Potenzial noch bestehen Hinweise auf Reproduktions- oder Entwicklungstoxizität.

Gesättigte aliphatische Kohlenwasserstoffe C17-C22 sind Verbindungen mit einer Sättigungsdampfkonzentration unter 5 mg/m³. Ein hypothetischer EU-LCI-Wert von 30 mg/m³ (1500 mg/m³ : 2 (Zeitextrapolation) : 2,5 (Interspeziesextrapolation) : 10 (Intraspeziesextrapolation) könnte auf der Grundlage des erhöhten Lebergewichts in Inhalationsstudien mit Read-Across-Substanzen abgeleitet werden, die eine kürzere Kettenlänge aufweisen und daher flüchtiger sind. Eine Exposition gegenüber gesättigten aliphatischen Kohlenwasserstoffen C17-C22 in Dampfform wird jedoch nicht als relevant angesehen.

In einem anderen Ansatz könnte die Sättigungsdampfkonzentration (0,02 - 4,5 mg/m³ bei 25 °C) der gesättigten aliphatischen C17-C22-Kohlenwasserstoffe als EU-LCI-Wert verwendet werden. Da dieser Ansatz im Methodenbericht über EU-LCI-Werte nicht beschrieben wird, wird derzeit kein EU-LCI-Wert für gesättigte aliphatische Kohlenwasserstoffe C17-C22 vorgeschlagen.

Stoffprofil und EU-LCI-Wert für 3-Caren

3-Caren ist ein ungesättigter Monoterpen-Kohlenwasserstoff. Die Substanz hat einen süßen und stechenden Geruch mit holzigem Charakter. Die Verbindung ist chiral, beide Formen und das Racemat sind in der Natur weit verbreitet, z. B. in ätherischen Ölen und in Terpentinöl.

3-Caren kann zusammen mit anderen Monoterpenen aus hölzernen Baumaterialien oder Möbeln emittiert werden, aber auch aus Reinigungsmitteln, Luftverbesserungsmitteln, Waschmitteln, Farben oder Lacken. Die Konzentrationen von 3-Caren in Innenräumen liegen meist in der Größenordnung von einigen µg/m³. Es werden jedoch auch sehr hohe Höchstwerte von mehr als 1000 µg/m³ (bis zu 8200 µg/m³) gemeldet, die wahrscheinlich aus anlassbezogenen Messungen stammen.

Studien mit kontrollierter Exposition von Menschen gegenüber 3-Caren ergaben, dass 70 % des 3-Carens in die Lunge aufgenommen wurden. In einer Metabolismusstudie mit oraler Aufnahme von 3-Caren beim Menschen machte die kumulative Ausscheidung von Metaboliten innerhalb von 24 Stunden nach der Aufnahme im Urin 28 % der verabreichten oralen Dosis aus.

Die akute Toxizität von 3-Caren ist gering. In einer Inhalationsstudie mit Ratten wirkten 5070 mg/m³ nach 4-stündiger Exposition letal, nicht aber 1050 mg/m³. Kurzzeitige (30 min) Exposition über 1400 ppm (7800 mg/m³) führte bei Mäusen zu leichter Sedierung oder Schläfrigkeit, aber nicht zum Tod. Flüssiges 3-Caren verursacht nur leichte und vorübergehende Reizungen von Augen und Haut. Oxidiertes 3-Caren wirkt jedoch hautsensibilisierend.

Daten aus Humanstudien deuten darauf hin, dass hohe Konzentrationen von 3-Caren in der Luft sensorische Reizungen hervorrufen können. Bei Probanden, die zwei Stunden lang 450 mg/m³ 3-Caren ausgesetzt waren, wurden sensorische Reizwirkungen festgestellt. In Tierversuchen wurde für (+)-3-Caren in einer Studie mit Mäusen ein RD50-Wert für sensorische Reizung von 1345 ppm (7532 mg/m³) ermittelt.

Nach wiederholter Exposition von Menschen gegenüber einem Gemisch aus 280 mg/m³ α-Pinen, 30 mg/m³ ß-Pinen und 140 mg/m³ 3-Caren (Gesamt-Terpenkonzentration 450 mg/m³) drei Stunden/Tag an vier Tagen innerhalb von zwei Wochen zeigte die bronchoalveoläre Lavage Anzeichen einer schwachen akuten Alveolarreaktion.

In einer subchronischen oralen (Fütterungs-)Toxizitätsstudie (gemäß OECD-Richtlinie 408) wurde bei weiblichen Ratten nach oraler Exposition gegenüber (+)-Caren bei Konzentrationen von 12000 ppm (752 mg/(kg KG x d)) eine verminderte Griffstärke beobachtet, nicht jedoch bei 4500 ppm (etwa 282 mg/(kg KG x d)). Die Veränderungen lagen außerhalb des Bereichs historischer Kontrollen und waren innerhalb der vierwöchigen Erholungsphase nur teilweise reversibel.

3-Caren war in *In-vitro*-Tests mit Bakterien und Säugetierzellen nicht genotoxisch. *In-vivo*-Daten und Studien zur Karzinogenität liegen nicht vor. Die verfügbaren Daten zur Genotoxizität und aus Studien zur Toxizität bei wiederholter Verabreichung geben keinen Anlass zur Besorgnis hinsichtlich einer karzinogenen Wirkung von 3-Caren.

Eine Vorstudie für eine erweiterte Reproduktionstoxizitätsstudie über eine Generation an Ratten ergab keine Auswirkungen auf die Reproduktion bis zur höchsten Dosis von 12000 ppm 3-Caren im Futter (zwischen 639 und 1622 mg/(kg KG x d)). Die Futteraufnahme war bei ≥ 6000 ppm (314 bis

841 mg/(kg KG x d)) geringer, wahrscheinlich wegen der geschmacklichen Beeinträchtigung des Futters durch die Testsubstanz. In einer Studie zur pränatalen Entwicklungstoxizität zeigten trächtige Ratten bei 350 mg/(kg KG x d) eine geringere Gewichtszunahme und Nahrungsaufnahme. In einer Vorstudie schienen die Präimplantationsverluste bei 600 mg/(kg Körpergewicht x Tag) erhöht zu sein. Bei 300 und 450 mg/(kg KG x d) wurde keine Entwicklungstoxizität beobachtet.

Der NOAEL-Wert von 282 mg/(kg KG x d) aus der subchronischen oralen Toxizitätsstudie mit (+)-3-Caren an Ratten wird als POD für die Ableitung eines EU-LCI-Wertes für 3-Caren verwendet. Die Ergebnisse der toxikokinetischen Studien mit 3-Caren beim Menschen deuten darauf hin, dass die pulmonale Aufnahme durch Inhalation etwa 70 % beträgt. Die orale Aufnahme kann geringer sein (28 %), worauf die Ausscheidung von Metaboliten im Urin hinweist. Daher wird der Standardfaktor von zwei zur Berücksichtigung von Unterschieden bei der Absorption nach oraler oder inhalativer Exposition berücksichtigt, und es werden die folgenden Extrapolationsfaktoren verwendet:

- Pfad-zu-Pfad-Extrapolation (Ratte): 1,15 m^3/(kg KG x d)
- Standardfaktor bei Extrapolation von oralen zu inhalativer Aufnahme: 2
- Zeitextrapolation: 2 (subchronische Exposition)
- Allometrisches Scaling: bereits in der Pfad-zu-Pfad-Übertragung berücksichtigt
- Interspeziesextrapolation (verbleibende Unterschiede): 2,5
- Intraspeziesextrapolation: 10.

Daraus ergibt sich ein Wert von 282 mg/(kg KG x d) : (1,15 x 2 x 50) = 2452 µg/m^3 für (+)-3-Caren.

Der vorgeschlagene EU-LCI-Wert für 3-Caren basiert auf einem NOAEL-Wert für systemische Wirkungen, der in einer Studie mit oraler Exposition von Ratten beobachtet wurde. Anzeichen einer Reizung der Schleimhäute (Augen und Nase) wurden beim Menschen in einer Kurzzeit-Inhalationsstudie mit 3-Caren bei einer Konzentration von 450 mg /m^3 beschrieben, d. h. bei einer 180-fach höheren Konzentration. Dies deutet darauf hin, dass eine sensorische Reizung bei dem vorgeschlagenen EU-LCI-Wert unwahrscheinlich ist.

Herkömmliche Analysemethoden für den Nachweis von 3-Caren in der Luft unterscheiden nicht zwischen den beiden Enantiomeren (+)- und (-)-3-Caren. Daher wird der Wert für (die Summe der beiden Isomere von) 3-Caren ohne Angabe des Enantiomers vorgeschlagen.

Für 3-Caren wird ein EU-LCI-Wert von 2500 µg/m^3 vorgeschlagen.

Eine Geruchswahrnehmung kann bei dem vorgeschlagenen EU-LCI-Wert für 3-Caren nicht ausgeschlossen werden.

Stoffprofil und EU-LCI-Wert für C4-C13 gesättigte n- und iso-Alkohole

"Andere C_4-C_{13} n- und Iso-Alkohole" bezieht sich im Rahmen dieses Projekts auf primäre aliphatische geradkettige oder verzweigte (aber nicht cyclische) Alkohole mit der angegebenen Anzahl von Kohlenstoffatomen. Da die toxikologische Datenbasis für C_4- und C_5-Alkanole derzeit von der EU-LCI-

Arbeitsgruppe getrennt bewertet wird, beschränkt sich diese Bewertung auf "C_6-C_{13} n- und Iso-Alkanole". Diese Gruppe enthält eine Vielzahl von Verbindungen, von denen nur wenige als Einzelstoffe oder in technischen Gemischen hergestellt und verwendet werden. Die Zusammensetzung der Handelsprodukte hängt vom Herstellungsweg und den verwendeten Rohstoffen ab. Die meisten Alkohole haben lineare Kohlenstoffketten, aber bestimmte Herstellungsverfahren erzeugen verzweigte Strukturen. Die technischen Produkte enthalten lineare gesättigte primäre unverzweigte aliphatische Alkohole (n-Alkanole) mit einer geraden Anzahl von Kohlenstoffatomen, während die so genannten technischen "essentially linear alcohols" gesättigte primäre Alkohole und ihre gesättigten einfach verzweigten primären Alkoholisomere mit entsprechender Kettenlänge beinhalten.

Lineare aliphatische Alkohole weisen eine geringe Toxizität auf. Die Anfangsvertreter dieser Reihe verursachen eine lokale Reizung an der Einwirkstelle und führen zu einer Lähmung des zentralen Nervensystems und zeigen respiratorische Effekte, wenn sie in sehr hohen Dosen als Bolus verabreicht werden. In einem kombinierten Screeningtest mit wiederholter Verabreichung und Reproduktions-/Entwicklungstoxizität mit Verabreichung von 3,5,5-Trimethyl-1-hexanol per Schlundsonde an Ratten wurde ein NOAEL-Wert von 12 mg/(kg KG x d) für die systemische Toxizität und die Fruchtbarkeit bei weiblichen Tieren ermittelt. Entwicklungstoxische Effekte von gerad- oder verzweigtkettigen Alkoholen wurden in Studien mit inhalativer Exposition von Versuchstieren nicht beobachtet. Auswirkungen traten nach oraler Verabreichung auf, meist bei hohen Dosen und typischerweise bei maternal toxischen Konzentrationen. Die verfügbaren Daten deuten nicht darauf hin, dass lineare und verzweigtkettige gesättigte primäre C_6-C_{22}-Alkohole ein genotoxisches Potenzial besitzen.

Die Auswertung der verfügbaren Daten für diese Stoffgruppe zeigt, dass die beim Menschen und in Tierversuchen beobachtete sensorische Reizung den kritischen Endpunkt für die Ableitung von gesundheitsbezogenen LCI-Werten darstellt. Die sensorische Reizung von C_6- bis C_{13}-Alkanolen nimmt bei Menschen und Versuchstieren mit zunehmender Kettenlänge zu.

Für die Ableitung eines EU-LCI-Wertes für C_6-C_{13} n- und Iso-Alkanole wird ein Read-Across von 2-Ethylhexan-1-ol durchgeführt und ein EU-LCI-Wert von 300 µg/m³ für diese Stoffgruppe vorgeschlagen[2].

Dies stellt einen "konservativen Ansatz" dar. Die Prüfung der berichteten NOAEC/NOAEL, die für andere Stoffe dieser Gruppe abgeleitet wurden, zeigt, dass ein EU-LCI-Wert von 300 µg/m³ auf der Grundlage der sensorischen Reizung auch vor anderen adversen Wirkungen schützt, die in Studien mit C_6-C_{13} n- und Iso-Alkoholen beobachtet wurden.

Es wird keine molare Adjustierung empfohlen. Eine Anpassung an niedrigere Mitglieder dieser Gruppe (C_6- und C_7-Alkohole) würde zu einem niedrigeren massenbasierten Wert führen, der durch die verfügbaren Daten nicht gestützt wird. Die Datenbasis für Alkohole mit einer höheren Anzahl von

[2] Anmerkung: Die Ableitung des EU-LCI-Wertes für 2-Ethyl-1-hexanol wird derzeit neu bewertet. Für den Fall, dass der EU-LCI-Wert geändert wird, sollte die hier dargestellte Begründung für die Gruppe der C_6-C_{13} n- und Isoalkanole überprüft und gegebenenfalls angepasst werden.

Kohlenstoffatomen als 2-Ethyl-1-hexanol ist begrenzt, deutet aber darauf hin, dass der abgeleitete Wert angemessen erscheint.

Soweit Daten verfügbar waren, weisen die C_6-C_{13} n- und Iso-Alkohole sehr niedrige Geruchsschwellenwerte auf. Die niedrigsten berichteten Werte für die einzelnen Verbindungen liegen im Bereich von 5 µg/m³ für 1-Decanol bis 73 µg/m³ für 2-Ethyl-1-hexanol. Daher muss bei dem vorgeschlagenen EU-LCI-Wert mit einer Geruchswahrnehmung gerechnet werden.

Stoffprofil und EU-LCI-Wert für „andere Methacrylate“

Methacrylatester bilden eine Gruppe mit einem gemeinsamen Methacrylat-Anteil und einer Alkylkette, die sich in der Anzahl der Kohlenstoffatome und bei höheren Vertretern (ab C_3) in möglichen Verzweigungen dieser Kette unterscheidet. "Andere Methacrylate" bezieht sich auf alle Ester der Methacrylsäure außer Methylmethacrylat, für den bereits ein EU-LCI-Wert abgeleitet wurde.

Im Vergleich zu Methylmethacrylat ist die Datenbasis für toxikologische Wirkungen von anderen Methacrylaten sehr limitiert. Aufgrund der Ähnlichkeit hinsichtlich ihrer Toxikokinetik und Toxizität ist für diese Gruppe der "anderen Methacrylate" ein "category approach“ gerechtfertigt.

Methylmethacrylat (MMA) verursachte in einer chronischen Inhalationsstudie bei Ratten eine konzentrationsabhängige Zunahme der Häufigkeit und des Schweregrads von Läsionen des nasalen Riechepithels. Ähnliche Läsionen des Riechepithels wie durch MMA wurden auch nach Inhalationsexposition von Ratten gegenüber aliphatischen Estern anderer gesättigter und ungesättigter Carbonsäuren mit gesättigten Alkanolen beobachtet. Die Läsion steht im Zusammenhang mit der Bildung der Carbonsäure durch Hydrolyse des entsprechenden Esters, die nach Überschreiten der spezifischen Pufferkapazität der Zellen zu einer Übersäuerung und in der Folge zu zytotoxischen Schäden führt. Ethylmethacrylat (EMA) führt nach akuter Exposition ebenfalls zu Schäden des Riechepithels, die mit denen von MMA vergleichbar sind. Alkylmethacrylatester mit längeren Alkylketten als EMA lösen nach akuter Exposition keine toxische Reaktion aus. Allerdings wurden nach wiederholter (subakuter) Inhalation von n-Butylmethacrylat (MBA) bei Ratten ähnliche olfaktorische Epithelläsionen beobachtet. Für weitere Alkylmethacrylate liegen keine ausreichenden entsprechenden Daten vor.

Für die Ableitung eines EU-LCI-Wertes für Ethylmethacrylat wird vorgeschlagen, den Read-across von Methylmethacrylat durchzuführen. Für Ethylmethacrylat wird ein EU-LCI-Wert von 850 µg/m³ vorgeschlagen. Ein ähnlicher Analogieschluss kann für n- und Isopropylmethacrylat vorgenommen werden, und es kann ein EU-LCI-Wert von 950 µg/m³ für n- und Isopropylmethacrylat vorgeschlagen werden.

In einer subakuten Inhalationsstudie (6 Std./Tag, 5 Tage/Woche für 4 Wochen) mit Ratten verursachte n-Butylmethacrylat (BMA) eine Degeneration des olfaktorischen Epithels der Nasenhöhle in Konzentrationen ≥ 952 ppm (≥ 5626 mg/m³). Die NOAEC von 310 ppm (1832 mg/m³) wird als POD für die Ableitung des EU-LCI verwendet. Die folgenden Faktoren werden verwendet:

- Anpassung für die Expositionsdauer: 5.6
- Studiendauer (subakut bis chronisch): 6
- Unterschiede zwischen den Spezies: 2.5
- Intraspezies-Unterschiede: 10

Gesamtbewertungsfaktor: 840,

was zu einem berechneten Wert von 2181 µg/m³ führt (gerundeter Wert: 2200 µg/m³).

Für n-Butylmethacrylat wird ein EU-LCI-Wert von 2200 µg/m³ vorgeschlagen. Derselbe Wert kann auch für die anderen isomeren Butylmethacrylate herangezogen werden.

Für 2-Ethylhexylmethacrylat liegt keine geeignete Inhalationsstudie vor, um auf deren Basis einen EU-LCI-Wert vorzuschlagen. In einer subchronischen oralen Toxizitätsstudie mit Ratten wurden systemische Effekte (Auswirkungen auf die Gewichtszunahme und blutchemische Parameter sowie erhöhte relative Organgewichte von Leber und Niere) bei 360 mg/(kg KG x d) beobachtet. Der in dieser Toxizitätsstudie ermittelte NOAEL von 120 mg/(kg KG x d) wird als POD für die Ableitung des EU-LCI verwendet. Die folgenden Faktoren werden verwendet:

- Pfad-zu-Pfad-Extrapolation (Ratte): 1,15 m³/(kg KG x d)
- Extrapolation von oraler zu inhalativer Aufnahme: 1 (unter der Annahme einer ähnlichen Absorption bei oraler und inhalativer Exposition)
- Zeitextrapolation: 2
- Allometrisches Scaling: bereits in der Pfad-zu-Pfad-Übertragung berücksichtigt
- Interspeziesextrapolation (verbleibende Unterschiede): 2,5
- Intraspeziesextrapolation: 10,

woraus sich ein berechneter Wert von 120 mg/(kg Körpergewicht x Tag) : (1,15 x 2 x 25) = 2087 µg/m³ (gerundeter Wert: 2100 µg/m³) ergibt.

Für 2-Ethylhexylmethacrylat wird ein EU-LCI-Wert von 2100 µg/m³ vorgeschlagen.

Für keines der Alkylmethacrylate waren Geruchsschwellenwerte verfügbar. Es können somit keine Aussagen hinsichtlich der Geruchswahrnehmung bei dem jeweils vorgeschlagenen EU-LCI-Wert getroffen werden.

1 Toxicological evaluation of "other alkylbenzenes" as basis for the derivation of an EU-LCI value

Substance selection

EU-LCI values were derived for a number of alkylbenzenes (EC, 2013; EU-LCI Working Group, 2021). "Other alkylbenzenes" refers thus to substances within this group for which up to now no EU-LCI values have been derived. An overview for alkylbenzenes up to undecylbenzene (phenylundecane) is presented in Table 1. Alkylbenzenes with alkyl side chains > C_{11} are not included because their very low vapour pressure limits their volatility and their theoretical maximum vapour concentration in air (e.g., the vapour pressure of phenyl undecane is $2.4x10^{-4}$ mm Hg (0.00032 hPa) at 25 °C (PubChem, 2022)).

Table 1: EU-LCI values for alkylbenzenes (EU-LCI Working Group, 2021)

Substance (CAS No.)	EU-LCI (µg/m³)	Year of adoption
Toluene	2900	2013
Ethylbenzene	850	2013
Xylenes (all isomers)	500	2013
Cumene (isopropylbenzene)	1700	2017
n-Propylbenzene	950 (RA[1] ethylbenzene)	2013
Trimethylbenzene (TMB, all isomers)	450	2013
2-Ethyltoluene	550 (RA xylenes)	2014
3-/4-Ethyltoluene	No value derived	
Cymene (isopropyl toluene, all isomers)	(1000) (o, m, p) (only ascribed, not derived yet[2])	
1,2,4,5-Tetramethylbenzene	250 (RA TMBs)	2016
1,2,3,4-/1,2,3,5-Tetramethylbenzene	No value derived	
n-Butylbenzene	1100 (RA ethylbenzene)	2014
Diethylbenzenes (all isomers)	No value derived	
1,2-Diisopropylbenzene	No value derived	
1,3-/1,4-Diisopropylbenzene	750 (RA xylenes)	2013
Hexylbenzene	No value derived	
Phenyl octane and isomers	1100 (RA ethylbenzene)	2013
Nonylbenzene	No value derived	
Phenyl decane and isomers	No value derived	
Phenyl undecane and isomers	No value derived	

1: RA Read-cross; 2: "Derived" EU-LCI values are based on the *de novo* evaluation of toxicological data according to the harmonised framework developed by the EU-LCI working group (EC, 2013). In contrast, "ascribed" EU-LCI values correspond to values assigned by the national authorities in earlier years. The ascribed value for cymene is based on an OEL in Belgium (EC, 2013).

EU-LCI values were derived based on substance-specific data for toluene, ethylbenzene, xylenes, isopropylbenzene, and trimethylbenzenes, whereas EU-LCI values for n-propylbenzene, 2-ethyltoluene, 1,2,4,5-tetramethylbenzene, n-butylbenzene, 1,3-/1,4-diisopropylbenzene and phenyl octane (octylbenzene and isomers) were based on read-across. No read-across was performed to derive values for 3-,4-ethyltoluene, 1,2,3,4- and 1,2,3,5-tetramethylbenzene, hexylbenzene and the C_9-C_{11}-alkylbenzenes.

For those alkylbenzenes without derived EU-LCI values, a search for relevant toxicity studies was conducted in bibliographic data bases (MEDLINE, Google Scholar, Scopus), portals (EChemPortal) and websites of relevant organisations (e.g., ECHA, EFSA, IARC, MAK-Commission, RIVM, WHO, US-EPA). This research revealed that the data base for most of these substances is extremely limited. Also, a search on the ECHA database revealed that REACH registration dossiers are only available for cymene (isopropyltoluene) and diethylbenzenes (Table 2). The lack of registration dossiers for most of these compounds indicates that these substances are only produced or imported in the European Union on a very low scale. Higher alkylbenzenes (undecyl- and dodecylbenzene) are also not produced in significant amounts as pure materials but may be present in commercially produced C_{10}-C_{16} alkylbenzene mixtures. However, these mixtures are nearly completely used as intermediates in the production of linear alkylbenzene sulfonate (LAS), a detergent surfactant (OECD SIDS, 1995).

Table 2: Availability of REACH registration dossiers for alkylbenzenes without derived EU-LCI values (ECHA, 2022)

Substance	REACH registration dossier	DNEL (µg/m³)
2-Ethyltoluene	No	
3-Ethyltoluene	No	
4-Ethyltoluene	No	
Cymene (isopropyl toluene, all isomers)	Yes	p: 220 (systemic: fertility; local: -); o, m: not derived
1,2,3,4-Tetramethylbenzene	No	
1,2,4,5-Tetramethylbenzene	No	
1,2,3,5-Tetramethylbenzene	No	
1,2-/1,3-Diethylbenzene	Yes (dossier “all isomers”)	No
1,4-Diethylbenzene	Yes	2610 (systemic)*
1,2-Diisopropylbenzene	“No data” dossier	
1,3-/1,4-Diisopropylbenzene	No	
Hexylbenzene	No	
Nonylbenzene	No	
Phenyl decane and isomers	No	
Phenyl undecane and isomers	No	

*: The substance is only used in an industrial site (ECHA Dissemination, 2018).

A search in the database of AGÖF restricted to the group of alkylbenzenes without derived EU-LCI values (Table 3) showed that p-cymene was most often detected in these measurements (in 45.3 % of 1661 measurements). 3- and 4-ethyltoluene were also frequently detected; other C_4- and higher alkylbenzenes were rarely if ever detected. These data indicate that the higher alkylbenzenes are

probably not relevant as indoor air contaminants and that there are no relevant sources including building products.

It is concluded that among those alkylbenzenes without derived EU-LCI values 3- and 4-ethyltoluene and the isopropyltoluenes, especially the p-isomer (p-cymene) are frequently detected indoor air contaminants. The toxicological database for 3- and 4-ethyltoluene is too limited for a substance-specific evaluation, whereas sufficient data are available for p-cymene. This compound was therefore selected for a detailed evaluation and to propose a substance-specific EU-LCI value.

Table 3: Frequency of detection and concentrations in indoor air of alkylbenzenes without derived EU-LCI values*

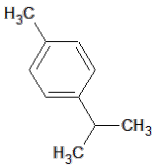
Substance (CAS No.)	No. of determinations	N > LoD (%)	Median (µg/m³)	P95 (µg/m³)	Maximum (µg/m³)
3-Ethyltoluene	114	72.2	1.4	19.5	650
3-Ethyltoluene#	489	39	< 1.0	6.0	41.2
3-/4-Ethyltoluene	546	81.3	2.0	29.0	4024
4-Ethyltoluene	1124	47.6	0.9	9.2	1049
4-Ethyltoluene#	489	15	< 1.0	4.1	19.7
Cymene (isopropyl toluene)	311 (o) 311 (m) **1661 (p)**	1.3 18.0 **45.3**	0.5 0.5 **0.5**	0.5 2.0 **5.6**	6 37 **57**
1,2,3,4-Tetramethylbenzene	No data				
1,2,3,5-Tetramethylbenzene	128	6.2	0.5	1.0	7
1,2-/1,3-Diethylbenzene	40 (1,2/1,3)	5.0	0.5	0.6	7
1,4-Diethylbenzene	784	0.1	0.5	2.5	10
1,2-Diisopropylbenzene	No data				
Hexylbenzene	31	3.2	0.5	0.5	2
Nonylbenzene	28	0	0.5	0.5	1
Phenyl decane (decylbenzene) and isomers	46	0	0.5	0.5	1
Phenyl undecane (undecylbenzene) and isomers	46	0	0.5	0.5	1

*: all values from (Hofmann and Plieninger, 2008) except those marked by #: (Schulz et al., 2010).

1.1 Substance identification

Substance identification data and physicochemical properties of p-cymene are shown in Table 4 and Table 5.

Table 4: Substance identification of p-cymene (ECHA Dissemination, 2021b)

CAS-No. EU-No. CLP-Index-No.	Systematic name, common name	Sum formula	Structural formula
99-87-6 202-796-7 601-094-00-1	1-isopropyl-4-methylbenzene, 4-isopropyl-toluene, p-cymene	$C_{10}H_{14}$	

1.2 Substance properties and uses

1-Methyl-4-isopropylbenzene (p-cymene, 4-isopropyltoluene) is a naturally occurring compound belonging to the large group of terpenes. The substance is widespread in plants and has been detected in in the essential oils of more than 100 plants and 200 foods, especially in herbs, but also in cypress, eucalyptus, or turpentine (Marchese et al., 2017). The odour of isolated p-cymene has been described as wood- and citrus-like, but also as fuel-like (Schreiner et al., 2020).

Para-cymene is also an industrial product (total tonnage band in the EU ≥ 100 to < 1000 t/a). Consumers uses of products include polishing, wax blends, washing and cleaning products, air care products, cosmetics and biocides (ECHA Dissemination, 2021b; RAC, 2019b). Para-cymene is included in emission test chamber measurements of volatile organic compounds (VOC) from building materials and products (Wilke et al., 2021).

Table 5: Substance properties of p-cymene (ECHA Dissemination, 2021b)

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 (mg/L)
134.21	-68.9	177.1	199.98	5.5	4.1	23.4 at 25 °C

1.3 Exposure

1.3.1 Indoor air

Probably because of its occurrence in essential oils, p-cymene is frequently detected in indoor air. The 1,2- and 1,3-isomer of isopropyl methylbenzene (o- and m-cymene), which have not or only very rarely been found in nature, are detected much less often and at lower concentrations in indoor air than p-cymene (Table 3).

1.3.2 Other sources

Because of the presence of p-cymene in a number of essential oils, spices and herbs, humans are exposed to p-cymene by oral exposure. However, no quantitative data on the amount of uptake from these sources are available. From the industrial production of p-cymene as flavouring compound in food, a daily intake of approximately 1100 µg/person in Europe can be roughly estimated (JECFA, 2006).

1.4 Toxicokinetics

The toxicokinetics of p-cymene was studied in rats and guinea pigs. Both species were treated orally with 100 mg/kg bw dissolved in propylene glycol by gavage or to the same total dose by "whole body" inhalation over 24 h in a static inhalation chamber which allowed for gradual evaporation of the test substance. Urine was collected over 48 hours and analysed for metabolites by gas-liquid chromatography (Walde and Scheline, 1983; Walde et al., 1983). Altogether, 18 metabolites were identified in urine which accounted for 60 to 80 % of the total applied dose. Recovery was slightly higher after oral than after inhalation exposure in both species (rats: 80 vs. 70 %, guinea pigs: 71 vs. 60 %).

Oxidation of both the methyl and the isopropyl group of p-cymene occurred intensively in both species, but only guinea pigs produced but in traces also phenolic metabolites. In rats, the main metabolites were p-isopropylbenzoic acid (cuminic acid), 2-(p-carboxyphenyl)propionic acid, 2-p-tolylpropan-2-ol, 2-p-carboxyphenylpropan-2-ol, and 2-p-carboxyphenylpropan-1-ol (accounting for 9 – 19 % of the applied dose). In guinea pigs, the main metabolite (31 %) was identified as p-isopropyl-hippuric acid, i. e. the glycine conjugate of p-isopropylbenzoic acid, 2-p-tolylpropan-2-ol, and 2-p-tolylpropionic acid. Species differences were apparent as p-isopropylbenzoic acid and 2-(p-carboxy-phenyl)propionic acid were the main metabolites in rats but were excreted only in traces by guinea pigs, while the glycine conjugate was excreted only in small amounts (2 – 3 %) in rats (Walde et al., 1983). In a similar study with oral and intraperitoneal exposure of rabbits, cumene was metabolised largely to 2-phenyl-2-propanol (40%), 2-phenyl-1-propanol (25%), and 2-phenylpropionic acid (25%). Oxidation at the methyl group was not detected in this study (Ishida et al., 1981).

A further study with rats found that the major metabolites in 0-48 hours urine after oral administration of 50 mg p-cymene/kg bw were 2-p-tolypropan-2-ol (39 % of dose recovered) and 2-p-carboxphenylpropan-2-ol (19 %). 2-p-carboxyphenylpropan-1-ol (10 %), 2- p-carboxyphenyl-propionic acid (14 %), and p-isopropylbenzoic acid (17 %) were further metabolites. About two thirds of the urinary metabolites were conjugated (66 %, 34 % free) to glucuronic acid or glycine. Conjugation was considerably lower (18 %) at the higher dose (Boyle et al., 1999; EFSA CEF, 2015).

1.5 Health effects

1.5.1 Acute toxicity, sensory irritation and local effects

Human data

Short-term inhalation exposure of humans to p-cymene in a concentration of 1100 - 2700 mg/m³ was reported to have caused dizziness, headache and nausea (no further information). Oral daily intake of bolus doses of about 3000 – 4000 mg/person led to nausea, vomiting and headaches after two or three exposures (Ziegler, 1873).

In dermal irritation tests with volunteers, ointments containing 30 % p-cymene were reported to have caused no irritation but local anaesthesia. No indications of skin sensitising were found in a maximization test on volunteers (n = 25) using 4 % p-cymene for both, induction and challenge (DGUV (Gestis), 2014).

A "sniff-test" with brief (few seconds) controlled exposure of humans to the test substance in mineral oil indicated an odour threshold of about 5 mg/m³ (as read from graphical presentation of the data) (this value should be regarded as probably too high, see chapter 1.5.5). Importantly, the threshold for eye and nasal irritation by p-cymene obtained in the same study was reported to be about three orders of magnitude higher, and about half the number of tests failed to determine this threshold at all (Cometto-Muñiz et al., 1998).

Animal and *in vitro* data

In acute inhalation exposure studies with rats, mice and guinea pigs, exposure to an atmosphere saturated with vapor of p-cymene (about 9700 mg/m³) for 5 hours led to signs of eye and nasal irritation within the first 30 minutes. Subsequently, severe CNS effects (loss of equilibrium, fine tremors, prolonged clonic convulsions, coma). Exposure was fatal for 5 of 8 rats and all 3 mice. Surviving rats and the guinea pigs recovered completely by the following day (DGUV (Gestis), 2014).

The oral toxicity of p-cymene is low (LD50 values: 3200 - 5110 mg/kg bw for rats and 2200 mg/kg bw for mice). At high to lethal doses, CNS effects (depression, tremor, lethargy, weakness) were observed, and the autopsy revealed irritation (bleeding) of mucous membranes in the gastrointestinal tract. The liquid substance also caused moderate irritation on the skin of rabbits (DGUV (Gestis), 2014).

1.5.2 Repeated dose toxicity

Only one study with repeated inhalation of animals with p-cymene is available:

Long-lasting effects of p-cymene exposure on brain neurochemistry were studied in male Long-Evans rats (7 – 12/group) exposed to 0, 50, or 250 ppm p-cymene (approximately 250 and 1230 mg/m³) 6 h/d, 5 d/week for four weeks followed by an exposure-free period of 8 weeks (Lam et al., 1996). The study was designed to examine the neurotoxic potential of p-cymene, following neurochemical parameters (rat brain concentrations of CNS neurotransmitters) and their metabolism. No clinical signs of toxicity or effects on body weight (determined weekly) were observed. There was no substance-induced effect on the terminal weight of the brain and no treatment-induced effects on the enzyme activities in the brain when expressed per g tissue or per mg protein. The concentration of noradrenaline, dopamine, and 5-hydroxytryptamine was unaffected by treatment. Inhalation exposure to p-cymene was associated with long-lasting changes in synaptosomal neurochemistry (decreased synaptosomal protein, increased noradrenaline and dopamine). Lam et al. (1996) concluded that it was not possible to decide whether or not these changes were indicative of any neurotoxicity. The registration dossier considered the NOAEC at 1230 mg/m³ (ECHA Dissemination, 2021b; RAC, 2019a). Similarly, EPA identified a NOAEL of 245 mg/m³ (adjusted for exposure duration) from this study based on the lack of overt toxicity (U.S.EPA, 2014).

A number of short-chain alkyl- and alkenylbenzenes have shown ototoxicity in rats characterised by an irreversible hearing loss[3]. P-Cymene was not included in a study on the ototoxicity of 21 aromatic solvents following oral two-week exposure of rats; however, none of the branched-chain alkylbenzenes tested proved ototoxic in this study (Gagnaire and Langlais, 2005).

In a range finding study, Sprague-Dawley rats (3 M + 3 F/group) were treated by gavage with 0, 50, 150 or 500 mg/(kg bw x d) for 14 days. At the highest dose, one female was sacrificed moribund (emaciated, rapid breathing) which was probably substance-related. Body weight or weight gain was reduced at ≥ 150 mg/(kg bw x d). Organ weight differences (increased liver and decreased spleen weight) and macroscopic abnormalities in the testes (small size/soft texture) were also noted at ≥ 150 mg/(kg bw x d) (ECHA Dissemination, 2021b).

In the main study, a combined repeat dose and reproductive/developmental toxicity screening test (OECD TG 422), Sprague-Dawley rats (10 M + 10 F/group) were treated by gavage with 0, 50, 100, 200 mg p-cymene/(kg bw x d) for at least 35 days (M) or (F) from pre-cohabitation and cohabitation periods, during gestation and lactation through lactation Day 13. There were no substance-related

[3] Note: The EU-LCI values for n-butylbenzene and phenyl octane /n-octylbenzene are based on read-across from ethylbenzene, regarding the ototoxicity which was observed for ethylbenzene also as critical for n-butyl-benzene. However, n-butylbenzene (or any of the other butylbenzenes) were not ototoxic in the study of Gagnaire and Langlais (2005).

mortalities at ≤ 100 mg/(kg bw x d) and no adverse clinical observations in males at ≤ 200 mg/(kg bw x d) and in females at ≤ 100 mg/(kg bw x d). There were no substance-related reductions in body weights, weight or food consumption at any dose. The hindlimb grip strength was significantly reduced in males at the highest dose. Haematological and clinical-chemical parameters were not affected at any dose. Liver weight was slightly increased at 100 mg/(kg bw x d) in females and markedly (absolute: +27 %) at 200 mg/(kg bw x d) in males. In females, no organ weight changes or histopathological effects were observed in the reproductive tract. In males, however, lower organ weight, germ cell depletion/degeneration, depletion and/or sperm retention, along with correlative changes in the epididymis were observed at 200 mg/(kg bw x d). A slight degree of sperm retention was also observed at 100 mg/(kg bw x d). The NOAEL for P0 males was 50 mg/(kg bw x d), based on epididymal and testicular changes with germ cell degeneration and sperm damage.

1.5.3 Genotoxicity and carcinogenicity

Genotoxicity

Para-Cymene was not considered as genotoxic based on results of *in vitro* studies in bacteria (Ames tests and test in *E. coli*) and mammalian cells (HPRT-test in V79 cells, chromosomal aberration test I human lymphocytes), both in the presence or absence of exogenous metabolising system (S9 mix) (ECHA Dissemination, 2021b; U.S.EPA, 2011). Furthermore, there was no evidence of mutagenicity in bacteria (S. typhimurium strain TA98 and 100) of p-cymene metabolites in rat urine in a host-mediated assay (RAC, 2019a; U.S.EPA, 2011). *In vivo* data on genotoxicity are not available.

Carcinogenicity

Carcinogenicity data for p-cymene are not available. p-Cymene is a naturally occurring component of food that has been used as a food additive. The substance was granted GRAS status by the FDA, and JECFA concluded that p-cymene did not present a safety concern at the current estimated intake (approximately 1100 µg/person in Europe). In addition, p-cymene does not appear to be metabolised to any highly reactive chemical species. Thus, the EPA stated that there is some evidence that suggests that p-cymene is unlikely to be a human carcinogen (U.S.EPA, 2005).

1.5.4 Toxicity to reproduction

In the combined repeat dose and reproductive/developmental toxicity screening test (OECD TG 422) described above, treatment-related reductions in male fertility and male fertility index were observed at ≥ 100 mg/(kg bw x d). Alterations of oestrous cyclicity, including a reduction of the number of animals with all regular cycles and an increase in the number of females with at least one irregular cycle, were observed at 200 mg/(kg bw x d). Furthermore, no pregnancy among P0 females was observed at 200 mg/(kg bw x d), probably the result of the testicular changes observed at this dose in males (see above). The less severe effects in males at 100 mg/(kg bw x d) (marginal sperm retention) may also have contributed to the effect of pregnancy being absent in 60 % of the females at 100 mg/(kg bw x d). Regarding the offspring, decreases of the pup live birth index, post-implantation survival index, pup viability, pup weights and litter weights were observed at 100 mg/(kg bw x d). No litters were delivered at 200 mg/(kg bw x d). The NOAEL for the P0 males and for the F1 offspring was considered to be 50 mg/(kg bw x d) (ECHA Dissemination, 2021b).

No developmental toxicity study is available with p-cymene. A terpenoid blend mixture (QRD 460) of α-terpinene, p-cymene and d-limonene (overall minimum purity 890 g/kg active components, thereof 22 % p-cymene) showed negative results in a teratogenicity study with rats ($NOAEL_{maternal}$ 60 mg/(kg bw x d), $NOAEL_{development}$ 120 mg/(kg bw x d)) (EFSA, 2014; EFSA, 2017).

Structure-activity relationships

Studies with substances structurally related to p-cymene indicate that the metabolism of p-cymene and other para-substituted isopropyl- (and t-butyl)benzenes which are metabolised to p-substituted branched-chain benzoic acids seems to play a critical role in the toxicity of p-cymene observed in male rats, especially the testicular and sperm toxicity (ECHA Dissemination, 2021a; Laue et al., 2020; Laue et al., 2017; Natsch et al., 2021).

Structure-activity relationship studies with 19 chemicals (9 reprotoxic, 10 non-reprotoxic) indicate that the formation and accumulation of p-alkyl-benzoyl-CoA in rat hepatocytes is strongly correlated with adverse effects on sperm parameters in male rats (Laue et al., 2020).

Especially, the metabolism and the toxicity of 3-(4-isopropylphenyl)-2-methylpropanal) (PMHCA, cyclamen aldehyde, a widely used fragrance material) has been studied in more detail.

A summary of these studies and their relevant findings has been recently presented (Natsch et al., 2021): Studies in rats revealed adverse effects on sperm maturation after repeated oral administration of this compound, and the effect on spermatogenesis appears to be linked to the formation of the metabolite *p*-isopropyl-benzoic acid (*p*-iPBA). Other studies with suspensions of rat, rabbit and human hepatocytes revealed that *p*-iPBA could only be detected in rat hepatocytes, indicating species differences. Furthermore, *p*-iPBA is conjugated to Coenzyme A (CoA) in rat hepatocyte cultures, and this CoA-conjugate accumulates to stable levels over 22 h. *In vitro* accumulation of CoA conjugates was shown to be correlated to male rat reproductive toxicity *in vivo* for related compounds. p-iPBA is also formed *in vivo* in rat liver and, in lower concentrations, in rat testes. Species differences become obvious when similar studies are conducted with rabbit and human hepatocytes. *p*-iPBA-CoA does not accumulate over time in rabbit and human hepatocytes, and, correlated with this observation, PMHCA had no effects on spermatogenesis in an *in vivo* study with rabbits. Natsch et al. (2021) concluded that lack of accumulation of *p*-iPBA-CoA in human hepatocytes indicates that humans, like rabbits, are unlikely to be vulnerable to *p*-iPBA hepatic and testicular toxicity.

1.5.5 Odour perception

The odour of isolated p-cymene can be detected at very low concentrations in air, an odour threshold of 43.2 µg/m³ (median, geometric mean 74.1 µg/m³, range 21.6–345.6 µg/m³, n = 10 panelists) was recently determined (Schreiner et al., 2020).

1.6 Evaluation

1.6.1 Existing regulations and classifications

There is no harmonised classification for p-cymene (ECHA C&L Inventory, 2021). Proposed harmonised classifications by the dossier submitter include Acute Tox. 3, H331, Asp. Tox. 1, H304, and Repr. 1B, H360F (ECHA Dissemination, 2021b). RAC has adopted an opinion for classification and labelling of p-cymene as (regarding toxicity) Acute Tox. 3, H331, and Asp. Tox. 1, H304 (RAC, 2019b), the regulation coming into force in December 2022 (EC, 2021).

Existing guide values for p-cymene are summarised in Table 6.

In the registration dossier, a DNEL of 0.22 mg/m³ is derived for the protection of the general population via inhalation. This DNEL is based on the NOAEL of 50 mg/(kg bw x d) for toxicity (testicular toxicity in males) obtained in the combined repeat dose and reproductive/developmental toxicity screening test (OECD TG 422) described above. Standard factors were used for route-to-route extrapolation, including a standard factor of two to account for differences between inhalation and oral absorption, for toxicodynamic interspecies and for intraspecies extrapolation. The time

extrapolation factor was set to four, since the duration of the exposure fell into an interval in between subacute (up to 28 days) and "standard" (90 d). A DNEL of 0.88 mg/m³ for workers was also derived, based on the same NOAEL, corresponding standard factors for workers and the factor of four for differences in duration of exposure as described.

Table 6: Guide values for p-cymene (1-isopropyl-4-methylbenzene) (for explanation, see text)

Guide value Parameter/ Organisation	**(ECHA Dissemination, 2021b)**
Substance	p-cymene (1-methyl-4-isopropylbenzene, 4-isopropyltoluene)
Name (reference period)	DNEL (general population, chronic, systemic)
Value (mg/m³)	0.22 mg/m³
Organ/critical effect	Testicular toxicity
Species	Rat
Basis	NOAEL: 50 mg/(kg bw x d)
Adjusted critical exposure	50 : 1.15 = 43.48 mg/m³
Extrapolation factors Route-to-route Time LOAEC to NOAEC Interspecies Intraspecies Other Total	 2 (differences in absorption) 4 2.5 10 100
Remark	*"The exposure duration of the OECD TG 422 study performed with the test item was up to 63 days for females and 29 days for males. In comparison to a subacute 28-day study the OECD TG 422 study provides additional information on fertility and developmental toxicity, which justifies the assessment factor of 4."*

1.6.2 Derivation of an EU-LCI value

Data from animal studies show that p-cymene is well absorbed after oral or inhalation exposure. A number of oxidised metabolites were identified in urine of rats and guinea pigs, mainly p-isopropyl-benzoic acid (in rats) and its glycine conjugate p-isopropylhippuric acid (in guinea pigs). Metabolism studies indicate that 60 – 80 % of an applied dose of p-cymene is excreted as metabolites in urine with slightly (about 10 %) higher percentages after oral administration (Boyle et al., 1999; EFSA CEF, 2015; Ishida et al., 1981).

The acute toxicity of p-cymene is low. Central nervous system effects (depression, dizziness, weakness) were described after inhalation of high concentrations (≥ 1100 mg/m³) in humans (Ziegler, 1873). Short-term (few seconds) exposure of humans to high concentrations (probably in the order of about 5000 mg/m³) may cause sensory irritation of eyes and nose (Cometto-Muñiz et al., 1998). Sensory irritation was also reported in animals at about 9700 mg/m³ in acute toxicity studies with five hours of exposure (DGUV (Gestis), 2014).

Neurotoxicity could not be demonstrated after repeated inhalation exposure of rats with up to 250 ppm (about 1230 mg/m³) for four weeks, followed by an exposure free interval of eight weeks (Lam

et al., 1996). The registration dossier and RAC considered the NOAEC at 1230 mg/m³, the highest concentration tested (ECHA Dissemination, 2021b; RAC, 2019a).

In a combined repeat dose and reproductive/developmental toxicity screening test (OECD TG 422) with oral exposure of rats for at least 35 days, no substance-related reductions in body weights, weight or food consumption were observed at any dose. The hindlimb grip strength was significantly reduced in males at the highest dose. The liver weight was slightly increased at 100 mg/(kg bw x d) in females and markedly (absolute: +27 %) at 200 mg/(kg bw x d) in males. In females, no changes were observed in the reproductive tract. In males, however, lower organ weight, germ cell depletion/degeneration, depletion and/or sperm retention, along with correlative changes in the epididymis were observed at 200 mg/(kg bw x d). A slight degree of sperm retention was also observed at 100 mg/(kg bw x d). The NOAEL for P0 males was 50 mg/(kg bw x d) (ECHA Dissemination, 2021b).

Studies with substances structurally related to p-cymene indicate that the metabolism of p-cymene seems to play a critical role in the observed toxicity of p-cymene in male rats, especially the testicular and sperm toxicity (ECHA Dissemination, 2021a; Laue et al., 2020; Laue et al., 2017; Natsch et al., 2021). The effect on spermatogenesis appears to be linked to the formation of the metabolite p-isopropylbenzoic acid (*p*-iPBA). This metabolite could only be detected *in vitro* in suspensions of rat hepatocytes, but not of rabbit and human hepatocytes. Additional studies indicate that the formation of this metabolite is related to the toxic effects on rat testes and sperm development and that humans, like rabbits, are unlikely to be vulnerable to *p*-iPBA hepatic and testicular toxicity (Natsch et al., 2021).

Para-cymene was not genotoxic in *in vitro* in assays (following OECD guidelines) with bacteria and mammalian cells and in a host-mediated assay. *In vivo* data are not available.

Carcinogenicity studies with p-cymene are not available. The available data on genotoxicity and the metabolism of p-cymene do not provide evidence for concern regarding carcinogenic effects.

Effects on male fertility were observed in rats at ≥ 100 mg/(kg bw x d) in the combined repeat dose and reproductive/developmental toxicity screening test. No pregnancy among P0 females was observed at 200 mg/(kg bw x d), and pregnancy was absent in 60 % of females at 100 mg/(kg bw x d). Effects on pups were also observed at 100 mg/(kg bw x d), and no litters were delivered at 200 mg/(kg bw x d). The NOAEL for fertility was 50 mg/(kg bw x d) (ECHA Dissemination, 2021b).

A terpenoid blend mixture of α-terpinene, p-cymene and d-limonene (overall minimum purity 890 g/kg active components, thereof 22 % p-cymene) showed negative results in a teratogenicity study with rats ($NOAEL_{maternal}$ 60 mg/(kg bw x d), $NOAEL_{development}$ 120 mg/(kg bw x d)) (EFSA, 2014; EFSA, 2017).

The NOAEL of 50 mg/(kg bw x d) for testes and sperm cell toxicity obtained in an oral Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test (OECD TG 422) with rats is used as the POD for the derivation of the EU-LCI.

- Route-to-route extrapolation: 1.15 m³/(kg bw x d)
- Differences in absorption: 1 (toxicokinetic data indicate similar absorption after oral and inhalation uptake)
- Adjusted study length factor: 2
- Interspecies differences: 1.0 (metabolism studies indicate that rats are the most sensitive species and humans are less sensitive)

- Intraspecies differences: 10,

leading to a value of 50 mg/(kg bw x d) : (1.15 x 20) = 2174 µg/m³ (rounded value: 2200 µg/m³).

An EU-LCI value of 2200 µg/m³ is proposed for p-cymene.

A median odour threshold of 43.2 µg/m³ air has been reported for p-cymene (Schreiner et al. 2020). Consequently, olfactory perception must be expected at the proposed EU-LCI value.

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A Appendix

A.1 Data collection and fact sheet for p-cymene

Table 7: Data collection sheet for p-cymene

Compound	**p-Cymene (1-methyl4-isopropylbenzene, 4-isopropyltoluene)**
Nº CAS 1 ppm = x mg/m³ (23 °C)	99-87-6 5.5
EU-Classification CLP, harmonised classification	202-796-7 601-094-00-1
Organisation name	**REACH Registrants**
Risk value name	DNEL (general population)
Risk value (mg/m³)	0.22 (systemic, local: no hazard identified)
Reference period	Chronic
Risk value (mg/m³) Short term (15 min)	-
Year	2021
Key study	ECHA (2021)
Study type	Combined Repeated Dose Toxicity Study with Reproduction/ Developmental Toxicity Screening Test (OECD TG 422) (2019)
Species	Rat, Sprague-Dawley (10 M, 10 F/dose)
Duration of exposure in key study	≥ 35 d (males), 63 d (females)
Critical effect	Testicular toxicity
Critical dose value	NOAEL: 50 mg/(kg bw x d)
Adjusted critical dose	50 : 1.15 mg/m³ = 43.48 mg/m³ : 2 = 21.74 mg/m³
Single assessment factors	UF_S: 4, UF_A: 2.5, UF_H: 10
Other effects	
Remarks	*"The exposure duration of the OECD TG 422 study performed with the test item was up to 63 days for females and 29 days for males. In comparison to a sub-acute 28-day study the OECD TG 422 study provides additional information on fertility and developmental toxicity, which justifies the assessment factor of 4."* Notified classification and labelling: Repr. 2 (H361)

Table 8: Fact sheet for p-cymene (1-isopropyl-4-methylbenzene)

Compound	**p-Cymene (1-isopropyl-4-methylbenzene) C10H14**		**Fact sheet**
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	2200
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2022
General information			
CLP-Index No.	4	INDEX	601-094-00-1
EC-No.	5	EINECS	202-796-7
CAS-No.	6	Chemical Abstract Service number	99-87-6
Harmonised CLP classification	7	Human health risk related classification	-
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	134.21 1 ppm = 5.5 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	ECHA (2021) Combined Repeated Dose Toxicity Study with Reproduction/ Developmental Toxicity Screening Test (OECD TG 422) (2019)
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	Rat, Sprague-Dawley (10 M, 10 F/dose)
Route / type of study	12	Inhalation, oral feed, etc.	Oral (gavage)
Study length	13	Days, subchronic, chronic, etc.	≥ 35 d (males), 63 d (females)
Exposure duration	14	h/d, d/w	Daily
Critical endpoint	15	Effect (s), site of	Testicular toxicity
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEL
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	50 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)

Compound	p-Cymene (1-isopropyl-4-methylbenzene) C10H14		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	1
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		1
Other adjustment factors Quality of database	26	Route-to-route absorption	1
Results			
Summary of assessment factors	27	Total Assessment Factor	20 x 1.15
POD/TAF	28	Calculated value [µg/m³ and ppb]	50 mg/(kg bw x d) : (1.15 m³/kg x 20) = 2174 µg/m³
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	2200
Additional comments	31	Cited in EC (2013)	*Subchronic: Repeated exposure by the oral, dermal, or inhalation route for more than 30 days… more than 30 days and up to 90 days in typically used laboratory animal species*
Rationale selection	32		

Data compilation and evaluation for p-cymene is based on a project funded by the German Environment Agency (Voss et al., 2022).

Rationale for critical effects

Data from animal studies show that p-cymene is well absorbed after oral or inhalation exposure. Once absorbed and distributed, p-cymene is oxidised to a number of metabolites which are excreted in urine, mainly p-isopropylbenzoic acid (in rats) and its glycine conjugate p-isopropylhippuric acid (in guinea pigs). Metabolism studies indicate that 60 – 80 % of an applied dose of p-cymene is excreted as metabolites in urine with slightly (about 10 %) higher percentages after oral administration (Boyle et al., 1999; EFSA CEF, 2015; Ishida et al., 1981).

The acute toxicity of p-cymene is low. Central nervous system effects were described after inhalation of high concentrations (≥ 1100 mg/m³) in humans (Ziegler, 1873). Short-term (few seconds) exposure of humans to high concentrations (probably in the order of about 5000 mg/m³) may cause sensory irritation of eyes and nose (Cometto-Muñiz et al., 1998). Sensory irritation was also reported in animals at about 9700 mg/m³ in acute toxicity studies with five hours of exposure (DGUV (Gestis), 2014).

Neurotoxicity could not be demonstrated after repeated inhalation exposure of rats with up to 250 ppm (about 1230 mg/m³) for four weeks, followed by an exposure free interval of eight weeks (ECHA Dissemination, 2021b; Lam et al., 1996; RAC, 2019).

In a combined repeat dose and reproductive/developmental toxicity screening test (OECD TG 422), Sprague-Dawley rats (10 M + 10 F/group) were treated by gavage with 0, 50, 100, 200 mg p-cymene/(kg bw x d) for at least 35 days (M) or (F) from pre-cohabitation and cohabitation periods, during gestation and lactation through lactation Day 13. There were no substance-related mortalities at ≤ 100 mg/(kg bw x d) and no adverse clinical observations in males at ≤ 200 mg/(kg bw x d) and in females at ≤ 100 mg/(kg bw x d). There were no substance-related reductions in body weights, weight or food consumption at any dose. The hindlimb grip strength was significantly reduced in males at the highest dose. Haematological and clinical-chemical parameters were not affected at any dose. Liver weight was slightly increased at 100 mg/(kg bw x d) in females and markedly (absolute: +27 %) at 200 mg/(kg bw x d) in males. In females, no organ weight changes or histopathological effects were observed in the reproductive tract. In males, however, lower organ weight, germ cell depletion/degeneration, depletion and/or sperm retention, along with correlative changes in the epididymis were observed at 200 mg/(kg bw x d). A slight degree of sperm retention was also observed at 100 mg/(kg bw x d). The NOAEL for P0 males was 50 mg/(kg bw x d), based on epididymal and testicular changes with germ cell degeneration and sperm damage.

Studies with substances structurally related to p-cymene indicate that the metabolism of p-cymene seems to play a critical role in the observed toxicity of p-cymene in male rats, especially the testicular and sperm toxicity (ECHA Dissemination, 2021a; Laue et al., 2020; Laue et al., 2017; Natsch et al., 2021). The effect on spermatogenesis appears to be linked to the formation of the metabolite p-isopropylbenzoic acid (p-iPBA). This metabolite could only be detected *in vitro* in suspensions of rat hepatocytes, but not of rabbit and human hepatocytes. Additional studies indicate that the formation of this metabolite is related to the toxic effects on rat testes and sperm development and that humans, like rabbits, are unlikely to be vulnerable to p-iPBA hepatic and testicular toxicity (Natsch et al., 2021).

Para-cymene was not genotoxic in *in vitro* in assays (following OECD guidelines) with bacteria and mammalian cells and in a host-mediated assay. *In vivo* data are not available.

Carcinogenicity studies with p-cymene are not available. The available data on genotoxicity and the metabolism do not provide evidence for concern regarding carcinogenic effects of p-cymene.

In the combined repeat dose and reproductive/developmental toxicity screening test (OECD TG 422) described above, treatment-related reductions in male fertility and male fertility index were observed at ≥ 100 mg/(kg bw x d). Regarding the offspring, decreases of the pup live birth index, post-implantation survival index, pup viability, pup weights and litter weights were observed at 100 mg/(kg bw x d). No litters were delivered at 200 mg/(kg bw x d). The NOAEL for the P0 males and for the F1 offspring was considered to be 50 mg/(kg bw x d) (ECHA Dissemination, 2021b).

A terpenoid blend mixture of α-terpinene, p-cymene and d-limonene (22 % p-cymene) showed negative results in a teratogenicity study with rats ($NOAEL_{maternal}$ 60 mg/(kg bw x d), $NOAEL_{development}$ 120 mg/(kg bw x d)) (EFSA, 2014; EFSA, 2017).

Rationale for starting point

The NOAEL of 50 mg/(kg bw x d) for testes and sperm cell toxicity obtained in the oral Combined Repeated Dose Toxicity Study with Reproduction/Developmental Toxicity Screening Test with rats is used as the POD for the derivation of an EU-LCI.

Rationale for assessment factors

The results of the metabolism studies with p-cymene in animals indicate that oral absorption of p-cymene is as high or slightly higher than absorption by inhalation. 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 derivation:

- Route-to-route extrapolation: 1.15 m³/(kg bw x d)
- Differences in absorption: 1
- Adjusted study length factor: 2
- Interspecies differences: 1.0 (metabolism studies indicate that rats are the most sensitive species and humans are less sensitive)
- Intraspecies differences: 10,

leading to a value of 50 mg/(kg bw x d) : (1.15 x 20) = 2174 µg/m³ (rounded value: 2200 µg/m³).

The proposed value is based on a NOAEL for systemic effects observed in a study with oral exposure of rats. The data base regarding local effects of p-cymene in the respiratory tract is very limited. No local irritation effects were mentioned in a neurotoxicity study with repeated inhalation (four weeks) exposure of rats at concentrations up to 250 ppm (about 1230 mg/m³). Sensory irritation of eyes and nose was described during acute short-term inhalation exposure of humans at concentrations in the order of 5000 mg/m³ (Cometto-Muñiz et al., 1998) and in animals at about 9700 mg/m³ during five hours of exposure (DGUV (Gestis), 2014). These concentrations are more than three orders of magnitude higher than the proposed EU-LCI value. It is concluded that sensory irritation is not to be expected at the EU-LCI value.

An EU-LCI value of 2200 µg/m³ is proposed for p-cymene (1-isoporopyl-4-methylbenzene).

A median odour threshold of 43.2 µg/m³ air has been reported for p-cymene (Schreiner et al. 2020). Consequently, olfactory perception must be expected at the proposed EU-LCI value.

A.2 Further alkyl benzenes

Ortho- and meta-cymene

The available substance-specific data are not sufficient for the derivation of EU-LCI values. Read-across could be performed based on the data for p-cymene. However, it is likely that, compared to p-cymene, the potency of the oxidation products of o- and m-cymene to induce testicular/sperm toxicity will be much lower (or absent) so simple transfer or read-across to o- and p-cymene seems to be inadequate and is therefore not recommended.

Ethyltoluenes

Ethyltoluene (all isomers) lack the specific structural characteristic of an isopropyl side chain which seems to be a prerequisite for the specific toxicity of p-cymene (1-isopropyl-toluene). Therefore, read-across to 3- and 4-ethyltoluene (which so far lack derived EU-LCI values) is not recommended.

In case emission of o-, m-cymene, 3- or 4-ethyltoluene or other alkylbenzenes without derived EU-LCI values and insufficient data have to be assessed within the framework for health based evaluation of indoor emissions from construction products it is recommended to apply read-across using the lowest available derived EU-LCI value within the group of alkyl benzenes. Currently, the lowest derived EU-LCI value is 450 µg/m³ for trimethylbenzenes (all isomers) (EU-LCI Working Group, 2021).

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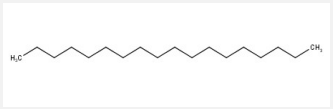
2 Toxicological evaluation of "other saturated aliphatic hydrocarbons C_{17}-C_{22}" as basis for the derivation of an EU-LCI value

2.1 Substance identification

Substance identification data and physicochemical properties of "other saturated aliphatic hydrocarbons C17-C22" are shown in Table 9 and Table 10.

Substances listed in Table 9 were named relevant for the assessment.

Table 9: Substance identification of "other saturated aliphatic hydrocarbons C17-C22" (ECHA Dissemination, 2022)

CAS-No. EU-No. CLP-Index-No.	Systematic name, common name	Sum formula	Structural formula
C17 n-alkane: 629-78-7 211-108-4 -	N-heptadecane, heptadecane	$C_{17}H_{36}$	
C18 n-alkane: 593-45-3 209-790-3 -	N-octadecane, octadecane	$C_{18}H_{38}$	
C19 n-alkane: 629-92-5 211-116-8 -	nonadecane	$C_{19}H_{40}$	
C20 n-alkane: 112-95-8 204-018-1 -	eicosane, icosane	$C_{20}H_{42}$	
C21 n-alkane: 629-94-7 211-118-9 -	henicosane, heneicosane	$C_{21}H_{44}$	
C22 n-alkane: 629-97-0 211-121-5 -	docosane	$C_{22}H_{46}$	

2.2 Substance properties and uses

C17-C22 saturated aliphatic hydrocarbons are waxy solids with melting points between 22 and 44 °C. They are either odourless (C20-C22) or have a fuel like odour (C17-C19)(NLM, 2022). No odour thresholds were identified.

Via several processing steps (e.g., distillation, purification) the substances are derived from crude petroleum oil (NLM, 2022; Pirow et al., 2020) and used in cosmetics, lubricants, and plasticisers.

Table 10: Physicochemical properties of "other saturated aliphatic hydrocarbons C17–C22" (NLM, 2022)

Molar mass (g/mol)	Mp. (° C)	Boiling point (° C)	Vapour pressure (Pa) (at 25 °C)	Conversion 1 ppm = x mg/m³ (23 °C)	log kow	Solubility in water (mg/L) at 25 °C
C17 n-alkane: 240.5	22.0	302.0	0.030	9.9	9.69	$2.3 * 10^{-3}$
C18 n-alkane: 254.5	28.2	316.3	0.045	10.48	8.36	$6.0 * 10^{-3}$
C19 n-alkane: 268.5	32.1	329.9	0.0065	11.05	9.67	$3.7 * 10^{-5}$
C20 n-alkane: 282.5	36.8	343.0	0.00062	11.63	10.16	$1.9 * 10^{-3}$
C21 n-alkane: 296.6	40.5	356.5	0.0116	12.21	10.65	$2.9 * 10^{-8}$
C22 n-alkane: 310.6	44.4	368.6	0.00017	12.78	11.15	$7.77* 10^{-7}$

2.3 Exposure

2.3.1 Indoor air

Values of C17-C22 saturated hydrocarbons in indoor air were only identified as reported by AGÖF (2013). P50 Values for all substances were below the level of quantification (see the following table).

Table 11: Concentrations (µg/m³) of saturated aliphatic hydrocarbons C17-C22 in indoor air (AGÖF, 2013)

Substance (CAS No.)	n	Normal value P50	Attention value P90	Guidance value
n-heptadecane (629-78-7)	2291	<1	2.0	2.0
n-octadecane (593-45-3)	2276	<1	1.0	1.0
n-nonadecane (629-92-5)	2279	<1	<1	
n-eicosane (112-95-8)	2233	<1	<1	
n-heneicosane (629-94-7)	1186	<1	<1	
n-docosane (629-97-0)	1185	<1	<1	

All values given with "<" are below the level of quantification.

2.3.2 Other sources

There are no data available.

2.4 Toxicokinetics

According to McKee et al. (2015) a higher carbon number (> C12) leads to a decreased systemic availability of inhaled hydrocarbons. This effect can be explained by a decreased vapour pressure. For

C17–C22 aliphatic hydrocarbons the amount of substance available as vapour is very limited due to the physical states (solid) and the low vapour pressures of the substances.

Generally, absorption after inhalation exposure is slow and limited (SCOEL, 2011). As stated by SCOEL, inhaled white mineral oils accumulate in the lung and are slowly eliminated. Via macrophages small amounts of white mineral oil hydrocarbons can be transported in the blood to the lymphatic system, the liver, and fatty tissue (SCOEL, 2011). Linear alkanes can be transformed via ω- and β-oxidation to form metabolites that may be used in biosynthesis reactions or excreted as CO_2 via exhaled air and hydroxylated fatty acids in the urine (McKee et al., 2015).

2.5 Health effects

The data base for the substances is very limited. For most toxicological endpoints read-across to other saturated hydrocarbons with different chain length is performed.

2.5.1 Acute toxicity, sensory irritation and local effects

The acute toxicity of saturated aliphatic hydrocarbons used in the read-across approach in the disseminated REACH registration file is low, in fact, LD50 and LC50 values are in most cases above the highest dose or concentration tested (ECHA Dissemination, 2021). Saturated aliphatic hydrocarbons do not show skin or eye irritation effects and are not sensitising.

Bhutia et al. (2010) studied acute oral and dermal toxicity of n-henicosane (C21) in Swiss Albino and Wistar rats. No mortalities were observed and the oral LD50 was established to be >5000 mg/kg bw in both species and sexes and >3200 mg/kg bw for dermal exposure. The same research group also performed a skin irritation study according to Draize with n-henicosane (Bhutia et al., 2010). New Zealand rabbits were exposed to 500 mg/kg bw under occlusive conditions. No signs of skin irritation were noted during the observation period of 14 days.

2.5.2 Repeated dose toxicity

Studies on repeated inhalation exposure in the registration dossiers of C17-, C18-, C20-, and C22- n-alkanes are reported for hydrocarbons C11-14 NIC, (Normal, Iso- and Cyclic alkanes) <2% aromatics (List no: 917-725-1 or 926-141-6) and C10-12 I (Iso alkanes), <2% aromatics (List no: 923-037-2). In both 90-day studies with rats the respective NOAEC reported in the disseminated REACH registration dossier is the highest concentration tested (6000 mg/m³ and 10400 mg/m³).

In the 90-day study with C11-14 NIC eighteen Albino rats per sex and concentration group were exposed to 0, 1500, 3000 and 6000 mg/m³ vapour for 6 h/d on 5 days per week. Kidney weight in male animals was increased in all groups. The histopathological examination identified the multiple hyaline, intracytoplasmic, inclusion-droplets in the epithelium of the proximal convoluted tubules of the kidneys and an increased incidence of focal cortical tubular basophilia. The kidney effects in males at all dose groups are consistent with the picture of alpha2u-globulin nephropathy which is a species-specific effect in male rats and of no relevance to humans. Liver weight was increased in the mid and high exposure group in males and in the high concentration group in females. The changes in liver weight were not accompanied by histological changes and are considered as an adaptive response. In the mid exposure group a low grade catarrhal inflammatory reaction was observed in the nasal cavities, no information is available for the high and low exposure group.

In the study with C10-12 I, inhalation concentrations in rats were 0, 2600, 5200 and 10400 mg/m³ and exposure lasted for 90 days (6 h/d, 5 days per week). Liver weight changes were observed in the mid and high exposure group in both sexes and in the low exposure group in males too. As reported in the study with C11-14 NIC, kidney weight changes and alpha2u-globulin nephropathy were observed in male animals of all groups.

OECD (2011) also cites an inhalation study with C20-50 hydrotreated oil (CAS no: 64742-54-7, average carbon number C35). The substance contains 2.4 % aromatics. According to the disseminated REACH registration dossier 10 Sprague Dawley rats per sex and concentration group were exposed to 0, 50, 210 or 1000 mg/m³ aerosol (0, 47, 220, 980 mg/m³ analytical concentration) for 28 days (6 h/d, 5 days per week) (ECHA Dissemination, 2021). The only findings in this study were a concentration-dependent increase in lung weight and associated lymph node weight. These effects were attributed to the increased number of alveolar macrophages and the presence of residual oil in the lung. The authors of the publication concluded on a NOEC of 220 mg/m³ (analytical concentration) based on these effects. The systemic NOAEC is given with 980 mg/m³ (analytical concentration) based on the absence of any systemic effects (OECD, 2011). In the OECD SIDS document, which covers C14-20 aliphatic hydrocarbons (< 2 % aromatics) it is outlined that the accumulation of macrophages in the lung is not expected for C14-20 hydrocarbons due to increased clearance from the lungs based on different physico-chemical properties of the shorter chain hydrocarbons. The study was not considered relevant for the derivation of an EU-LCI value since the observed effects are associated with the exposure to aerosol and not vapour.

Results from oral and dermal studies reported in the REACH registration dossiers of the relevant substances support the findings from the repeated inhalation studies. Read-across to several shorter chain hydrocarbon mixtures (C10-13 NIC, < 2 % aromatics (List no: 918-481-9), C11-14 NIC, < 2 % aromatics (List no: 917-725-1), C10-12 I, < 2 % aromatics (List no: 923-037-2) reported no adverse effects except for increased organ weights and alpha2u-globulin nephropathy. For C10-13 NIC for example a 90-day oral gavage study with Sprague-Dawley rats is reported. The animals were exposed to 0, 500, 2500 or 5000 mg/(kg bw x d). Liver weights were elevated in both sexes in the mid and high dose group which is considered to be an adaptive response. In addition, testes weights were elevated in the highest dose group. Relative kidney weight for male and female animals was significantly different in all dose groups.

In a repeated oral study a white mineral oil with an average carbon number of C20 (C14 - C32, EC no. 265-156-6) was administered to Fischer F344 rats for 90 days (McKee et al., 2012). Liver and kidney weights were increased in the two highest dose groups (120 and 1200 mg/(kg bw x d)) but there were no histological changes other than the appearance of microgranulomas in liver and mesenteric lymph nodes. Since the effects were only minimal and were not observed in rats of other strains or dogs, the authors concluded on a NOAEL of >1200 mg/(kg bw x d). Pirow et al. (2020) and the CONTAM Panel of EFSA (EFSA, 2020) noted that findings in Fischer F344 rats after exposure to MOSH (mineral oil saturated hydrocarbons) “may not be relevant for humans” (see also Adenuga et al. (2017)). Therefore, this study was not considered for the derivation of an EU-LCI value.

For n-henicosane (C21) an oral and a dermal repeated dose study are available (Bhutia et al., 2010). In the oral study male and female Wistar rats were exposed via gavage to 0, 125, 250 and 500 mg/(kg bw x d) for 90 days. Body and organ weights were measured at the end of exposure as well as haematological and biochemical parameters in blood samples. No histopathological evaluation was performed. According to the authors, the only relevant effect was an increase in AST (aspartat-aminotransferase). However, the effect was not dose-dependent. In addition, liver, kidney, and spleen weight showed non-dose-dependent changes with indications of an increase at higher doses. The inconsistency may be associated with the fact that only six animals were studied per dose group. The authors concluded on a NOAEL of 500 mg/(kg bw x d); the highest dose tested.

No effects were observed in the 90-day dermal toxicity study with 1000 and 2000 mg/(kg bw x d).

2.5.3 Genotoxicity and carcinogenicity

Genotoxicity

Genotoxicity tests reported in the REACH registration dossiers for C17, C18, C20, and C22 n-alkane were all performed with read-across substances (e.g., C18-50 distillates branched cyclic and linear (CAS no: 848301-69-9) and C14-18 NIC, < 2 % aromatics (List no: 927-632-8)). All of these studies reported negative results.

Carcinogenicity

Carcinogenicity studies or chronic studies with saturated aliphatic hydrocarbons C17-C22 are not available. The available data on genotoxicity and from repeated dose toxicity studies do not provide evidence for concern regarding carcinogenic effects of the substances.

2.5.4 Toxicity to reproduction

For the endpoint reproductive toxicity, the REACH registration dossiers for C17, C18, C20, and C22 n-alkanes report studies with read-across substances. Read-across is performed to hydrocarbons C16-20 NIC (< 2 % aromatics, List no: 917-725-1), GTL diesel (Distillates (Fischer-Tropsch), C8-26 branched and linear, CAS no: 848301-67-7), white mineral oil C16-30 (CAS no: 8042-47-5), JP8 (Jet Propellant, EC no. 232-366-4), and C18-50 distillates branched, cyclic and linear (CAS no: 848301-69-9). Only one study is reported with inhalation exposure. In this developmental toxicity study similar to OECD test guideline 414, 20 pregnant Sprague Dawley rats were exposed to 1000 mg/m³ white mineral oil C16-30 (aerosol) for 6 h/d from gestation days 6 – 19. No maternal toxicity (food consumption, body weight gain) or adverse effects on reproductive or foetal parameters (number of implantation sites, resorptions, foetal viability, foetal body weight or crown-rump length) were observed. In addition, no teratogenicity was observed. Therefore, the NOAEC for all reproductive endpoints is > 1000 mg/m³. Other reproductive studies with dermal or oral exposure with the substances listed above, also showed no effects on the relevant parameters in dams or foetuses. The NOAELs in all studies are the highest tested dose.

For one substance, n-henicosane (C21), a prenatal developmental toxicity study is available (Kumar et al., 2013). The study was performed following the OECD test guideline 414. C21 was administered via the diet at a dose of 0 or 1000 mg/(kg bw x d) to 20 male and 20 female Wistar rats per dose group. No mortalities and maternal toxicity were observed at any point of the study. Reproductive endpoints concerning the dams and developmental endpoints in the foetus in the exposure group were not different compared to the control animals. Therefore, the NOAELs for fertility and developmental toxicity were 1000 mg/(kg bw x d).

2.5.5 Odour perception

Saturated aliphatic hydrocarbons C17-C22 are either odourless (C20-C22) or have a fuel like odour (C17-C19) (NLM, 2022). No quantitative data are available on thresholds.

2.6 Evaluation

2.6.1 Existing regulations and classifications

There is no harmonised classification available for saturated aliphatic hydrocarbons C17-C22 (ECHA C&L Inventory, 2022).

Existing guide values for saturated aliphatic hydrocarbons C17-C22 and white mineral oil in air are summarised in Table 12.

Table 12: Guide values for saturated aliphatic hydrocarbons C17-C22 or white mineral oils

Guide value Parameter/ Organisation	AgBB	MAK Commission	SCOEL	Health Council of the Netherlands (HCN)
	saturated aliphatic hydrocarbons C17-C22	White mineral oil, pharmaceutical (CAS no. 8042-47-5) and Mineral oils (petroleum), severely refined (several CAS no.)	Aerosols of severely Refined Mineral Oils	Mineral oil mists (highly refined)
Name (reference period)	NIK value	MAK value (2017, 2019)	SCOEL value (2011)	OEL (2011)
Value (mg/m³)	1	5 (respirable fraction)	5 (respirable fraction)	1.6
Organ/critical effect	-	Local effects in the lung (microgranulomas in the lung)	Local effects in the lung (microgranulomas in the lung)	Local effects in the lung (microgranulomas in the lung)
Species	-	Sprague-Dawley rat and Beagle dogs in both studies	Sprague-Dawley rat and Beagle dogs in both studies	Sprague-Dawley rat and Beagle dogs in both studies
Basis	-	NOAEC: 5 mg/m³	NOAEC: 5 mg/m³	NOAEC: 5 mg/m³
Adjusted for continuous exposure	-	-	-	-
Extrapolation factors				
Route-to-route	-	-	-	-
Time	-	-	-	-
LOAEC to NOAEC	-	-	-	-
Interspecies	-	-	-	-
Intraspecies	-	-	-	3
Other	-	-	-	-
Total	-	-	-	-

The NIK value of 1 mg/m³ is reported by AgBB (2021). This value is generic and is not based on an individual assessment for these substances. It presumably applies to the group of saturated aliphatic hydrocarbons C17-C22 (this is not explicitly mentioned).

No further guide values for saturated aliphatic hydrocarbons C17-C22 are reported. The MAK commission (Hartwig and MAK Commission, 2017; Hartwig and MAK Commission, 2019), SCOEL (SCOEL, 2011) and HCN (HCN, 2011) derived OEL values for highly refined mineral oil.

2.6.2 Derivation of an EU-LCI value

Saturated aliphatic hydrocarbons C17-C22 are waxy solids with saturated vapour concentrations ranging from < 1 mg/m³ up to 4.63 mg/m³ for C18 (calculated based on the molecular weight and the vapour pressure at 25 °C). Inhalation exposure to vapour is not considered a relevant exposure route for these substances.

This is also in accordance with the ECHA guidance on Information Requirements and Chemical Safety Assessment Chapter R.7c where a vapour pressure below 0.5 kPa is considered as cut-off value indicating very low volatility and therefore a low availability for inhalation as a vapour (ECHA, 2017).

In an attempt to estimate where a hypothetical EU LCI value for these substances might lie, a derivation was made according to the concept of EC (2013). The derivation of this hypothetical value is described in the following section.

The data basis for saturated aliphatic hydrocarbons C17-C22 is limited. No reliable inhalation study with a substance belonging to the group of saturated aliphatic hydrocarbons C17-C22 n-alkanes is available. Therefore, studies with read-across substances had to be considered.

The NOAEC of 1500 mg/m³ from the 90-day inhalation study with C11-14 (NIC, < 2 % aromatics) could be used as POD for the derivation of an EU-LCI value. The value is based on increased liver and kidney weight in male animals at the mid and high exposure groups (at 3000 and 6000 mg/m³).

Kidney weight changes were also observed in the low exposure group, but this effect is not considered relevant for the derivation of an EU-LCI value since it was associated with alpha2u-globulin nephropathy which is a species-specific effect in male rats and of no relevance to humans. According to McKee et al. (2015), liver weight increases are common after repeated exposure to hydrocarbons and should be considered as adaptive response in the absence of pathological changes or elevated liver enzymes. However, the interpretation of liver effects (especially liver weight changes) is highly discussed in the scientific community (Anon., 2018). In the absence of precise information on the percentage of weight change the effect on liver weight is therefore considered relevant for the derivation of an EU-LCI value.

The substances are waxy solids with low vapour pressure. Absorption after inhalation exposure is assumed to be complete by default. The following assessment factors (EC, 2013; ECHA, 2012) could be used for the derivation:

- Adjusted study length factor: 2 (90-day study, subchronic exposure)
- Allometric scaling (rat to human): not required since inhalation study
- Interspecies differences: 2.5 (default value for systemic effects)
- Intraspecies differences: 10,

leading to a value of 1500 mg/m³ : 50 = 30 mg/m³.

The NOAEC of 1500 mg/m³ is supported by observations from other repeated dose studies with related substances:

In the aerosol inhalation study with C20-C50 hydrotreated oil (containing 2.4% aromatics) a systemic NOAEC of 980 mg/m³ (highest concentration tested, analytical) was derived. Effects on the lung were observed at a lower concentration but associated to residual oil deposits in the organ due to aerosol exposure. The result of this study shows that at a comparable concentration (980 mg/m³ vs. 1500 mg/m³) no additional effects are expected after exposure to hydrocarbons with higher carbon numbers than C11-C14 as used in the study selected for the POD derivation.

For C21 n-alkane results from an oral 90-day study show, that up to the highest dose tested (500 mg/(kg bw x d)) no clear effects were observed. There are indications of higher liver and kidney weights and increased levels of AST, however, the results can only be regarded as indicative.

With the same substance (C21 n-alkane) an oral developmental toxicity study showed no effects at one dose tested (1000 mg/(kg bw x d)) neither in dams nor in pups. The absence of any effects was

also observed in a developmental toxicity study with white mineral oil C16-30 after inhalation (NOAEC = > 1000 mg/m³).

However, as outlined above, it has to be acknowledged that saturated aliphatic hydrocarbons C17-C22 are waxy solids with saturated vapour concentrations below 5 mg/m³. The hypothetical EU-LCI value of 30 mg/m³ derived above is based on a study with C11-C14 NIC, a more volatile UVCB (Unknown or Variable composition, Complex reaction products or Biological materials) substance due to the shorter carbon chains (vapour pressure of 135 Pa at 20 °C according to ECHA Dissemination (2021)). For C11-C14 NIC a saturated vapour concentration of 9294 mg/m³ could be calculated (based on an average molecular weight of 170 g/mol and a vapour pressure of 135 Pa at 20 °C). This shows that in the case of C17-C22 saturated hydrocarbons the exposure via inhalation is comparably low due to the low saturated vapour pressure of the substances.

Based on the very low vapour pressure of the C17-C22 hydrocarbons no LCI value for this group of substances is suggested.

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B Appendix

B.1 Data collection and fact sheet for saturated aliphatic hydrocarbons C17-C22

Table 13: Data collection sheet for the group of saturated aliphatic hydrocarbons C17-C22

Compound	**Saturated aliphatic hydrocarbons C17-C22**	**Data collection sheet**		
CAS numbers: 629-78-7, 593-45-3, 629-92-5, 112-95-8, 629-94-7, 629-97-0	**EU-Classification: -** **CLP,** harmonised classification: none			
		White mineral oil, pharmaceutical (CAS no. 8042-47-5) and Mineral oils (petroleum), severely refined (several CAS no.)	Aerosols of severely Refined Mineral Oils	Mineral oil mists (highly refined)
Organisation name	**AgBB**	**MAK Commission**	**SCOEL**	**HCN**
Risk value name	NIK ('Lowest Concentration of Interest')	MAK value	SCOEL value	OEL
Risk value (mg/m³)	1	5 (respirable fraction)	5 (respirable fraction)	1.6
Reference period	Chronic (general population)	Chronic (workers)	Chronic (workers)	Chronic (workers)
Risk value (mg/m³) Short term (15 min)	-	not derived	not derived (not deemed necessary)	Not derived
Year	-	2017, 2019	2011	2011
Key study	-	Stula and Kwon, 1978 and Wagner et al., 1964	Stula and Kwon, 1978	Stula and Kwon, 1978
Study type	-	Inhalation study with 0, 5, 100 mg/m³ mineral oil (aerosol exposure)	Inhalation study with 0, 5, 100 mg/m³ mineral oil (aerosol exposure)	Inhalation study with 0, 5, 100 mg/m³ mineral oil (aerosol exposure)
Species	-	Sprague-Dawley rat and Beagle dogs in both studies	Sprague-Dawley rat and Beagle dogs in both studies	Sprague-Dawley rat and Beagle dogs in both studies
Duration of exposure in key study	-	12 – 24 months	12 – 24 months	12 – 24 months
Critical effect	-	Local effects in the lung (microgranulomas in the lung)	Local effects in the lung (microgranulomas in the lung)	Local effects in the lung (microgranulomas in the lung)

Compound	Saturated aliphatic hydrocarbons C17-C22	Data collection sheet		
Critical dose value	-	NOAEC: 5 mg/m³	NOAEC: 5 mg/m³	NOAEC: 5 mg/m³
Adjusted critical dose	-	-	-	
Single assessment factors	-	-	-	UF_H (3)
Other effects	-			
Remarks		Since a LOAEC of 100 mg/m³ from the same study (Stula and Kwon, 1978) and a NOAEC from a 13 week study of 50 mg/m³ was derived, no relevant interindividual variation is expected (overload effect) and no systemic uptake, no assessment factors were selected.		

AgBB = Ausschuss zur gesundheitlichen Bewertung von Bauprodukten, UF_H Intraspecies variability

Table 14: Fact sheet for the group of saturated hydrocarbons C17-C22

Compound	Saturated hydrocarbons C17-C22		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptors**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	-
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2022
General information			
CLP-Index No.	4	INDEX	-
EC-No.	5	EINECS	211-108-4 (n-C17), 209-790-3 (n-C18), 211-116-8 (n-C19), 204-018-1 (n-C20), 211-118-9 (n-C21), 211-121-5 (n-C22)
CAS-No.	6	Chemical Abstract Service number	629-78-7 (n-C17), 593-45-3 (n-C18), 629-92-5 (n-C19), 112-95-8 (n-C20), 629-94-7 (n-C21), 629-97-0 (n-C22)
Harmonised CLP classification	7	Human health risk related classification	-
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	C17: 240.5 g/mol, 1ppm = 10.00 mg/m³ C18: 254.5 g/mol, 1 ppm = 10.58 mg/m³ C19: 268.5 g/mol, 1 ppm = 11.16 mg/m³ C20: 282.5 g/mol, 1 ppm = 11.75 mg/m³ C21: 296.6 g/mol, 1 ppm = 12.33 mg/m³ C22: 310.6 g/mol, 1 ppm = 12.92 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	-
Read across compound	10	Where applicable	-
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]	-
Assessment factors (AF)			
Adjustment for exposure duration	19	Study exposure h/d, d/w	-

Compound	Saturated hydrocarbons C17-C22		Fact sheet
Study length	20	sa→sc→c	-
Route-to-route extrapolation factor	21	-	-
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]	-
Molar adjustment factor	29		
Rounded value	30	[µg/m³]	-
Additional comments	31		

Rationale selection	32		No EU-LCI value suggested for the group of substances since exposure to vapour considered very unlikely

Data compilation and evaluation for saturated aliphatic hydrocarbons C17-C22 is based on a project funded by the German Environment Agency (Voss et al., 2022).

Rationale for critical effects

The n-alkanes C17, C18, C19, C20, C21 and C22 are waxy solids with melting points between 22 and 44 °C.

No human data are available. For most toxicological endpoints read-across to other saturated hydrocarbons with different chain length is performed in the REACH registration dossiers.

According to McKee et al. (2015) a higher carbon number (> C12) leads to a decreased systemic availability of inhaled hydrocarbons. For C17–C22 aliphatic hydrocarbons the amount of substance available as vapour is very limited due to the physical states (solid) and the low vapour pressures of the substances.

The acute toxicity of saturated aliphatic hydrocarbons used in the read-across approach in the disseminated REACH registration dossiers is very low, in most cases the LD50/LC50 values are above the highest dose or concentration tested (ECHA Dissemination, 2021).

The substances are not skin- or eye irritating and they do not show a sensitising or sensory irritation potential.

No repeated inhalation studies with the relevant substances are available. In the REACH registration dossiers of C17-, C18-, C20-, and C22-n-alkanes two 90-day inhalation studies with hydrocarbons C11-14 NIC, (Normal, Iso- and Cyclic alkanes) < 2 % aromatics (List no: 917-725-1 or 926-141-6) and C10-12 I (Iso alkanes), < 2 % aromatics (List no: 923-037-2) are reported in a read-across approach. In both studies with rats the respective NOAEC is reported as the highest concentration tested (6000 mg/m³ and 10400 mg/m³). In male animals, kidney effects in all dose groups were observed. These effects were consistent with the picture of alpha2u-globulin nephropathy which is a species-specific effect in male rats and of no relevance to humans. In addition, liver weight was increased in the mid and high exposure group in males and in the high exposure group in females. The changes in liver weight were not accompanied by histological changes and are considered as an adaptive response. These liver effects in the mid and high exposure groups (at 3000 and 6000 mg/m³) were considered the most relevant toxicological effect and the basis for the derivation of a potential EU-LCI value (POD: 1500 mg/m³).

The substances did not show a genotoxic or carcinogenic potential nor is there a concern for reproductive or developmental toxicity.

Saturated aliphatic hydrocarbons C17-C22 are waxy solids with saturated vapour concentrations below 5 mg/m³. A hypothetical EU-LCI value of 30 mg/m³ (1500 mg/m³ : 2 (adjustment for study length) : 2.5 (interspecies differences) : 10 (interspecies differences)) could be derived based on increased liver weight in inhalation studies with read-across substances that have shorter chain length and are therefore much more volatile. However, vapour exposure to saturated aliphatic hydrocarbons C17-C22 is not considered relevant due to the solid state and the low vapour pressure of the substances.

In a different approach the saturated vapour concentration of the C17-C22 saturated aliphatic hydrocarbons (0.02 - 4.5 mg/m³ at 25 °C) could be used as an EU-LCI value. Since this approach is not described in the methodological report on EU-LCI values (EC, 2013), currently no EU-LCI value is suggested for saturated aliphatic hydrocarbons C17-C22.

References

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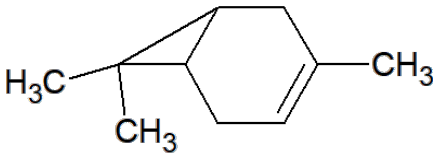
3 Toxicological evaluation of 3-carene as basis for the derivation of an EU-LCI value

3.1 Substance identification

Substance identification data and physicochemical properties of 3-carene are shown in Table 15 and Table 16.

Table 15: Substance identification of 3-carene (Api et al., 2018; ECHA Dissemination, 2021)

CAS-No. EU-No. CLP-Index-No.	Systematic name, common name	Sum formula	Structural formula
13466-78-9 (unspecified) 236-719-3 - 498-15-7 (1S-carene, (+)-carene) 207-856-6 - 20296-50-8 (1R-carene, (-)-3-carene) - -	3,7,7-trimethyl-bicyclo[4.1.0]-hept-3-ene, Δ-3-carene, 3-carene	$C_{10}H_{16}$	

3.2 Substance properties and uses

3-Carene is an unsaturated monoterpene hydrocarbon consisting of a bicyclic ring system of a fused cyclohexene and cyclopropane ring. Carene has a sweet and pungent odour with woody character. The substance is chiral. Both forms and the racemate are widespread in nature, e. g. in essential oils from many herbs, citrus fruit and cannabis Hartwig and MAK-Kommission, 2017(AICIS, 2020; USDA, 2016)

Table 16: Substance properties of 3-carene (ECHA Dissemination, 2021)

Molar mass (g/mol)	Mp. (° C)	Boiling point (° C)	Vapour pressure (Pa) (at 20 °C)	Conversion 1 ppm = x mg/m³ (23 °C)	log pow	Solubility in water (mg/L)
136.24	< - 80	170	273	5.61	4.38 at 37 °C	3.7 at 20 °C

Carene also is a constituent of turpentine oils derived from various conifer species, especially pines. The amount of 3-carene and also its enantiomer composition in turpentine oils strongly depends on the geographic origin, the season of harvest and the conifer species (Hartwig and MAK-Kommission, 2017). Turpentine oil from North European conifers may contain up to 40 % of (+)3-carene (Sagunski and Heinzow, 2003).

3.3 Exposure

3.3.1 Indoor air

Besides from wooden construction materials or furniture, 3-carene, together with other monoterpenes may be emitted in considerable amounts into indoor air from cleaning agents, air refreshers, laundry products, paints or varnishes (AICIS, 2020; Schmidt et al., 2015b). Concentrations of 3-carene in indoor air are mostly low, in the order of several µg/m³ (Table 17). In rooms with solid wood furniture, the mean concentrations of δ-3-carene, other bicyclic monoterpenes (α-pinene, β-pinene), and the sum of terpenes were significantly higher than in rooms without such furniture. Regarding 3-carene, the mean concentration in rooms with solid wood furniture was 3.48 µg/m³, twice as high as in rooms without such furniture (1.58 µg/m³) (Schulz et al., 2010). In a study on air quality in seven residential homes in Poland, the average monthly concentrations of 3-carene ranged between 46 and 373 µg/m³ (maximum: 579 µg/m³) (Król et al., 2014). In some studies, very high maximum levels exceeding 1000 µg/m³ were reported, probably in case of complaint-related measurements.

Table 17: Data on the occurrence of 3-carene 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)	Max. (µg/m³)	Ref.
Public buildings, evaluation of complaints	1138	0.5	683 (60 %)	3	36	546	(Petzold, 2015)
Offices, homes, (pre)-schools, Germany	2379	1.0	1713 (72.0 %)	2.5	65.0	1300	(Hofmann and Plieninger, 2008)
Homes with children 3 – 14 a, Germany	555	1.0	414 (75 %)	2.6	22.7	336	(Schulz et al., 2010)
Homes and offices, Germany	3574	1.0	2266 (63.4 %)	1.00	59.0	8200	(Hofmann et al., 2014)
Daycare centres, Germany	45	1.0	21 (47 %)	< 1.0	3.2	11	(Schmidt et al., 2015b)
Retirement and nursing homes, Germany	38	0.2 – 0.5	33 (86 %)	0.5	3.0	3.8	(Ostendorp and Heinzow, 2013)
Schools and kindergartens, Germany	285	0.5	217 (76 %)	2.0	23	130	(Ostendorp et al., 2009)
Offices, homes, (pre)-schools, Germany	294	N.r.*	N.r.	3.9	44.3	N.r.	(Sagunski and Heinzow, 2003)
Offices, homes, (pre)-schools, Germany	188	N.r.*	N.r.	17.0	112	443	(Sagunski and Heinzow, 2003)

*: Not reported

3.4 Toxicokinetics

Bicyclic terpenes in general are rapidly absorbed upon inhalation. Studies with controlled exposure of humans against 3-carenes (450 mg/m³, 2 hours) or mixtures of bicyclic terpenes (160 mg/m³ carene, 240 mg/m³ alpha-pinene, 50 mg/m³ ß-pinene) revealed that about 70 % of 3-carene were taken up in the lungs. Studies with rats showed a distribution in fat-rich tissues (fat, brain, liver, kidney, spleen). The metabolism of bicyclic terpenes involves hydroxylation by monooxygenases, followed by glucuronidation of the produced hydroxy compounds or their further oxidation to carboxylic acid. Only small amounts (2 – 8 %) are excreted unchanged by exhalation. The clearance after a 2-hour inhalation in humans was rapid following triphasic kinetics with an elimination half-life for the slowest phase of 0.4 d for 3-carene as individual substance and 1.8 d in terpene mixtures (Duisken et al., 2006; Falk et al., 1991; Filipsson, 1996; Sagunski and Heinzow, 2003).

In a metabolism study with oral intake of 10 mg 3-carene in humans, the volunteers reported a smell or odour of the compound for 1 – 2 hours after intake which indicates a pulmonary excretion of 3-carene (or metabolites of similar sensory properties). However, no quantification of pulmonary elimination was performed in this study. A number of urinary metabolites could be detected and part of them identified by GC/MS. Carene-10-COOH was detected 2-3 h after administration, but carene-10-OH and carene-3,4-OH could not be detected in any of the samples. Excretion was rapid with a half-time of about 3 h for the renal excretion of carene-10-COOH. The cumulative excretion of carene-10-COOH within 24 h after exposure reached about 2 % of the applied dose. A number of further metabolites could be detected and some of them tentatively identified. Overall, these metabolites in urine accounted for 28 % of the amount of the oral intake of 3-carene (Schmidt, 2015; Schmidt et al., 2015a). Similar results were obtained with pinene (Schmidt and Göen, 2017).

3.5 Health effects

3.5.1 Acute toxicity, sensory irritation and local effects

Human data

Freshly distilled non-oxidised terpenes including 3-carene caused skin irritation when applied as a 70 – 80 % solution in olive oil but not 20 – 35 %. Oxidised samples containing about 2 % or more hydroperoxides caused skin irritation in most of exposed 30 volunteers (DFG, 2000). 3-Carene is a frequent component of turpentine oils (in some oils, up to 40 %) (Sagunski and Heinzow, 2003), which are classified as skin sensitisers (ECHA C&L Inventory, 2022).

A number of studies were conducted regarding sensory irritation of 3-carene in humans.

After very brief exposure of 1 to 3 seconds through one nostril, a pungency threshold of 2777 ppm (15551 mg/m³ at 23 °C) was reported (Cometto-Muñiz et al., 1998a; Cometto-Muñiz et al., 1998b). Additionally, an eye irritation threshold of about 1800 ppm (10000 mg/m³) can be read from a graph presented by Commetto-Muñiz et al. (1998a). A threshold for eye irritation below 1250 mg/m³ (measured using goggles in 12 subjects) was reported for 3-carene, however, responses appeared at too few of the tested exposure levels to allow trivariate estimates. The ranking of eye irritation potency in increasing order in this study was alpha-pinene, limonene, n-butanol, 3-carene, alpha-terpineol (Mølhave et al., 2001).

Based on an algorithm for RD50 values in mice and applying an assessment factor of five Wolkoff and Nielsen (2017) calculated a NOAEC for sensory irritation of 9500 µg (+)-3-carene/m³. The authors also calculated a LOAEC value range of 45000 – 90000 µg (+)-3-carene/m³ from human exposure studies divided by an assessment factor of 5.

During a 2-h exposure of 8 subjects against 10 (control, odour detectable), 225, or 450 mg 3-carene/m³, the subjects experienced irritation in eyes and nose at the highest concentration. An increase in airway resistance was noted but the difference was not significant compared to control, other pulmonary functional parameters showed no alterations. Compared to a similar study with (+)-alpha-pinene, eye irritation was about two-fold more marked with 3-carene than with alpha-(+)-pinene (Falk et al., 1991; Falk et al., 1990).

A 2-h exposure of 8 men against a mixture 54 % α-pinene, 11 % ß-pinene, and 35 % 3-carene (total concentration: 450 mg/m³) led to significant increase in airway resistance compared to control (10 mg/m³ 3-carene) or exposure only against 450 mg 3-carene/m³. Other lung function parameters were not affected (Filipsson, 1996).

15 volunteers were exposed for two hours against 3.5, 5.0, or 9.5 mg/m³ terpenes (plus other VOC) from pinewood, containing mainly α-pinene (up to 70 %) and 3-carene (up to 28 %). No concentration-dependent effects were observed with respect to sensory irritation, pulmonary function, exhaled NO, and eye blink frequency. Odour of the emissions perceived by some of the subjects was rated as being closer to “pleasant” than to “unpleasant” (Gminski et al., 2011).

Skulberg et al. (2019) exposed 30 volunteers for two hours against 288 ppb TVOC emitted from pinewood *(Pinus sylvestris)* (control: 35 ppb). The emissions consisted mainly of monoterpenes (172 ppb = 963 µg/m³, control: 1 ppb) with α-pinene and 3-carene dominating (no further data presented). No sensory irritation, no inflammatory reactions and no effects in neurobehavioural tests were reported.

Animal and *in vitro* data

The acute toxicity of 3-carene is low with LD50 values for oral administration in rats of ≥ 3700 mg/kg bw and for dermal exposure of rabbits of ≥ 2000 mg/kg bw. In an inhalation study according to OECD guideline 436, a limited number of rats was exposed “nose only” against 1050 or 5070 mg/m³, respectively, for four hours. At the higher concentration, one animal died, the others showed signs of CNS-effects with abnormal respiration and convulsions and were euthanized for humane reasons. Hypoactivity and abnormal respiration, but no deaths were observed at the lower concentrations (ECHA Dissemination, 2021). In another study with mice, 30 min exposure above 1400 ppm (7800 mg/m³) caused slight sedation or drowsiness. Recovery was rapid and no macroscopic effects were seen 1 h or 7 days after the end of the exposure (AICIS, 2020).

Undiluted carene caused temporary eye irritation and skin irritation in a test with human epidermis model (EPISKIN). 3-Carene was found to be a skin sensitiser in a non-guideline test (“cumulative contact enhancement test”) in guinea pigs (ECHA Dissemination, 2021).

Oxidised 3-carene containing about 5 % hydroperoxides was reported to be sensitising in domestic pigs (DFG, 1996).

An RD50 (concentration which elicits a respiratory rate decrease of 50 %) for sensory irritation of 1345 ppm (7532 mg/m³) was obtained for (+)-3-carene in a study with mice (Kasanen et al., 1999).

No such data are available for (-)-3-carene. Marked differences were observed in the irritation potency as determined by the RD50 values in studies with the structural bicyclic terpene isomers α- and β-pinene. Rather similar ranges of RD50 values were reported for (+)-α-pinene (1053 – 1107 ppm) and of (+)-β-pinene (1279 – 1419 ppm), respectively, whereas no RD50 could be determined for (-)-α-pinene due to its very low or absent irritant potency, and the RD50 value for (-)-β-pinene was about four-fold lower than for (+)-β-pinene (Hartwig and MAK-Kommission, 2017).

3.5.2 Repeated dose toxicity

Human data

Eight adult volunteers were exposed against a mixture of 280 mg/m³ α-pinene, 30 mg/m³ ß-pinene and 140 mg/m³ 3-carene (overall terpene concentrations 450 mg/m³) three hours/day on four days within two weeks. Twenty hours after the last exposure, the bronchoalveolar lavage revealed a two-fold increase in alveolar macrophages and a five-fold increase in mast cells as signs of an acute alveolar reaction. Albumin, fibronectin, hyaluronic acid, and tryptase were not elevated. FEV1 (Forced Expiratory Volume during the first second) showed a non-significant decrease up to 20 % (Johard et al., 1993).

A cross-sectional study of 38 workers was carried out in four Swedish joinery shops. Exposure to monoterpenes (α-pinene, β-pinene and 3-carene) in joinery shops was studied during the processing of Scot's pine, and the acute respiratory effects among the employees were evaluated. The personal exposure to monoterpenes in the joinery shops was 10 - 214 mg/m³ (no data on individual compounds). There were no acute effects on forced vital capacity or forced expiratory volume during 1 s. However, the workers had significantly reduced pre-shift lung function values when compared with the values of a local reference group, even when smokers and ex-smokers were excluded. The results from the lung function tests may indicate chronic rather than acute reactions in the airways (Eriksson et al., 1997).

Animal data

In a subchronic oral toxicity study following OECD guideline 408, Sprague-Dawley rats (10 M + 10 F/group) were exposed to (+)-carene (purity 82.2 %, impurities other mono- and bicyclic monoterpenes) at concentrations of 0, 2000, 4500, or 12000 ppm in food for a total of 13 weeks (ECHA Dissemination, 2021). An additional control and high-dose group (5 M + 5 F/group) were treated similarly and examined after a final four-week recovery period. The highest concentration in food corresponded to a substance intake of 744 mg/(kg bw x d) in males and 752 mg/(kg bw x d) in females. No mortality occurred in any of the groups, and no clinical signs or changes in behaviour of the animals were observed. Food consumption was low in males and females receiving 4500 or 12000 ppm which was attributed to markedly low values during the first days of treatment. Body weight gain was low in males and females receiving 12000 ppm and females receiving 4500 ppm during treatment. The lower food intake and the body weight gain were likely related to the unpalatable taste of the carene-containing diets. (Similar effects on food intake and body weight were noted in dose-finding study at ≥ 6000 ppm after 3 weeks.)

The grip strength investigations performed in week 12 of treatment revealed statistically significantly low fore and hind limb grip strength in females receiving 12000 ppm, with 6/10 individual means for each hind and fore limb grip strength being below the historical control range, although the same animals were not consistently affected. Fore hind grip strength remained low at the end of the four weeks recovery period. There were no associated clinical signs (such as abnormal gait) and no histopathological findings in the nervous or musculoskeletal tissues. After 13 weeks of treatment, prothrombin time in females was below the background control range but the number of females with a value above the concurrent control was elevated. No treatment-related effect on the activated partial prothrombin time was observed. Liver and kidney weights were elevated and urine output was decreased in males given 4500 or 12000 ppm at the end of the study. Histopathology revealed the presence of hyaline droplets in the renal cortical tubules of all males receiving 12000 ppm; the presence of alpha-2u-globulin was confirmed by immunohistochemical staining. These changes can be attributed to the sex- and species-specific alpha-2u-globulin of male rats which has no relevance for human risk assessment.

The effects on grip strength were considered non-adverse in the registration dossier and the NOAEC considered to be 12000 ppm (ECHA Dissemination, 2021). However, since the effects were not within the background control range and were only partially reversible within the four-week recovery period, adversity cannot be excluded. Thus, within the context of the derivation of an EU-LCI value for 3-carene, the highest concentration will be regarded as a LOAEL (NOAEL: 4500 ppm, by linear extrapolation to about 282 mg/(kg bw x d)).

No repeated dose toxicity study is available with exposure of mice to 3-carene.

Read-across: In a subchronic inhalation study with alpha-pinene, a structural isomer of 3-carene, groups of F344/N rats and B6C3F1 mice (each 10 M + 10 F/group) were exposed to α-pinene by whole body inhalation at concentrations of 0, 25, 50, 100, 200, or 400 ppm, 6 h/d, 5 d/week for 14 weeks. The major targets for α-pinene toxicity were the liver, urinary system, and male reproductive system. The absolute liver weights were significantly increased in high-dose male rats (13 %), male mice (21%), and female mice (18%), and in female rats at ≥ 50 ppm (14 – 17 %). However, there were no treatment-related histopathologic lesions in the liver. Changes in the kidneys of male rats (increased organ weight, hyaline droplet accumulation, granular casts) were observed in male rats indicating sex- and species-specific effects (α-2u-globulin nephropathy). In male and female mice, increased incidences of transitional epithelium hyperplasia of the urinary bladder were observed at ≥ 100 ppm. There were also significantly lower numbers of sperm per cauda compared to controls in male rats at ≥ 200 ppm and in male mice at ≥ 100 ppm (NOAEC: 50 ppm (281 mg/m³), based on minor to moderate hyperplasia of the bladder urothel in mice) (NTP, 2016).

3.5.3 Genotoxicity and carcinogenicity

Genotoxicity

No mutagenicity of 3-carene was observed *in vitro* in the absence or presence of exogenous metabolic activation system in two assays with bacteria (according to OECD Guideline 471) and in an HPRT assay in (according to OECD guideline 487) in Chinese hamster ovary cells (CHO-K1 cells). No clastogenic activity (induction of micronuclei) was observed in a study following OECD Guideline 487 in human lymphocytes (ECHA Dissemination, 2021).

Data from *in vivo* studies with 3-carene are not available.

Read-across: No increase in micronucleate erythrocytes was seen in male or female mice after subchronic (three month) inhalation with α-pinene at concentrations up to 400 ppm (2240 mg/m³) (NTP, 2016).

Carcinogenicity

No studies were identified relevant for the evaluation of 3-carene.

3.5.4 Toxicity to reproduction

The results of the above-mentioned subchronic oral toxicity study with rats were principally confirmed in a pre-study for an extended one-generation reproductive toxicity study in rats (the main study following OECD guideline 443 is ongoing) (ECHA Dissemination, 2021). The study was conducted to assess the general systemic toxic potential, including reproductive/developmental effects, after dietary administration of dietary (+)-3-carene for at least seven weeks. In the F0 generation, Sprague Dawley rats (8 M + (F/Group) were fed diets containing 0, 3000, 6000 or 12000 ppm (+)-3-carene. Males were treated for three weeks before pairing, throughout pairing and up to necropsy after litters were weaned. Females were additionally treated up to Day 20 of lactation. The F1 generation was treated from weaning for up to week 7 of age at the same dietary concentrations as the F0 generation.

Treatment with (+)-3-carene up to the highest dose had no effect on reproductive performance. Food intake was lower at ≥ 6000 ppm, probably due to reduced palatability, and body weight gain at these carene doses in food was also lowered. Lower body weight gain and food consumption, delayed female sexual maturation and increased liver and kidney weights in F1 animals were also observed at 12000 ppm. Depending on the age, sex and life stage of the animals, 12000 ppm in food corresponded to doses between 639 and 1622 mg/(kg bw x d), and 6000 ppm corresponded to 314 to 841 mg/(kg bw x d) (ECHA Dissemination, 2021).

In a prenatal developmental toxicity study according to OECD Guideline 414, pregnant Sprague-Dawley rats (20/group) received 0, 90, 175 or 350 mg/(kg bw x d) of (+)-carene-3 (purity as an in the subchronic study) by gavage on GD 6-19. The treatment led to a small body weight loss after the first dose at all concentrations and subsequent to a low weight gain (-24%) and food intake at 350 mg/(kg bw x d). No data have yet been presented regarding effects of treatment on offsprings. In a pre-study with six dams/group, mean pre-implantation loss (%) appeared high at 600 mg/(kg bw x d) and resulted in a slightly low litter size. No developmental toxicity was observed at 300 and 450 mg/(kg bw x d); however, food intake and weight gain of dams were reduced at all doses (ECHA Dissemination, 2021).

In rabbits, local and systemic effects were observed at ≥ 500 mg/(kg bw x d) after one or two weeks of gavage exposure (decreased faecal output, persistent weight loss, reduced food consumption, dark areas on the glandular mucosa of the stomach) in a dose-finding study of an ongoing developmental toxicity study (ECHA Dissemination, 2021).

3.5.5 Odour perception

In studies with controlled exposure of humans, the odour of 3-carene was detectable at 10 mg/m³ (Falk et al., 1991). Odour thresholds of 4 and 10 mg/m³ have been reported for (+)-3-carene and 3-carene, respectively (Sagunski and Heinzow, 2003). Data for (-)-3-carene are not available.

For the enantiomers (+)-α-pinene and (−)-α-pinene, odour thresholds of 23 mg/m³ and 107mg/m³ were reported. Odour perception thresholds of 36 mg/m³ or 56 - 107 mg/m³ were reported for β-pinene or (-)-β-pinene, respectively. These data may indicate that the odour thresholds for 3-carene and (+)-3-carene could be somewhat lower than those for α- und β-pinene (Sagunski and Heinzow, 2003).

However, the reported odour thresholds have been questioned because of the inappropriate and poorly characterized methods for determination (Wolkoff, P.; Schuster, A., 2022, personal communication). Indeed, much lower odour thresholds of 0.018 ppm (0.101 mg/m³) for α-pinene and of 0.033 ppm for β-pinene (0.213 mg/m³) (enantiomers not reported) were obtained in studies using the “triangle odor bag method (Nagata, 2003). No data are available for 3-carene, but it seems reasonable to assume that much lower thresholds than the values reported above would be obtained by the “triangle bag method”.

3.6 Evaluation

3.6.1 Existing regulations and classifications

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

Existing guide values for 3-carene and for bicyclic terpenes using α-pinene as indicator substance are summarised in Table 18.

In the registration dossier, a DNEL of 1.52 mg/m³ is derived for the protection of the general population via inhalation. This DNEL is based on the NOAEL of 175 mg/(kg bw x d) for maternal

toxicity obtained in a developmental toxicity study with rats by means of a route-to-route extrapolation. Standard factors were used for route-to-route extrapolation (obviously including, but not explicitly stated, a standard factor of two accounting for differences in inhalation and oral absorption), for toxicodynamic interspecies and for intraspecies extrapolation. Since the effects occurred during gestation, no factor for extrapolation to chronic exposure was used. However, an additional factor of two was used to consider the absence of exposure during the first 5 days of gestation. A DNEL of 8.63 mg/m³ for workers was also derived, based on the same NOAEL, corresponding standard factors for workers and the additional factor of two as described (ECHA Dissemination, 2021).

An EU-LCI of 2500 µg/m³ was derived for α-pinene, a structural isomer of 3-carene with a cyclobutane instead of a cyclopropane ring. This value is based on the NOAEL for a systemic effect (bladder epithelium damage in mice) obtained with α-pinene and not, as in the derivation of Sagunski and Heinzow (2003) (see below), based on a local effect (sensory irritation) caused by a mixture of α- and β-pinene and 3-carene. The EU-LCI Working Group emphasizes that although α-pinene is often used an indicator substance for the group of bicyclic monoterpenes that other monoterpenes showed a metabolic pattern different from that of α-pinene, so simple transfer or read-across to other bicyclic monoterpenes seem to be inadequate (EC, 2013; EU-LCI Working Group, 2021).

The Guidance value II ("Richtwert II") of the Ad-hoc Working Group of the German Indoor Air Commission (Sagunski and Heinzow, 2003) for bicyclic monoterpenes is based on a LOAEC of 450 mg/m³ for inflammation reactions observed in studies in which volunteers were exposed intermittently to a mixture of 280 mg α-pinene, 30 mg β-pinene und 140 mg 3-carene/m³ for two weeks (Johard et al., 1993). Support comes from another study with humans in which eye and nasal irritation were reported by the participants at 450 mg/m³ 3-carene or (+)-α-pinene, respectively (Falk et al., 1991; Falk et al., 1990)

A factor of 12 was used to extrapolate to chronic extrapolation A standard factor of 10 for intraspecies extrapolation and an additional factor of two for a possibly higher susceptibility of children were considered to derive a guidance value II of 2 mg/m³. One tenth of this concentration was set as guidance value I ("Richtwert I") (Sagunski and Heinzow, 2003).

Based on an algorithm for RD50 values in mice and applying an assessment factor of five, Wolkoff and Nielsen (2017) calculated a NOAEC for sensory irritation in humans of 9500 µg (+)-3-carene/m³. The authors also calculated a LOAEC value range of 45000 – 90000 µg (+)-3-carene/m³ from human exposure studies divided by an assessment factor of five. As these derivations are based solely on irritation, not considering possible other systemic effects of 3-carene they have not been included in Table 18. Indeed, comparison of the data presented in Table 18 with the values calculated by Wolkoff and Nielsen (2017) seems to indicate that sensory irritation may not be the critical effect of 3-carene.

Table 18: Guide values for 3-carene and bicyclic terpenes (for explanation, see text)

Guide value Parameter/ Organisation	(ECHA Dissemination, 2021)	(Sagunski and Heinzow, 2003)
Substance	(+)-3-carene	Bicyclic terpenes (indicator substance: α-pinene)
Name (reference period)	DNEL (chronic)	Hazard guide value (RW II) (chronic) Precautionary guide value (RW I) (chronic)
Value (mg/m³)	1.52 mg/m³	RW II: 2 mg/m³ RW I: 0.2 mg/m³
Organ/critical effect	Low weight gain in dams	Irritation / inflammation reactions in respiratory tract
Species	Rat	Human
Basis	NOAEL: 175 mg/(kg bw x d)	LOAEC: 450 mg/m³
Adjusted for continuous exposure	175 : 1.15 = 152.17 mg/m³ : 2 = 76.1 mg/m³	
Extrapolation factors Route-to-route Time LOAEC to NOAEC Interspecies Intraspecies Other Total	 1.15 m³/(kg bw x d) 2.5 10 2 50	 12 RW II to RW I: 10 10 2 (children) 240 (RW I: 2400)
Remark	Study according to OECD guideline 414 with (+)-carene, evaluation ongoing (no data for foetal effects yet provided).	Values for bicyclic monoterpenes (α- and ß-pinene, 3-carene); supporting study performed with 3-carene

3.6.2 Derivation of an EU-LCI value

Bicyclic terpenes in general are rapidly absorbed upon inhalation. Studies with controlled exposure of humans against 3-carenes revealed that 70 % of 3-carene were taken up in the lungs. Studies with rats showed a distribution in fat-rich tissues. The metabolism of bicyclic terpenes involves hydroxylation by monooxygenases, followed by glucuronidation of the produced hydroxy compounds or their further oxidation to carboxylic acid. Only small amounts (2 – 8 %) are excreted unchanged by exhalation. The clearance after a 2-hour inhalation in humans was rapid following triphasic kinetics with an elimination half-life for the slowest phase of 0.4 d for 3-carene as individual substance and 1.8 d in terpene mixtures (Sagunski and Heinzow, 2003).

In a metabolism study with oral intake of 3-carene in humans, a number of urinary metabolites could be detected and part of them identified, including Carene-10-COOH. The cumulative excretion of metabolites in urine within 24 h after accounted for 28 % of the oral dose of 3-carene applied (Schmidt, 2015; Schmidt et al., 2015a).

The acute toxicity of 3-carene is low with LD50 values for oral administration in rats of ≥ 3700 mg/kg bw and for dermal exposure of rabbits of ≥ 2000 mg/kg bw. In an inhalation study with “nose only” exposure of rats, death was observed at 5070 mg/m³ after 4-hour exposure but not at 1050 mg/m³ (ECHA Dissemination, 2021). Short-term (30 min) exposure above 1400 ppm (7800 mg/m³) caused

slight sedation or drowsiness in mice. Recovery was rapid and no macroscopic effects were seen 1 h or 7 days after the end of the exposure (AICIS, 2020).

3-carene causes only mild and temporary irritation of eyes and skin. However, oxidised 3-carene was found to be a skin sensitiser (ECHA Dissemination, 2021).

Studies with humans revealed that high concentrations of 3-carene may cause sensory irritation. After very brief exposure of 1 to 3 seconds, a nasal pungency threshold of 2777 ppm (15551 mg/m³ at 23 °C) was reported (Cometto-Muñiz et al., 1998a; Cometto-Muñiz et al., 1998b). Additionally, an eye irritation threshold of about 1800 ppm (10000 mg/m³) can be read from a graph presented by Commetto-Muñiz et al. (1998a). An eye irritation threshold below 1250 mg/m³ was reported for 3-carene in another study (Mølhave et al., 2001).

Sensory irritating effects were noted by volunteers exposed to 450 mg/m³ 3-carene for two hours. Eye irritation was about two-fold more marked with 3-carene than with alpha-(+)-pinene (Falk et al., 1991; Falk et al., 1990). No concentration-dependent effects were observed with respect to sensory irritation, pulmonary function, exhaled NO, and eye blink frequency in a study with exposure of humans for two hours against 3.5, 5.0, or 9.5 mg/m³ terpenes (plus other VOC) from pinewood, containing mainly α-pinene (up to 70 %) and 3-carene (up to 28 %) (Gminski et al., 2011).

No sensory irritation, no inflammatory reactions and no effects in neurobehavioural tests were reported after two hours of exposure against 288 ppb TVOC emitted from pinewood. The emissions consisted mainly of monoterpenes (172 ppb = 963 µg/m³) with α-pinene and 3-carene dominating (Skulberg et al., 2019).

An RD50 for sensory irritation of 1345 ppm (7532 mg/m³) was obtained for (+)-3-carene in a study with mice (Kasanen et al., 1999). No such data are available for (-)-3-carene. However, studies with (+)- and (-)-α-pinene and (+)- and (-)-β-pinene indicate that the (-)-enantiomers are less irritant than the (+)-enantiomers (Hartwig and MAK-Kommission, 2017).

After repeated exposure of humans against a mixture of 280 mg/m³ α-pinene, 30 mg/m³ ß-pinene and 140 mg/m³ 3-carene (overall terpene concentrations 450 mg/m³) three hours/day on four days within two weeks, the bronchoalveolar lavage revealed signs of a weak acute alveolar reaction (Johard et al., 1993).

In a subchronic oral toxicity study following OECD guideline 408, reduced grip strength was observed in female rats after oral exposure to (+)-3-carene at concentrations of 12000 ppm in food for a total of 13 weeks. The effects on grip strength were considered non-adverse in the registration dossier and the NOAEC considered to be 12000 ppm (752 mg/(kg bw x d)), the highest concentration. However, since the effects were outside the background control range and were only partially reversible within the four-week recovery period, adversity cannot be excluded. Thus, within the context of the proposal for an EU-LCI value for 3-carene, the highest concentration in this study will be regarded as a LOAEL (NOAEL: 4500 ppm, by linear extrapolation: about 282 mg/(kg bw x d)).

3-carene was not genotoxic in *in vitro* in assays (following OECD guidelines) with bacteria and mammalian cells (ECHA Dissemination, 2021). *In vivo* data are not available.

Carcinogenicity studies with 3-carene are not available. The available data on genotoxicity and from repeated dose toxicity studies do not provide evidence for concern regarding carcinogenic effects of 3-carene.

Turpentine oils, which contain variable amounts of 3-carene, have been reported to act as tumor promotors at the skin of mice in initiation-promotion studies. However, a recent evaluation of turpentine oils concluded that the suspicion of a carcinogenic effect by turpentine oil on the skin in

humans can be regarded as so slight that turpentine oils are no longer classified as “Group 3A carcinogen” (Hartwig and MAK-Kommission, 2017).

A pre-study for an extended one-generation reproductive toxicity study in rats (the main study following OECD guideline 443 is ongoing) revealed no effects on reproductive performance up to the highest dose of 12000 ppm 3-carene in food (between 639 and 1622 mg/(kg bw x d)). Food intake was lower at ≥ 6000 ppm (314 to 841 mg/(kg bw x d)), probably due to reduced palatability (ECHA Dissemination, 2021).

In a prenatal developmental toxicity study according to OECD Guideline 414, pregnant rats showed a low weight gain (-24%) and food intake at 350 mg/(kg bw x d). In a pre-study, pre-implantation losses seemed to be increased at 600 mg/(kg bw x d). No developmental toxicity was observed at 300 and 450 mg/(kg bw x d) (ECHA Dissemination, 2021).

The NOAEL of 282 mg/(kg bw x d) obtained in the subchronic oral (feeding) toxicity study with (+)-3-carene in rats is used as POD for the derivation of an EU-LCI value.

The results of toxicokinetic studies with 3-carene in humans indicate that pulmonary uptake by inhalation is about 70 %. After oral intake of 3-carene by humans, 28 % could be recovered as metabolites in urine. Some pulmonary excretion of the parent compound was noted but not quantified. Thus, the default factor of two to account for differences in absorption after oral or inhalation exposure will be considered, and the following assessment factors (EC, 2013; ECHA, 2012):

- Route-to-route extrapolation factor: 1.15 m³/(kg bw x d) (default factor for rats)
- Default factor in case of oral-to-inhalation extrapolation: 2
- 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 282 mg/(kg bw x d) : (1.15 x 2 x 50) = 2452 µg/m³ for (+)-3-carene.

The proposed EU-LCI value for 3-carene value is based on a NOAEL for systemic effects observed in a study with oral exposure of rats. Signs of irritation of mucous membranes (eyes and nose) have been noted in humans in a short-term inhalation study with 3-carene at 450 mg /m³, i.e., at an about 180fold higher concentration, indicating that irritation is unlikely at the proposed EU-LCI value. Furthermore, no local effects in the respiratory tract were described in the NTP study (2016) after subchronic inhalation exposure of rats or mice with the structurally similar α-pinene. It is concluded that there is no concern for acute or long-term local respiratory effects of 3-carene at the proposed EU-LCI value.

It should be noted that conventional analytical methods normally applied for the detection of 3-carene in air do not differentiate between both enantiomers, (+)- and (-)-3-carene. Consequently, the value is proposed for (the sum of both isomers of) 3-carene without specification of the enantiomer.

An EU-LCI value of 2500 µg/m³ is proposed for 3-carene.

For 3-carene and (+)-3-carene, odour thresholds of 10 and 4 mg/m³, respectively, have been reported. Comparison with similarly determined odour thresholds for α- und β-pinene indicate that

the odour thresholds for 3-carene and (+)3-carene could be somewhat lower than those for α- und β-pinene.

However, much lower odour thresholds of 0.018 ppm (100 µg/m³) and 0.033 ppm (185 µg/m³) for α- and β-pinene (enantiomers not specified) were obtained by a sensitive method (Nagata, 2003). No values are reported in Nagata (2003) for 3-carene, but it seems reasonable to assume that odour thresholds much lower than those previously reported are likely. It is concluded that an odour perception cannot be excluded at the proposed EU-LCI value for 3-carene.

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C Appendix

C.1 Data collection and fact sheet for 3-carene

Table 19: Data collection sheet for 3-carene

Compound	3-Carene	Data collection sheet
Nº CAS 13466-78-9 (unspecified) 498-15-7 ((1S,6R)-(+)-3-carene) 20296-50-8 ((1R,6S)-(-)-3-carene) 20296-50-8 ((1R,6S)-(−)-3-Carene) 1 ppm = 5.6 mg/m³ at 23 °C	**EU-Classification: -** **CLP,** harmonised classification: none	
Organisation name	Sagunski and Heinzow (2003)	Reach registrants
Risk value name	Hazard guide value (RW II) Precautionary guide value (RW I)	DNEL
Risk value (mg/m³)	RW II: 2 mg/m³ RW I: 0.2 mg/m³	1.52
Reference period	Chronic (general population)	Chronic (general population)
Risk value (mg/m³) Short term (15 min)	Not derived	not derived
Year	2003	2021
Key study	Johard et al. (1993)	Anonymus (2018)
Study type	Controlled clinical study with exposure to overall 450 mg/m³ mixture of α- and ß-pinene and 3-carene (10:1:5)	Developmental toxicity study with 0, 90, 175, 350 mg delta 3-carene/(kg bw x d) by gavage
Species	Human (n = 8)	Sprague-Dawley rat (n= 20 F/dose)
Duration of exposure in key study	3 h/d, 4 d/week, 2 weeks	GD6-21
Critical effect	Irritation /inflammation reactions in respiratory tract	Weight loss, low weight gain, reduced food intake in dams
Critical dose value	LOAEC: 450 mg/m³	NOAEL: 175 mg/(kg bw x d)
Adjusted critical dose		Adjustment not described in detail, probably 175 : 1.15 = 152.17 mg/m³ : 2 = 76.1 mg/m³
Single assessment factors	UF_S 12, UF_H 10, $UF_{children}$ 2 RW II to RW I, additional: 10	UF_S 2, UF_A 2.5, UF_H 10 = 50

Compound	3-Carene	Data collection sheet
		"The effects observed happened during gestation, which is a specific period of life, therefore, there is no need for chronic exposure extrapolation. However, an AF of 2 was used to take into account the absence of exposure during the first 5 days of gestation."
Other effects		
Remarks	Values for bicyclic monoterpenes (α- and ß-pinene, 3-carene)	Study according to OECD guideline 414 with (+)-carene, evaluation ongoing (no data for foetal effects yet provided).

AgBB = Ausschuss zur gesundheitlichen Bewertung von Bauprodukten
UFL Used LOAEL; UFH Intraspecies variability; UFA interspecies variability; UFS Used subchronic study; UFD data deficiencies.

Table 20: Fact sheet for 3-carene

Compound	3-Carene C10H16		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	2500
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2022
General information			
CLP-Index No.	4	INDEX	-
EC-No.	5	EINECS	236-719-3 (unspecified)
CAS-No.	6	Chemical Abstract Service number	13466-78-9 (unspecified)
Harmonised CLP classification	7	Human health risk related classification	-
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	136.24 1 ppm = 5.61 mg/m³
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) (2018)
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	Rat, Sprague-Dawley (10 M, 10 F/dose)
Route / type of study	12	Inhalation, oral feed, etc.	Oral (food)
Study length	13	Days, subchronic, chronic, etc.	13 weeks
Exposure duration	14	h/d, d/w	daily
Critical endpoint	15	Effect (s), site of	Behaviour (functional findings): reduced grip strength
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEL (males)
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	4500 ppm in food, (about 282 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)

Compound	3-Carene C10H16		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	Oral-to-inhalation extrapolation	2
Results			
Summary of assessment factors	27	Total Assessment Factor	100 x 1.15
POD/TAF	28	Calculated value [µg/m³ and ppb]	2452 µg/m³ (437 ppb)
Molar adjustment factor	29		
Rounded value	30	[µg/m³]	2500
Additional comments	31		No data available from studies with other animal species
Rationale selection	32		

Data compilation and evaluation for 3-carene is based on a project funded by the German Environment Agency (Voss et al., 2022).

Rationale for critical effects

Bicyclic terpenes in general are rapidly absorbed upon inhalation. Studies with controlled exposure of humans against 3-carenes revealed that 70 % of 3-carene were taken up in the lungs (Sagunski and Heinzow, 2003). In a metabolism study with oral intake of 3-carene in humans, the cumulative excretion of metabolites in urine within 24 h after accounted for 28 % of the oral dose of 3-carene applied (Schmidt, 2015; Schmidt et al., 2015a).

Acute toxicity, irritation, sensitisation

The acute toxicity of 3-carene is low. In an inhalation study with “nose only” exposure of rats, death was observed at 5070 mg/m³ after 4-hour exposure but not at 1050 mg/m³ (ECHA Dissemination, 2021). Short-term (30 min) exposure above 1400 ppm (7800 mg/m³) caused slight sedation or drowsiness but no death in mice (AICIS, 2020). 3-carene causes only mild and temporary irritation of eyes and skin. However, oxidised 3-carene is a skin sensitiser (ECHA Dissemination, 2021).

Studies with humans revealed that high concentrations of 3-carene may cause sensory irritation. Sensory irritating effects were noted by volunteers exposed to 450 mg/m³ 3-carene for two hours.

Eye irritation was about two-fold more marked with 3-carene than with alpha-(+)-pinene (Falk et al., 1991; Falk et al., 1990). No concentration-dependent effects were observed with respect to sensory irritation, pulmonary function, exhaled NO, and eye blink frequency in a study with exposure of humans for two hours against 3.5, 5.0, or 9.5 mg/m³ terpenes (plus other VOC) from pinewood, containing mainly α-pinene (up to 70 %) and 3-carene (up to 28 %) (Gminski et al., 2011).

An RD50 for sensory irritation of 1345 ppm (7532 mg/m³) was obtained for (+)-3-carene in a study with mice (Kasanen et al., 1999). No such data are available for (-)-3-carene. However, studies with (+)- and (-)-α-pinene and (+)- and (-)-β-pinene indicate that the (-)-enantiomers are less irritant than the (+)-enantiomers (Hartwig and MAK-Kommission, 2017).

Repeated dose toxicity

After repeated exposure of humans against a mixture of 280 mg/m³ α-pinene, 30 mg/m³ ß-pinene and 140 mg/m³ 3-carene (overall terpene concentrations 450 mg/m³) three hours/day on four days within two weeks, the bronchoalveolar lavage revealed signs of a weak acute alveolar reaction (Johard et al., 1993).

In a subchronic oral toxicity study following OECD guideline 408, reduced grip strength was observed in female rats after oral exposure to (+)-3-carene at concentrations of 0, 2000, 4500, or 12000 ppm in food for a total of 13 weeks. The effects on grip strength were considered non-adverse in the registration dossier and the NOAEC considered to be 12000 ppm (752 mg/(kg bw x d)), the highest concentration. However, since the effects were outside the background control range and were only partially reversible within the four-week recovery period, adversity cannot be excluded. Thus, within the context of the proposal for an EU-LCI value for 3-carene, the highest concentration in this study will be regarded as a LOAEL (NOAEL: 4500 ppm, by linear extrapolation: about 282 mg/(kg bw x d)).

3-carene was not genotoxic in *in vitro* in assays (following OECD guidelines) with bacteria and mammalian cells (ECHA Dissemination, 2021). *In vivo* data are not available.

Carcinogenicity studies with 3-carene are not available. The available data on genotoxicity and from repeated dose toxicity studies do not provide evidence for concern regarding carcinogenic effects of 3-carene.

A pre-study for an extended one-generation reproductive toxicity study in rats revealed no effects on reproductive performance up to the highest dose of 12000 ppm 3-carene in food (between 639 and 1622 mg/(kg bw x d)). Food intake was lower at ≥ 6000 ppm (314 to 841 mg/(kg bw x d)), probably due to reduced palatability (ECHA Dissemination, 2021). In a prenatal developmental toxicity study according to OECD Guideline 414, pregnant rats showed a low weight gain (-24%) and food intake at 350 mg/(kg bw x d). In a pre-study, pre-implantation losses seemed to be increased at 600 mg/(kg bw x d). No developmental toxicity was observed at 300 and 450 mg/(kg bw x d) (ECHA Dissemination, 2021).

Rationale for starting point

The NOAEL of 282 mg/(kg bw x d) obtained in the subchronic oral (feeding) toxicity study with (+)-3-carene in rats is used as POD for the derivation of an EU-LCI value.

Rationale for assessment factors

The results of toxicokinetic studies with 3-carene in humans indicate that pulmonary uptake by inhalation is about 70 %. After oral intake of 3-carene by humans, 28 % could be recovered as metabolites in urine. Some pulmonary excretion of the parent compound was noted but not quantified. Thus, the default factor of two to account for differences in absorption after oral or inhalation exposure will be considered, and the following assessment factors are used (EC, 2013; ECHA, 2012):

- Route-to-route extrapolation factor: 1.15 m^3/(kg bw x d) (default factor for rats)
- Default factor in case of oral-to-inhalation extrapolation: 2
- 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 282 mg/(kg bw x d) : (1.15 x 2 x 50) = 2452 µg/m^3 for (+)-3-carene.

The proposed EU-LCI value for 3-carene value is based on a NOAEL for systemic effects observed in a study with oral exposure of rats.

Signs of irritation of mucous membranes (eyes and nose) have been noted in humans in a short-term inhalation study with 3-carene at 450 mg /m^3, i.e., at an 180fold higher concentration, indicating that irritation is unlikely at the proposed EU-LCI value. Furthermore, no local effects in the respiratory tract were described in the NTP study (2016) after subchronic inhalation exposure of rats or mice with the structurally similar α-pinene. It is concluded that there is no concern for acute or long-term local respiratory effects of 3-carene at the proposed EU-LCI value.

It should be noted that conventional analytical methods normally applied for the detection of 3-carene in air do not differentiate between both enantiomers, (+)- and (-)-3-carene. Consequently, the value is proposed for (the sum of both isomers of) 3-carene without specification of the enantiomer.

An EU-LCI value of 2500 µg/m^3 is proposed for 3-carene.

For 3-carene and (+)-3-carene, odour thresholds of 10 and 4 mg/m^3, respectively, have been reported. Comparison with similarly determined odour thresholds for α- und β-pinene indicate that the odour thresholds for 3-carene and (+)-3-carene could be somewhat lower than those for α- und β-pinene.

However, much lower odour thresholds of 0.018 ppm (100 µg/m^3) and 0.033 ppm (185 µg/m^3) for α- and β-pinene (enantiomers not specified) were obtained by a sensitive method (Nagata, 2003). No values are reported in Nagata (2003) for 3-carene, but it seems reasonable to assume that odour thresholds much lower than those previously reported are likely. It is concluded that an odour perception cannot be excluded at the proposed EU-LCI value for 3-carene.

It is concluded that an odour perception cannot be excluded at the proposed EU-LCI value for 3-carene.

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4 Toxicological evaluation of "other C_4-C_{13} saturated n- and iso alcohols" as basis for the derivation of an EU-LCI value

4.1 Substance identification

"Other C_4-C_{13} n- and iso-alcohols" within the context of this project refers to primary aliphatic straight or branched (but non-cyclic) alcohols of the specified number of carbon atoms[4]. Up to now, EU-LCI values were derived only for a very few selected n- and iso-alcohols (EC, 2013; EU-LCI Working Group, 2021), i.e. 2-methyl-1-propanol (isobutanol), 2-ethyl-1-hexanol and 1-octanol.

Currently, the LCI Working Group is evaluating the toxicological data base for n-butanol in order to derive an EU-LCI value for this compound (personal communication from the Working Group, 2022). Moreover, a project funded by the German Environment Agency[5] is currently under way in which the toxicological data base for for n- and iso-pentanols (all isomers with primary OH-group) will be evaluated to derive EU-LCI values, if possible. Therefore, within the scope of this project, the focus will be on C_6-C_{13} n- and iso-alcohols which are not covered by current (n-butanol) or shortly starting evaluations (1-pentanols). Data for butanols and pentanols will only be included when providing supportive information in the evaluation of C_6-C_{13} n- and iso-alcohols.

The group of C_6-C_{13} n- and iso-alcohols contains a great many of compounds of which only a few are produced and used as individual substances or in technical mixtures. Commercial products may include several aliphatic alcohol components, with a range of carbon chain lengths present. Composition depends on the route to manufacture and the related feedstocks. Most of the alcohols have linear carbon chains but certain manufacturing processes create branched structures. The technical products contain linear saturated primary non-branched aliphatic alcohols (n-alkanols) with an even number of carbon atoms, while the so-called technical "essentially linear alcohols" are saturated primary alcohols and their saturated mono-branched primary alcohol isomers of corresponding chain length (OECD SIDS, 2007).

The toxicological data base for this wide group of chemicals was compiled and evaluated in a number of reviews and reports (Ad-hoc AG, 2013; AGS, 2017; AGS, 2019; Belsito et al., 2010; Hellwig and Jäckh, 1997; McGinty et al., 2010; Nelson et al., 1989; Nelson et al., 1990; OECD SIDS, 2007; Schultz et al., 2017a; Schultz et al., 2017b; U.S.EPA, 2019; Veenstra et al., 2009). The evaluation within this document is largely based on data reported in these reviews and reports.

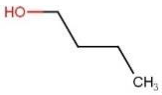
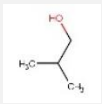
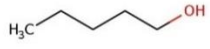
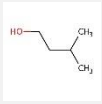
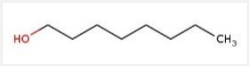
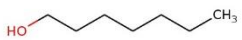
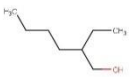
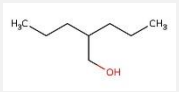
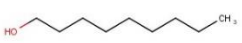
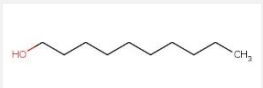
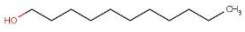
Only few C_4-C_{13} saturated n- and iso-alcohols are frequently or at least occasionally detected in indoor air (Table 23). The data compilation and evaluation within this report focuses on these n- and iso-alcohols that have been detected in indoor air.

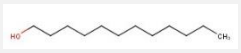
Substance identification data and physicochemical properties of relevant "C_4-C_{13} n- and iso-alcohols" are shown in Table 21 and Table 22.

[4] Under IUPAC nomenclature, the term "*iso-"* should be limited to a methyl group attached to the end of the alkyl group (i.e., 8-methylnonan-1-ol) but here, the term is used in a broader sense including branched-chain **primary alkanols** and mixtures thereof for which the structure may not be further defined or known.

[5] Voss JU, Kaiser E et al. (2022) Toxicological basic data for the derivation of EU LCI values for β-pinene, other terpenes, 1-pentanol (all isomers), 5-chloro-2-methyl-4-isothiazolin-3-one (CIT) and 2-methyl-4-isothiazolin-3-one (MIT)". UBA FKZ 3722 62 205 0, current project.

Table 21: Substance identification of selected "C_4-C_{13} n- and iso-alcohols"*

CAS-No. EU-No. CLP-Index-No.	Systematic name, common name	Sum formula	Structural formula
71-36-3 200-751-6 603-004-00-6	1-Butanol	$C_4H_{10}O$	
78-83-1 201-148-0 603-108-00-1	2-Methylpropan-1-ol (isobutanol)	$C_4H_{10}O$	
71-41-0 200-752-1 603-200-00-1	1-Pentanol	$C_5H_{12}O$	
123-51-3 204-633-5 -	3-Methyl-1-butanol (isoamyl alcohol)	$C_5H_{12}O$	
137-32-6 205-289-9 -	2-Methyl-1-butanol	$C_5H_{12}O$	
112-27-3 203-852-3 603-059-00-6	1-Hexanol	$C_6H_{14}O$	
111-70-6 203-852-3 603-059-00-6	1-Heptanol	$C_7H_{16}O$	
111-87-5 203-917-6 -	1-Octanol	$C_8H_{18}O$	
104-76-7 203-234-3 -	2-Ethyl-1-hexanol	$C_8H_{18}O$	
58175-57-8 611-630-6 -	2-Propyl-1-pentanol	$C_8H_{18}O$	
143-08-8 205-583-7 -	1-Nonanol	$C_9H_{20}O$	
112-30-1 203-959-9 -	1-Decanol	$C_{10}H_{22}O$	
112-42-5 203-970-5 -	1-Undecanol	$C_{11}H_{24}O$	

CAS-No. EU-No. CLP-Index-No.	Systematic name, common name	Sum formula	Structural formula
112-53-8 203-982-0 -	1-Dodecanol	$C_{12}H_{26}O$	
112-70-9 203-998-8 -	1-Tridecanol	$C_{13}H_{28}O$	

*: Data from AGS (2019) and ECHA search data base (https://echa.europa.eu). Table includes C4-C13- n- and iso-alcohols which have been detected in indoor air (Hofmann and Plieninger, 2008; Schulz et al., 2010) plus C_{11} to C13-n-alcohols

4.2 Substance properties and uses

The lower members of this group of alcohols are liquids at room temperature, the highest members (≥ C_{12}) are low melting waxy solids. The solubility in water and the vapour pressure decrease with increasing molar mass, while the octanol-water partition coefficient and the boiling point increase in that order. Alcohols within this group often have an unpleasant odour which can be detected at very low concentrations (Table 26).

Table 22: Physicochemical properties of selected "C_4-C_{13} n- and iso-alcohols"*

Compound	Molar mass (g/mol)	Mp. (° C)	Bp. (° C)	Vapour pressure (hPa) (at 25 °C)	Conversion 1 ppm = x mg/m³ (23 °C)	log kow	Solubility in water (mg/l) at 25 °C
1-Butanol	74.12	-90	119	10@20 °C	3.05	1	66000@20 °C
2-Methylpropan-1-ol (isobutanol)	74.1	< -90	108	<16@20 °C	3.05	1	70000@20°C
1-Pentanol	88.2	-78.6	138	2.0@20 °C	3.63	1.51	21000@20 °C
3-Methyl-1-butanol (isoamyl alcohol)	88.2	-147	130.7	3@20 °C	3.63	1.35	26400
2-Methyl-1-butanol	88.2	< -95	128	2.7@20 °C	3.63	1.29	30000
1-Hexanol	102.2	-44 to -51	158	1.22	4.21	2.03	5900@20 °C
1-Heptanol	116.2	-34	176	0.28	4.78	2.57	1313@20 °C
1-Octanol	130.2	15.5 to -17	194	0.10	5.36	3.15	551
2-Ethyl-1-hexanol	130.2	-89	185	1.2	5.36	2.9	900@20 °C
2-Propyl-1-pentanol	130.2	No data	No data	No data	5.36	No data	No data
1-Nonanol	144.3	-5	194 to 213	0.03	5.94	3.77	128@20 °C
1-Decanol	158.3	6.4	229	0.0113	6.51	4.57	39.5

Compound	Molar mass (g/mol)	Mp. (° C)	Bp. (° C)	Vapour pressure (hPa) (at 25 °C)	Conversion 1 ppm = x mg/m³ (23 °C)	log kow	Solubility in water (mg/l) at 25 °C
2-Propylheptan-ol	158.3	-116.6	218.4	0.02	6.51	4.1	82@20 °C
1-Undecanol	172.3	14.3	245	0.0039	7.09	4.72	8@20 °C
1-Dodecanol	186.3	22.6 to 24	264.6	0.0011	7.67	5.36	1.93@20 °C
1-Tridecanol	200.4	32 to 33	233.3	0.00057	8.25	5.51	0.38@20 °C

*: Data compiled from (AGS, 2019; NLM, 2022; OECD SIDS, 2007) and the REACH registration dossiers identified via the ECHA search data base (https://echa.europa.eu).

Most of the alcohols listed in Table 21 and Table 22 are large-scale industrial products with tonnage band in the European Union between ≥ 100 to < 1 000 tonnes/year (e.g., nonan-1-ol), >= 10 000 to 100 000 tons/year (e.g., octan-1-ol and hexan-1-ol), and ≥ 100 000 to 1 000 000 tons/year (e.g., for 2-ethyl-1-hexanol) (ECHA, 2022).

Table 23: C_4-C_{13} n- and iso-alkanols: occurrence in indoor air

Substance (CAS No.)[1, #]	No. of determinations	N > LoD (%)	Median (µg/m³)	P95 (µg/m³)	Maximum (µg/m³)
n-Butanol (71-36-3)	2284 555*	89.3 98*	11.0 5.4*	73.9 17.6*	3422 71.6*
Isobutanol (78-83-1)	1277 555*	60.8 9*	3.0 < 3.5*	41.9 4.9*	360 40.7*
1-Pentanol (71-41-0)	462	60.6	1.8	9.3	39
Isoamyl alcohol (3-methyl-1-butanol) (123-51-3)	729	4.7	0.3	0.7	3
2-Methyl-1-butanol (137-32-6)	89	16.9	0.1	0.5	3
1-Hexanol (111-27-3)	445	20.9	0.4	2.5	13
1-Heptanol (111-70-6)	160	17.5	0.5	2.2	11
1-Octanol (111-87-5)	467	13.3	0.5	2.0	42
2-Ethyl-1-hexanol (104-76-7)	2283 555*	64 85*	2.4 2.6*	20.5 11.4*	3301 67.0*
2-Propyl-1-pentanol (58175-57-8)	32	0	0.5	0.5	1.0
1-Nonanol (143-08-8)	155	3.9	0.5	0.5	35
1-Decanol (112-30-1)	403	2.5	0.5	0.5	3

1: Compounds were selected based on reported use in technical or consumer products and on availability of toxicological data in reviews and registration dossiers (see also Table 27). #: All values from Hofmann and Plieninger (2008) except those marked by * (Schulz et al., 2010).

These aliphatic alcohols have widespread and dispersive use in several industrial sectors and find many commercial uses, including processing aids and additives in paper, plastics, textile and leather industry. Uses in consumer products include household and cosmetic products (OECD SIDS, 2007).

Many of the C4-C13 n- and -iso-alcohols also occur in nature, e.g. in plants or as products of microbial fermentation reactions (JECFA, 2004; Mudge, 2005; Mudge et al., 2008).

2-Ethyl-1-hexanol may be released from plastic materials, e.g. floor coverings and carpets. Microbial or abiotic hydrolysis of still widely found plastics containing diethylhexyl phthalate (DEHP) may be an important source of 2-ethyl-1-hexanol in indoor air (Ad-hoc AG, 2013).

During recent years, di-2-propylheptylphthalate (DPHP) has been increasingly used as a substitute for other phthalate esters used as plasticizers, e. g. in soft-PVC for roof coverings, cable sheaths or car interiors (HBM-Kommission, 2015). Although no studies were identified in which 2-propyl-1-heptanol was quantified in indoor air, it may be expected that, analogously to the liberation of 2-ethyl-1-hexanol, this substance may be liberated from such products.

4.3 Exposure

4.3.1 Indoor air

A number of C_4-C_{13} n- and iso-alkanols are frequently detected in indoor air. As an example, data compiled by AGÖF (Hofmann and Plieninger, 2008) and from the German Environmental Survey (GerES), a representative population study to determine the exposure of Germany's general population to pollutants (Schulz et al., 2010), are summarised in Table 23. Based on the frequency of detection in investigations, the following groups can be formed: n- and isobutanol, 1-pentanol and 2-ethyl-1-hexanol are most frequently detected (about 60 – 98 %), followed by 2-methylbutanol, 1-hexanol, 1-heptanol and 1-octanol (> 10 % to about 20 %). The remaining compounds (isoamyl alcohol and the higher alcohols) are rarely or only in few samples detected; no data were presented in these two publications for undecanol, dodecanol and tridecanol. It is likely that the low volatility of the alcohols with higher number of carbon atoms limits their occurrence in air.

The median values of the compounds listed in Table 23 are mostly in the range below 10 µg/m³, with 95. percentiles mostly also below 10 µg/m³ and only somewhat higher (below 100 µg/m³) for n- and isobutanol and 2-ethyl-1-hexanol. However, very high maximum levels exceeding 3000 µg/m³ are reported for n-butanol and 2-ethyl-1-hexanol, probably from complaint-related measurements.

4.3.2 Other sources

A number of n- and iso-alcohols occur naturally in foods and beverages (fruit drinks, alcoholic beverages) or are used as flavour compounds in foods. Oral exposure is therefore to be expected for these compounds. Dermal exposure is also expected from the use in personal care products and cosmetics (JECFA, 1999; Veenstra et al., 2009).

4.4 Toxicokinetics

Aliphatic alcohols are expected to be absorbed by all common routes of exposure (OECD SIDS, 2007).

After oral administration of 2-ethyl-1-hexanol to rats, 69 – 75 % of the applied dose was excreted in urine within 96 hours. About 13 – 15 % of the dose was excreted in the faeces, about the same amount was exhaled. More than 50% of the dose was excreted within 24 hours (Belsito et al., 2010).

Based on comparative *in vitro* skin permeation data and dermal absorption studies in hairless mice, aliphatic alcohols show an inverse relationship between absorption potential and chain length with the shorter chain alcohols having a higher absorption potential than the longer chain alcohols consistent with the established relationship between skin penetration and physicochemical properties (Veenstra et al., 2009). A similar relationship is expected for orally administered aliphatic

alcohols, with shorter chain aliphatic alcohols having a higher absorption potential than longer chain alcohols (OECD SIDS, 2007).

No information was available whether a similar relationship was observed at inhalation exposure. Respiratory uptake of isoamyl alcohol was investigated in four healthy volunteers who were exposed against 25 – 200 ppm for 10 min. The mean uptake for the last 5 min of exposure was 63 % (Belsito et al., 2010).

A small fraction of the aliphatic alcohols may be eliminated unchanged or as the glucuronide conjugate, but most of the alcohol is rapidly metabolised. The initial step in the mammalian metabolism of primary alcohols is the oxidation to the corresponding carboxylic acid, with the corresponding aldehyde being a transient intermediate. These carboxylic acids are susceptible to further degradation via acyl-CoA intermediates by the mitochondrial β-oxidation process. This mechanism removes C2 units in a stepwise process and linear acids are more efficient in this process than the corresponding branched acids (OECD SIDS, 2007).

For decan-1-ol it is reported that 65 % of the ^{14}C-labelled dose was expired via breath (most probably as CO_2) (AGS, 2019).

Typically, the presence of a side chain does not terminate the oxidation process of alkanols. However, in most cases, it alters it. The position and size of the alkyl substituent plays a role in metabolism with degradation to CO_2 decreasing and glucuronidation increasing with branching and increasing chain length (Schultz et al., 2017a).

Alkyl acids formed during metabolic transformation of branched alkanols have their own set of metabolic pathways. Acids with a methyl substituent located at an even-numbered carbon (e.g., 2-methyl pentanoic acid or 4-methyl decanoic acid) are extensively metabolised to CO_2 via β-oxidative cleavage in the fatty acid pathway. If the methyl group is located at the 3-position, β-oxidation is inhibited and omega-oxidation predominates, primarily leading to polar, acidic metabolites capable of being further oxidised or conjugated and excreted in the urine. As chain length and lipophilicity increase, omega-oxidation competes with β-oxidative cleavage. Methyl-substituted acids (e.g., 3- methylnonanoic acid) are, to some extent, omega-oxidized in animals to form diacids which can be detected in the urine (Schultz et al., 2017a).

The presence of an ethyl or propyl substituent at the alpha position, such as in 2-ethyl-1-hexanol, inhibits beta-oxidation (ECHA Dissemination, 2022a). An alternative metabolic pathway for aliphatic acids exists through microsomal degradation via omega-or omega-1 oxidation followed by β-oxidation. This mechanism provides an efficient stepwise chain-shortening pathway for branched aliphatic acids. The acids formed from the longer chained aliphatic alcohols can also enter the lipid biosynthesis and may be incorporated in phospholipids and neutral lipids (OECD SIDS, 2007).

In a study with rats exposed orally or dermally with 2-ethyl-1-hexanol, metabolites in urine included 2-ethylhexanoic acid, 5-hydroxy-2-ethylhexanoic acid, 5-keto-2-ethylhexanoic acid, 2-ethyl-1,6-hexanedioic acid and 6-hydroxy-2-ethylhexanoic acid, mainly as their glucuronides, and expired carbon dioxide. One to three percent 2-ethyl-1-hexanol was excreted unchanged or as glucuronide (Belsito et al., 2010). Overall, 6 – 7 % were recovered as CO_2 8 – 9 % in faeces and 80 – 82 % in urine (ECHA Dissemination, 2022a). Metabolic saturation was seen with 500 mg/kg bw applied. These data confirm the above-described metabolic pathways. Species-specific differences were observed between rats and rabbits as the main metabolite in rabbits was the glucuronide of 2-ethylhexanoic acid (Belsito et al., 2010).

In summary, long chained alcohols are generally highly efficiently metabolised and there is limited potential for retention or bioaccumulation for the parent alcohols and their biotransformation products (OECD SIDS, 2007).

4.5 Health effects

4.5.1 Acute toxicity, sensory irritation and local effects

Overall, the category of long-chain alcohols is of low acute toxicity upon oral, inhalation, or dermal application (AGS, 2019; Belsito et al., 2010; OECD SIDS, 2007; Veenstra et al., 2009). Similar conclusions apply to branched-chain alcohols (Belsito et al., 2010).

Inhalation of vapours of C_6-C_{22} n-alcohols at levels up to the saturated vapour pressure is unlikely to be associated with significant toxicity (OECD SIDS, 2007). Transient signs of CNS depression may be noted at these high concentrations (see also Table 24). E.g., 1-hour exposure of rats to an atmosphere containing 21 000 mg/m³ of 1-hexanol (about 5000 ppm, vapour and aerosol, nominal concentration) led to hypoactivity and/or ataxia, lethargy and prostration. The animals recovered within 2 hours of removal from the exposure chamber and appeared normal throughout the 14-days post-exposure observation period (ECHA Dissemination, 2022b).

Inhalation exposure of rats to 2-ethyl-1-hexanol for 4 h to 890 or 5300 mg /m³ (vapour/aerosol mixture) led to no abnormal findings at the lower concentration during or after exposure. At the high concentration, one male and one female died during exposure and all other animals died within 2 h after exposure. The animals showed signs of mucous membrane irritation (respiratory distress, red lacrimation, nasal discharge and closed eyes) (Ad-hoc AG, 2013). Slight to moderate effects were also observed during a 6-hour exposure to 1217 mg/m³ (Table 24) (Scala and Burtis, 1973).

Liquid n- and iso-alcohols are irritating to skin and eyes. The effect decreases with increasing molar mass and is most pronounced for C_6 to C_{10} alcohols (AGS, 2019).

Sensory irritation

The most relevant effect of exposure to vapours of higher n- and iso-alcohols in air is sensory irritation to eyes and mucous membranes of the respiratory tract (AGS, 2019; Belsito et al., 2010).

Human data

Experiments with very brief exposure of humans for a few seconds to **1-pentanol** indicated a threshold for nasal irritation of about 2000 ppm (7260 mg/m³). Similar studies with **1-hexanol** indicated a threshold for eye irritation in the order of 400 ppm (1680 mg/m³) and of about 1000 ppm (4200 mg/m³) for nasal irritation and of 200 ppm (960 mg/m³) as a threshold for nasal irritation for **1-heptanol**. Other studies with short-term exposure to **1-octanol** revealed thresholds for eye irritation of 40 ppm (214 mg/m³) and for nasal irritation of 56.2 ppm (300 mg/m³) and 100 ppm (536 mg/m³) (the nasal threshold concentration was too high to be determined in a third study). For **2-ethyl-1-hexanol** a threshold for nasal irritation of 66.6 ppm was reported (357 mg/m³) (AGS, 2019).

These data indicate that the thresholds for sensory irritation decrease with increasing chain length and that eye irritation is a more sensitive indicator than nasal irritation. Also, the nasal threshold for 2-ethyl-1-hexanol fell within the range of its structural isomer 1-octanol indicating that branching of the carbon chain may not lead to gross effects.

The reported values were determined in studies with very brief exposure. Generally, exposure to longer time frames may lead to a marked drop of the irritation threshold (AGS, 2019). Studies with such brief exposure therefore are not suitable to derive concentration values protective against sensory irritation at longer exposure.

No eye irritation was reported in a study in which 26 volunteers were exposed with 4.5 ppm (29.3 mg/m³) **1-decanol** vapour for two to three hours, but experimental details are lacking (AGS, 2019).

Sensory irritation was studied in clinical studies with exposure of humans to 2-ethyl-1-hexanol (Blaszkewicz et al., 2007; DFG, 2012; Ernstgård et al., 2010; Kiesswetter et al., 2005; van Thriel et al., 2007; van Thriel et al., 2005; van Thriel et al., 2003b). Data from a similar study with 1-octanol are also available (Haumann et al., 2003; Seeber et al., 2002; van Thriel et al., 2003a; van Thriel et al., 2003b).

In the studies of van Thriel et al. and Seeber et al. irritancy and annoyance were studied in groups of volunteers. In a study with **1-octanol**, 24 male students were exposed to two concentrations (0.1 and 6.4 ppm). The lower concentration was in the order of the odour threshold and was kept constant during the exposure. At the high exposure concentration, the concentration fluctuated between 0.4 and 12.5 ppm with a mean concentration of 6.4 ppm. In a crossover design, each subject was exposed for 4 hours to the conditions. 12 subjects reported enhanced chemical sensitivity; the other 12 were age-matched controls. At the onset and end of the exposures neurobehavioral tests were administered and symptoms were rated. All results are based on self-reported ratings of effects and perceptions. The authors aimed to detect the perception of irritation, odour and annoyance as independent factors, independent of the personal attitude. For both concentrations, the annoyance ratings increased during the exposure, but did not show a dose-response relation. The subjects reported olfactory symptoms during the exposure to both 1-octanol concentrations. Reports of sensory irritation were elevated exclusively during the high 1-octanol exposure. 'Irritation' was a combined score for eye and nasal irritation, and the reported level was rather low (baseline corrected), max. 10 % of the 100 % scale range for irritation at the beginning of the 'high' exposure. Among the subjects with self-reported enhanced chemical sensitivity both 1-octanol concentrations were associated with a stronger increase in annoyance, and lower detection rates were observed in a neurobehavioral test (van Thriel et al., 2003a; van Thriel et al., 2003b).

The studies design and results with **2-ethyl-1-hecanol** were summarised by Ad-hoc AG (2013). 22 to 24 male subjects were exposed "whole body" an average concentration of 8 mg/m³ (kept nearly constant throughout exposure) or 54 or 108 mg/m³ (constant or variable concentration course) for 4 h. Half of the participants had a self-reported multiple chemical sensitivity. The variable concentration curve started at the maximum and decreased to the minimum within 30 min and then increased again, resulting in 5 exposure peaks (exposure range at an average of 8 mg/m³: 7.5 - 8.6 mg/m³; at 54 mg/m³: 7 - 110 mg/m³; at 108 mg/m³: 10 - 230 mg/m³). All subjects were exposed to all concentrations, with the sequence varying. The following parameters were recorded: Annoyance experience, sensory irritation of eyes and nose, odour, eyelid closure frequency, nasal air resistance (rhinomanometry; method for measuring nasal irritation), as well as the content of the neuropeptide substance P in the lavage fluid as an indicator of nasal chemosensory irritation. The nasal irritation, eye irritation and olfactory experience were assessed on the one hand with an extended methodology of the "Swedish Performance Evaluation System" (SPES; linear scale) to record the acute symptoms and on the other hand by means of the "Labeled Magnitude Scale" (LMS) to record the intensity.

Observed effects at constant course of exposure were: statistically significantly increased eye blinking frequency at 108 mg/m³ compared with 8 mg/m³ (factor approx. 1.5) and 54 mg/m³ (factor approx. 1.2); eye blinking frequency at 54 mg/m³ not significantly different from 8 mg/m³; nasal and eye irritation increased "moderately" at 54 mg/m³ and "strongly" at 108 mg/m³, compared with 8 mg/m³ ("weak"). There was also a dose-dependent odour perception with only slight adaptation over time. Overall, a higher assessment level was recorded in persons with chemical sensitivity according to the SPES method, but there were no differences in the described intensity described by the LMS method. Effects at variable exposure were an increased eyelid closure frequency (2- or 3-fold at peak concentrations of 108 mg/m³ or 216 mg/m³) with no differences between persons with and without chemical sensitivity, a decreased nasal flow after exposure decreased compared to the value before

exposure (statistically significant at 108 mg/m³). The concentration of substance P in the nasal lavage fluid increased after exposure compared to before at 54 and 108 mg/m³ (statistically significant only at 108 mg/m³). Nasal and eye irritation increased at 54 and 108 mg/m³ ("moderate" and "strong") compared with 8 mg/m³ ("weak") with no differences between persons with and without chemical sensitivity. There was also a concentration-dependent odour and annoyance perception in all groups with only slight adaptation to the odour over time (Kiesswetter et al., 2005; van Thriel et al., 2005).

In a further study of this group of investigators, using the same exposure scheme as described above, a total of 46 male subjects (19 of them with self-reported chemical sensitivity; 24 and 22 subjects in total exposed to variable and constant exposure concentrations, respectively) were exposed to 8, 54 or 108 mg **2-ethyl-1-hexanol**/m³. The exposure had no effect on neurobehavioral tests, except for the results of an attention test in which the subjects with chemical sensitivity showed decreased performance with increasing concentration. Annoyance, eye and nose irritation increased in a concentration-dependent manner. Annoyance was reported as strong or very strong at 54 or 108 mg/m³, but the intensity of eye and nose irritation was described as weak, moderate or strong at 8, 54 or 108 mg /m³ (similar intensity at variable and constant concentration levels). Subjects with chemical sensitivity experienced the irritant effect on eyes and nose more strongly than the control group at constant concentrations, but less strongly at variable concentrations (Blaszkewicz et al., 2007; van Thriel et al., 2007). The results of these studies with 2-ethyl-1-hexanol indicate that the lowest concentration of 8 mg/m³ (1.5 ppm) can be considered as a NOAEL.

The results of a further study from another group (Ernstgård et al., 2010) are in line with the described results above. 16 males and 14 females were in random order exposed to 1 mg/m³ **2-ethyl-1-hexanol** vapours or to clean air (control exposure) in an exposure chamber during 2 h at rest. The subjects performed symptom ratings on Visual Analog Scales. During exposure to 2-ethyl-1-hexanol subjective ratings of smell and eye discomfort were minimally but significantly increased. Ratings of nasal irritation, throat irritation, headache, dyspnoea, fatigue, dizziness, nausea, and intoxication were not significantly affected. Objective measurements showed no exposure-related effects on eye blinking frequency, eye break-up time, vital staining of the eye, nasal lavage biomarkers, transfer tests, spirometric and rhinometric parameters. No differences in response were seen between sexes or between atopic and non-atopic subjects (Ernstgård et al., 2010).

Animal data

Mice, rats, and guinea pigs (10/species) were exposed to about saturated vapour concentrations of various alcohols (Table 24). The following alcohols were: hexanol (typically 44 % 1-hexanol, 53 % methyl-1-pentanols, 3 % 2-ethyl-1-butanol), 2-ethylhexanol (typically 99.5 % 2-ethyl-1-hexanol), isooctanol (typically 70 – 80 % dimethyl-1-hexanols, 10 – 20 % methyl-1-heptanols, 5 – 10 % other homologous primary alcohols, isononanol (typically 75 – 85 % dimethyl-1-heptanols, 5 – 10 % methyl-1-octanols, 10 – 20 % other homologous primary alcohols), decanol (typically 95 % trimethyl-1-heptanols, 5 % other homologous primary alcohols), tridecanol (mainly tetramethyl-1-nonanols) (Scala and Burtis, 1973).

Local irritation from the alcohol vapour was seen to a variable extent. This irritation involved the mucous membranes of the eyes, nose, throat, and respiratory passages and was manifest as blinking, lacrimation, preening, nasal discharge, salivation, gasping, and chewing movements. The effect was greatest with hexyl and 2-ethylhexyl alcohols and least with tridecyl alcohol. In each case the responses were temporary, and all animals had recovered within 1 hour after termination of exposure (Scala and Burtis, 1973).

Table 24: Acute toxicity and irritation from 6-hour vapour exposure of animals (for explanation, see text) (Scala and Burtis, 1973)

Substance	Nominal concentration in ppm* (mg/m³)	Irritation	Systemic effects
Hexanol	1060 (4463)	Moderate	Questionable
Isooctanol	200 (1072)	Slight to moderate	None
2-Ethyl-1-hexanol	227 (1217)	Moderate	Slight to moderate
Decanol	95 (618)	Slight to moderate	None
Tridecanol	12 (100)	Slight	None

*Calculated from net loss of substances from bubblers and air flow, no analytical determination.

As a measure of sensory irritation in the respiratory tract, RD values for a number of alcohols were determined in mice; similarly, RD0-values were calculated which represent calculated thresholds for receptor binding of sensory irritants (Table 25). Due to differences in the experimental protocols (exposure time may vary between 5 and 15 min, and different strains of mice may not react identically), the values obtained in different experiments vary to a considerable extent. Nevertheless, the data indicate a trend that the RD50 values decrease, i. e. the sensory irritation potency increases with increasing chain length. The RD50 value for 1-hexanol are about four- to fivefold higher than for the C_8- alcohols 1-octanol and 2-ethyl-1-hexanol. No values were available for higher alcohols with nine carbon atoms or more. However, the vapour pressure and thus the saturated vapour concentration sharply decrease for these alcohols more and more limiting the exposure to these compounds in air.

Signs of systemic toxicity were weak and consisted primarily of CNS depression. This effect was most pronounced for 2-ethyl-1-hexanol. All acute effects cleared rapidly after cessation of exposure. Gross necropsy findings were confined to slight lung congestion in animals exposed to hexyl alcohol and areas of slight haemorrhage in animals exposed to 2-ethylhexyl alcohol. No deaths occurred during the exposure or within the 14 days postexposure period (Scala and Burtis, 1973).

Table 25: Vapour pressure and RD values for primary C_4 – C_{13} alkanols (AGS, 2019; Alarie, 2015; Bos et al., 1992; Kane et al., 1980; Muller and Greff, 1984)

Substance or mixture	Vapour pressure (hPa) at ambient temperatures	Calculated maximum vapour in ppm (mg/m³ at 23 °C)	RD50 (ppm)	RD0 (ppm)
n-Butanol	10 (20 °C)*	9870 (30000)	3870 – 35670 (1268 – 11696)	
Pentan-1-ol	2.04 (20 °C)*	2014 (7300)	607 (810) 4039 3000	120
Isopentanol (3-methyl-butan-1-ol, isoamyl alcohol)	3 (20 °C)*	2960 (10740)	4452 729	
Hexan-1-ol	1.3 (20 °C)	1280 (5380)	(200) 220 239	
Heptan-1-ol	0.7 (20 °C)	690 (3300)	98 770	28
Octan-1-ol	0.1 (25 °C)	100 (536)	48 47	
2-Ethylhexan-1-ol	0.93 (20 °C)* 0.3 (20 °C)+	918 (4920) 296 (1590)	45 44	
Nonan-1-ol	0.017 (20 °C)	17 (101)		
Nonanol, branched and linear	0.017 – 0.345 (20 - 50 °C)	17 – 340 (101 – 2020)		
Decan-1-ol	0.0113 (25 °C)	11 (71.6)		
Decanol, branched and linear	0.005 – 0.098 (20 - 50 °C)	5 – 97 (0.45 – 8.82)		
Undecanol, branched and linear	0.05 (20 – 50 °C)	49 (347)		
Alkanols, C12-C13	0.05 (20 – 50 °C)	49		
Isotridecanol	0.00078 (20 °C)	0.7 (5.77)		

* from ECHA Disseminations (ECHA, 2022) or AGS (2019); + (Ad-hoc AG, 2013)

4.5.2 Repeated dose toxicity

Linear alcohols

No inhalations studies are available with repeated exposure of animals and sufficient clinical chemical, haematological and histopathological evaluations according to current standards (AGS, 2019).

In a study following OECD guideline 408, rats were exposed orally (gavage) to 1-pentanol for 90 days. No adverse effects were noted up to the highest dose (NOEL 1000 mg/(kg bw x d)) (Schultz et al., 2017b).

Rats exposed to 1-hexanol via the diet for 13 weeks showed no signs of significant toxicity when administered at nominal concentrations up to 1 – 6 % (equivalent to 1127 mg/(kg bw x d)). Examination of testes and the ovaries did not show any abnormalities (OECD SIDS, 2007).

Dogs exposed to 1000 mg/(kg bw x d) 1-hexanol in capsules suffered from severe local irritation with severe inflammation of the upper gastro-intestinal tract and transient but marked CNS effects (ataxia, tremors and narcosis). Mortality occurred due to aspiration while the animals were in a narcotic state. Other groups of dogs which received 1-hexanol incorporated in the daily ration at nominal concentrations of 0 (control), 0.5 or 1.0 % showed local irritation of the gastro-intestinal tract in the 1.0 % dose group, but no adverse systemic effects were observed in these animals (OECD SIDS, 2007).

In a combined repeated dose and reproductive/ developmental toxicity screening test (OECD guideline 422) with rats exposed orally to 1-heptanol, no treatment-related effects were noted up to the highest dose of 1000 mg/(kg bw x d) (Schultz et al., 2017b).

In a developmental toxicity study administration of 1-octanol by daily gavage of doses in the range 130 - 1300 mg/kg to pregnant rats caused dose-related clinical signs of toxicity, including nasal discharge, pneumonia, and signs consistent with slight, transient CNS depression at levels of 650, 975 and 1300 mg/kg/day (NOAEL 130 mg/(kg bw x d)) (OECD SIDS, 2007).

1-Dodecanol was tested in rats in a combined repeated-dose and reproductive / developmental toxicity screen. Animals received dietary concentrations of 1500, 7500 or 30000 ppm during all phases in the production of a single generation. The NOAEL was 30000 ppm (2000 mg/(kg bw x d), the highest dose tested (OECD SIDS, 2007).

In summary, linear aliphatic alcohols are of a low order of toxicity upon repeated exposure. Lower alcohols caused local irritation at the site of first contact and induced signs of CNS depression and respiratory effects when administered at very high dose levels as a bolus dose (OECD SIDS, 2007).

Branched-chain alcohols

Three repeated dose oral toxicity studies were done with isoamyl alcohol. In a 90-day study according to OECD TG 408, isoamyl alcohol was administered in the drinking water in concentrations of 0, 1000 ppm (about 80 mg/kg/d), 4000 ppm (about 340 mg/kg/d), and 16000 ppm (about 1250 mg/ kg/d). The NOAEL of isoamyl alcohol was concluded to be 340 mg/(kg bw x d) in males and 1250 mg/(kg bw x d) in females (Belsito et al., 2010).

In a 17-week toxicity study with gavage exposure of rats to doses of 0 (vehicle), 150, 500, or 1000 mg/(kg bw x d), the only observed effect was a statistically significant reduced body weight in males at the highest dose level. The NOAEL was 500 mg/(kg bw x d) for males and 1000 mg/(kg bw x d) for females (Belsito et al., 2010).

No treatment-related effects were seen when Wistar rats received isoamyl alcohol as a 2 % solution in drinking water (about 2000 mg/(kg bw x d)) for 56 weeks (Belsito et al., 2010).

Inhalation exposure of rats with 0, 15, 40, or 120 ppm 2-ethyl-1-hexanol (0, 80, 215, 640 mg/m³) for 6 h/d, 5 d/week, 90 days caused no local effects in the respiratory tract or systemic effects (NOAEL 640 mg/m³). The highest concentration represented the maximum achievable vapour concentration at room temperature. (AGS, 2019; Belsito et al., 2010).

2-Ethyl- 1-hexanol was administered by gavage to rats and mice as an aqueous solution (0, 25, 125, 250, or 500 mg/(kg bw x d)) for 13 weeks. Histopathology was undertaken on tissues recommended in US EPA guidelines. The NOAEL was 125 mg/(kg bw x d) for rats and mice. In a carcinogenicity study 2-ethyl- 1-hexanol was given to rats and mice by gavage 5 d/week at doses of 0, 50, 150, 500 mg/(kg bw x d) for two years (rats) or 0, 50, 200, 750 mg/(kg bw x d) for 18 months (mice). The NOAEL for systemic toxicity for mice was 200 mg/kg body weight/day. In rats, the NOAEL for systemic toxicity was 50 mg/kg body weight/day (Belsito et al., 2010).

A subchronic oral toxicity study according to OECD guideline 408 was conducted with 2-propyl-1-heptanol (ECHA Dissemination, 2020). The test substance was administered daily to rats by gavage at doses of 0, 30, 150 or 600 mg/(kg bw x d) for 3 months. Controls received vehicle (Cremophor® EL) or water (two control groups). Increased liver weights, diffuse hypertrophy and loss of fatty infiltration of the liver cells was observed, accompanied by an increase in cyanide-insensitive palmitoyl-CoA-oxidation in the serum, which is probably caused by hepatic peroxisome proliferation. Effects on the thyroid gland were considered to be a rat specific adaption. Treatment-related decreases in platelet counts, increases in albumin and decreases in globulin were also seen. The disturbance in protein metabolism was considered to be test substance-related, as were changes in urinary parameters. The changes were seen as indicative signs of a mild nephrotoxic potential. Test substance-related effects were seen at 600 mg/(kg bw x d) in both sexes and at 150 mg/(kg bw x d) in females only. Considering the rodent specific effects observed in the mid dose, i.e. peroxisomal proliferation, the NOAEL relevant for human hazard was set at 150 mg/(kg bw x d) (ECHA Dissemination, 2020).

4.5.3 Genotoxicity and carcinogenicity

Genotoxicity

In vitro genotoxicity tests with a number of individual long-chain alcohols (C_4-C_{22}) and mixtures were performed with bacteria (Ames test) and mammalian cells (assays for mutations, chromosomal aberrations, and micronuclei). These data show a consistent lack of mutagenic activity across the whole range of linear alcohols. In addition to these *in vitro* results, 1-dodecanol was also negative in an *in vivo* mouse bone marrow micronucleus test (AGS, 2019; OECD SIDS, 2007).

The industrially important branched chain primary alcohol 2-ethyl-1-hexanol was not genotoxic in a comprehensive data set covering *in vitro* (bacterial and mammalian cell gene mutation assays, a chromosomal aberration and an Unscheduled DNA Synthesis [UDS] assay) and *in vivo* assays (mouse micronucleus and a dominant lethal test) (OECD SIDS, 2007). Its structural isomer 2-propyl-1-heptanol was not mutagenic *in vitro* in bacteria and mammalian cells (HPRT-assay in CHO cells) (ECHA Dissemination, 2020). Other branched-chain primary alcohols as 3,5,5-trimethyl-1-hexanol, isotridecan-1-ol (isomeric mixture), 2-methyl- and 3-methyl-1-butanol (isoamyl alcohol) were also not genotoxic in the corresponding *in vitro* or *in vivo* tests performed with these substances (Belsito et al., 2010).

In summary, it is concluded that C_6-C_{22} linear and branched chain saturated primary alcohols do not have a genotoxic potential (Belsito et al., 2010; OECD SIDS, 2007; Veenstra et al., 2009).

Carcinogenicity

There are no data available for the category of long straight-chain alcohols reporting in detail about carcinogenicity studies according to current testing standards. Several of the linear alcohols have been tested in experimental investigations studying the potential for initiation, promotion or co-carcinogenicity. However, as a rule these data have a low reliability and suffer from significant shortcomings regarding, among others, the reporting details and a lack of control of confounders (e.g. local irritation) (OECD SIDS, 2007).

Dermal administration of 200 mg decan-1-ol /(kg bw x d) after intraperitoneal initiation with 7,12-dimethylbenz[a]anthracene showed a tumour-promoting effect at the skin. Decan-1-ol also caused severe irritation at the application site. With prior initiation, papillomas developed in three of 30 mice, which turned into squamous cell carcinomas in two animals. A similar, but weaker effect was overserved with dodecan-1-ol. Some evidence for a co-carcinogenic effect of dodecan-1-ol were also overserved in another study with mice when the alcohol was co-administered with benzo[a]pyrene (AGS, 2019).

Without initiation with 7,12-dimethylbenz[a]anthracene, hexanol-1, 1-octanol, 1-decanol and 1-dodecanol did not induce skin tumours in one or more mouse skin painting studies using applications 2 - 3 times weekly for periods up to 60 -70 weeks (AGS, 2019; OECD SIDS, 2007).

In screening studies for lung adenomas, A/He mice received intraperitoneally 100 or 500 mg /kg bw octan-1-ol or dodecan-1-ol, respectively, three times per week for a total of 8 weeks. The studies were terminated 24 weeks after the first application. No increase in lung tumour rate was observed (AGS, 2019).

AGS concluded that the predominantly weak cocarcinogenic or tumour-promoting effect on mouse skin observed with long-chain alcohols was accompanied in each case by substance-related irritant effects on the skin. Such skin tumours, which are caused by non-specific irritant effects and are only observed at comparatively high doses or concentrations, are not relevant for humans (AGS, 2019).

2-ethyl-1-hexanol was tested in a carcinogenicity study with male and female rats and mice. The animals received 2-ethyl-1-hexanol by gavage 5 times a week in Cremophor at doses of 0, 50, 150, 500 mg/(kg bw x d) for two years (rats) or 0, 50, 200, 750 mg/(kg bw x d) for 18 months (mice). Controls received water or Cremophor in water. 2-Ethyl-1-hexanol was not oncogenic to rats. The incidences of basophilic foci (male mice at mid-dose only) and of carcinomas in the liver of female mice at the highest dose group was statistically higher compared with the vehicle but not with the water control group. The time-adjusted incidence of hepatocellular carcinomas was outside the normal range in female, but not in male mice. No adenomas were observed. The authors considered the liver tumours in the mouse to be inconclusive because the incidence of hepatocarcinoma precursors did not significantly increase with the dose. Nevertheless, they concluded that 2-ethyl-1-hexanol is weakly or questionably carcinogenic for the female mouse (Belsito et al., 2010). As the substance is not genotoxic and as the maximum tolerated dose (MTD) was exceeded, the MAK-commission concluded that it seems more likely that toxic effects on the liver are responsible for the tumour development and that observance of a MAK value [addition: or any value] which excludes toxic effects on the liver would exclude the development of liver tumours (DFG, 2003).

4.5.4 Toxicity to reproduction

4.5.4.1 Fertility

Rats exposed to 1-hexanol via the diet for 13 weeks showed no signs of significant toxicity when administered at nominal concentrations up to 1 – 6 % (equivalent to 1127 mg/(kg bw x d)). Examination of testes and the ovaries did not show any abnormalities (OECD SIDS, 2007).

In a 90-day inhalation study in rats, no effects on the reproductive organs were seen at concentrations up to 120 ppm (643 mg/m³) 2-ethyl-1-hexanol. Also, gavage administration at doses up to 500 mg/(kg bw x d) for 90 days had no effects on the reproductive organs of rats and mice (Belsito et al., 2010).

In a combined repeated dose and reproductive/ developmental toxicity screening test (OECD guideline 422), 3,5,5-trimethyl-1-hexanol was administered by gavage to male rats for 46 days and to female rats from 14 days before mating to day 3 of lactation at dose levels of 12, 60 and 300 mg/(kg

bw x d). Histopathological examination in male rats revealed kidney lesions confirmed to be mediated by an accumulation of alpha2u-globulin. In female rats, a slight degree of renal epithelial fatty change in the 60 and 300 mg/(kg bw x d), and atrophy of the thymus in the 300 mg/(kg bw x d) were observed. Furthermore, in females a dose-dependent decrease in implantation index was noted at doses ≥ 60 mg/(kg bw x d). Based on these findings, the NOAELs for systemic toxicity and for fertility were 12 mg/(kg bw x d) for females and 300 mg/(kg bw x d) for males (Belsito et al., 2010; OECD SIDS, 2004).

4.5.4.2 Developmental toxicity

Structure-activity relationships

The structure-activity relationships for the developmental toxicity of aliphatic carboxylic acids have been well established. Linear alcohols will be metabolised to the corresponding carboxylic acid. Aliphatic carboxylic acids with a single alkyl-branch at the C_2 position with the side chain being C_2 or higher have a potential for developmental toxicity. Carboxylic acids with a single methyl-branch at the C_2 position or acids branched at a position other than C_2, irrespective of the length of the side chain or the backbone, lack a potential for developmental toxicity. The foetoxicity appears to be associated in particular with carboxylic acids with a total carbon chain length in the range of C_7-C_9 (OECD SIDS, 2007).

Linear alcohols

For 1-hexanol, inhalation of 3500 mg/m³, the maximum vapour concentration achievable, on 7 h/d throughout the gestation period did not result in any adverse effects in dams and foetuses. A slight increase of questionable significance in the number of resorptions was noted. However, in another developmental toxicity study using the oral route of exposure, the number of resorptions was unaffected by treatment even at dose level up to 1000 mg/(kg bw x d), supporting the conclusion that this finding represents a chance observation (OECD SIDS, 2007).

Administration of 1-octanol at daily gavage doses of 0, 130, 650, 975 or 1300 mg/kg during GD6 - 15 resulted in significant, dose-related maternal toxicity, including clinical signs (CNS depression, nasal discharge and pneumonia), and slight decreases in body weight gain and food consumption at doses ≥ 650 mg/(kg bw x d). No adverse effects were recorded on foetal and developmental parameters (Hellwig and Jäckh, 1997; OECD SIDS, 2007).

Inhalation exposure of pregnant rats with 1-octanol, 1-nonanol or 1-decanol at the maximum achievable vapour concentrations (400, 140 and 100 mg/m³, respectively) from GD 1 - 19 did not result in any treatment-related changes on maternal, uterine and foetal parameters (OECD SIDS, 2007).

The available information (including studies with oral exposure) confirms the absence of a potential for developmental toxicity for the category of the linear alcohols (OECD SIDS, 2007).

Branched-chain alcohols

A developmental inhalation toxicity study was conducted with isoamyl alcohol (3-methyl-1-butanol) in rats. The animals were exposed “whole body” to an atmosphere of 0, 510, 2500 or 9800 mg/m³ (0, 138, 675, 2646 ppm) 6 h/d during GD6 – 15. Body weight gain was decreased at the highest concentration between days 6 and 9 but there were no compound-related effects on development and no malformations were observed. The NOAEL for maternal toxicity was 2500 mg/m³ and the NOAEL for developmental toxicity 9800 mg/m³ (Belsito et al., 2010).

In a similar study with pregnant rabbits, exposure with 3-methyl-1-butanol during GD7 – 19 to reduced weight gain and irritant eye effects in dams at 9800 mg/m³. The maternal NOAEL was 2500

mg/m³ and the NOAEL for developmental toxicity was 9800 mg/m³, the highest test concentration (Belsito et al., 2010).

In a study with 2-ethyl-1-hexanol, rats were exposed "whole body" 7 h/d on GD 0 – 19 to 850 mg/m³ (160 ppm), the maximum vapor concentration that could be achieved. Aside from a decrease in feed consumption in dams compared to control, there were no significant differences in maternal, reproductive, or developmental parameters (NOAEL 850 mg/m³) (Belsito et al., 2010). Some evidence of developmental toxicity and an increase of developmental variations were observed after oral administration of 2-ethyl-1-hexanol to pregnant rats. The doses also caused maternal toxicity (NOAEL 130 mg/(kg bw x d) (Belsito et al., 2010).

2-ethyl-1-hexanol was teratogenic in a study with a single oral exposure of pregnant rats. The animals were given a single dose of 833 or 1666 mg/(kg bw x d) by gavage on GD12 and underwent caesarean section on GD20. At the higher dose, 22.2% of the surviving foetuses had various malformations (lower dose: 2 %, control: 0%), and the average foetal weight was reduced. Implantation index, numbers of dead and resorbed foetuses were unaffected. Although the dose of 1666 mg/kg body weight is around half of the oral LD50, no maternal toxicity was reported (Belsito et al., 2010).

Gavage administration of 2-ethyl-1-hexanol to pregnant rats on GD6 - 15 at doses of 0, 130, 650, and 1300 mg/(kg bw x d) caused no maternal and foetal effects at the lowest dose. Slight maternal toxicity (reduced weight gain) was observed at 650 mg/(kg bw x d) and marked effects were observed at the highest dose (reduced body weight, salivation, nasal discharge, CNS depression, six dams died). Developmental toxicity was observed at 650 mg/(kg bw x d) (lower foetus weight, skeletal variations and retardations). Postimplantation effects, malformations, variations and retardations occurred at the highest dose. The NOAEL for maternal and developmental toxicity was 130 mg/(kg bw x d) (Belsito et al., 2010; Hellwig and Jäckh, 1997).

No inhalation study is available with 3-propyl-1-heptanol. In a study with oral exposure of pregnant rats on GD6 – 19, clear signs of maternal toxicity (clinical observations, reduced bodyweight gain, mild thrombocytopenia, slight changes in serum electrolytes, mild impairment of kidney function, changes in protein metabolism and a slight induction of peroxisomal enzymes) were observed at dose levels of 200 mg/(kg bw x d) and above. There were dose-related effects on the gestational parameters and no test substance-induced indications of teratogenicity as well as prenatal developmental toxicity up to the highest dose level of 600 mg/(kg bw x d). A slight retardation of embryo-/foetal development only observed at the highest dose was considered to be secondary to the clear disturbance of maternal homeostasis during pregnancy (ECHA Dissemination, 2020).

After oral exposure of pregnant rats on GD6 – 15 with C7-C9-branched alcohol (mainly iso-octanol, CAS No. 68526-830), an increase in skeletal variations occurred at 100 mg/(kg bw x d). The NOAEL for maternal toxicity was 500 mg/(kg bw x d) (Belsito et al., 2010).

In studies with oral exposure of pregnant rats to two different isomeric mixes of isononyl alcohol I and II (I: mainly dimethylheptanol, II mainly dimethylheptanols and methyloctanols), the NOAEL for maternal and developmental toxicity were the same (mixture I: 144 mg/(kg bw x d), mixture II: 158 mg/(kg bw x d)). In a similar study with isodecyl alcohol, the maternal NOAEL was also 158 mg/(kg bw x d), while developmental effects (malformations) were observed at high doses (NOAEL 790 mg/(kg bw x d) (Belsito et al., 2010).

A much lower NOAEL of 12 mg/(kg bw x d) was reported in a combined repeated dose and reproductive/developmental toxicity study with oral exposure of rats to 3,5,5-trimethyl-1-hexanol. Maternal toxicity and foetoxicity were observed at 60 mg/(kg bw x d) (Belsito et al., 2010). Because

of the limitation of the methodology employed, it is not possible to distinguish if the cause was due to maternal toxicity or due to a direct effect on the foetus (OECD SIDS, 2004).

No developmental effects were observed after oral exposure of pregnant rats with isotridecan-1-ol on GD6 – 19 up to 750 mg/(kg bw x d), the highest dose tested (NOAEL 250 mg/(kg bw x d)) (AGS, 2019).

Overall, it is concluded that developmental toxicity of straight- or branched-chain alcohols is not expressed in studies with inhalation exposure of animals. Effects were observed after oral administration, mostly at high doses, and typically at maternally toxic concentrations.

4.5.5 Odour perception

Very low odour thresholds were reported for C4-C12 n- and iso-alcohols by Nagata (2003) and Ruth (1986) (Table 26). The higher values reported by the AGS (2019) are derived from studies in which humans were very briefly exposed for a few seconds ("sniff-tests") and rather represent nearly immediate odour recognition. These values are therefore not directly comparable with the other, lower values reported in Table 26.

Table 26: Odour thresholds of C4-C13 n- and iso alkanols

Substance	Odour characteristic	Odour threshold in mg/m³	Odour threshold in ppm	Reference
n-Butanol		*0.116**	0.038	(Nagata, 2003)
Isobutanol		*0.0336*	0.011	(Nagata, 2003)
Isobutanol		0.0027	*0.00089*	(Ruth, 1986)
1-Pentanol		*0.363*	0.10	(Nagata, 2003)
1-Pentanol	Sweet, alcohol	0.756	*0.208*	(Ruth, 1986)
1-Pentanol		*0.275*	1	(AGS, 2019)
Isoamyl alcohol (3-methyl-1-butanol)		*0.006*	0.0017	(Nagata, 2003)
2-Methyl-1-butanol	Sour, sharp	0.3826	*0.105*	(Ruth, 1986)
1-Hexanol	Sweet, alcohol	*0.0253*	0.0060	(Nagata, 2003)
1-Hexanol		0.0417	*0.01*	(Ruth, 1986)
1-Hexanol		*2.38* *0.238* *0.950*	10 1 4	(AGS, 2019)
2-Ethylbutanol	Musty, sweet	0.2919	*0.0693*	(Ruth, 1986)
1-Heptanol		*0.023*	0.0048	(Nagata, 2003)
1-Heptanol		*0.448*	0.1	(AGS, 2019)
1-Octanol		*0.014*	0.0027	(Nagata, 2003)
1-Octanol		*0.073* *0.093* *0.0019*	0.39 0.5 0.01	(AGS, 2019)

Substance	Odour characteristic	Odour threshold in mg/m³	Odour threshold in ppm	Reference
2-Ethyl-1-hexanol	Musty	0.4	*0.074*	(Ruth, 1986)
2-Ethyl-1-hexanol		*0.0728*	0.39	(AGS, 2019)
1-Nonanol		*0.0053*	0.00090	(Nagata, 2003)
1-Decanol		*0.0050*	0.00077	(Nagata, 2003)
"Decanol"		0.0006	*0.000092*	(Ruth, 1986)
Isodecanol	Musty, alcohol	0.1292	*0.0198*	(Ruth, 1986)
1-Dodecanol		0.0152	*0.00198*	(Ruth, 1986)

*: values in *italics* were calculated from the original values using the ppm to mg/m³ conversion factor

4.6 Evaluation

4.6.1 Existing regulations and classifications

Existing regulations and classifications with respect to human toxicity, DNEL and NIK values for C_4 to C_{13} n- and iso-alcohols are summarised in Table 27.

Table 27: C4-C13 n- and iso alkanols: harmonised classification, existing EU-LCI or DNEL values (general population) (for explanation, see text)

Substance (CAS No.)	Harmonised classification#	EU-LCI or NIK[1] (µg/m³)	DNEL[3] (µg/m³)	Remarks
C7-C13 "other sat. iso-alkanols"		**NIK: 300**		**RA 2-ethylhexan-1-ol**
C7-C13 "other sat. n-alkanols"		**NIK: 1700**		**RA octan-1-ol**
n-Butanol (71-36-3)	Skin irrit. 2, Eye Dam. 1, Acute Tox. 4, STOT SE3	3000 (ascribed)	55357 (sys) 155000 (local)	EU-LCI derivation pending
Isobutanol (78-83-1)	Skin irrit. 2, Eye Dam. 1, STOT SE3	11000	Low hazard (sys) 55000 (local)	
1-Pentanol (71-41-0)	Skin irrit. 2, Acute Tox. 4, STOT SE3		No hazard id. (sys) 13000 (local)	EU-LCI derivation pending
Isoamyl alcohol (3-methyl-1-butanol) (123-51-3)	-v	730 (ascribed) In EU-LCI, several others are listed as 1-pentanol (all isomers), but are not primary alcohols	No hard id. (sys) 13000 (local)	RA 1-Pentanol, EU-LCI derivation pending
2-Methyl-1-butanol (137-32-6)	-	730 (ascribed)	No hard id. (sys) 13000 (local)	RA 1-Pentanol, EU-LCI derivation pending

Substance (CAS No.)	Harmonised classification#	EU-LCI or NIK[1] (µg/m³)	DNEL[3] (µg/m³)	Remarks
2,2-Dimethyl-1-propanol (75-84-3)			No dossier	Preregistered
1-Hexanol (111-27-3)	Acute Tox. 4	2100 (ascribed)	24500 (systemic) No hazard id. (local)	Local effects possibly not covered by DNEL
1-Heptanol (111-70-6)	Acute Tox. 4		No hazard identified	
1-Octanol (111-87-5)		1700	43500 (systemic) No hazard id. (local)	
2-Methyl-1-heptanol (60435-70-3)			65000	RA 1-hexanol
2-Ethyl-1-hexanol (104-76-7)		300	2300 (systemic) 26600 (local)	
2-Propyl-1-pentanol			No dossier	
Alcohols, C7-9-iso-, C8-rich (68526-83-0)			No hazard identified	RA isooctanol (CAS number 68526-83-0) and isotridecanol
1-Nonanol (143-08-8)			43500 (systemic) No hazard id. (local)	
2-Propylheptanol (10042-59-8)			1300 no hazard identified (local)	Substance-specific data
3,5,5-Trimethylhexan-1-ol (27458-94-2)			Not derived	
Nonanol, branched and linear (68515-81-1)			65000 (local and systemic)	RA 1-hexanol
1-Decanol			870	Based on dermal study
3,7-Dimethyl-1-octanol (106-21-8)			1300 no hazard identified (local)	RA 2-propylheptanol
2-Butyl-1-octanol (3913-02-8)			31100 (systemic) No hazard expected (local)	RA 2-octyldodecan-1-ol

1: (AGBB, 2021; EU-LCI Working Group, 2021); 2: RA Read-cross; 3: (ECHA, 2022); #: with respect to toxicity (ECHA C&L Inventory, 2022);

4.6.2 Derivation of an EU-LCI value

The evaluation of the available data for this group of substances shows that sensory irritation as observed in humans and in animal studies represents the critical endpoint for the derivation of health-based LCI values.

Table 28: Comparison of EU-LCI derivation for octan-1-ol and 2-ethyl-hexan1-ol (EC, 2013)

Compound	Octan-1-ol	2-Ethylhexan-1-ol
N° CAS 1 ppm = x mg/m³ (23 °C)	**111-87-5** 5.36	**104-76-7** 5.36
EU-Classification **CLP, harmonised classification**		
Organisation name	**EU-LCI WG**	**EU-LCI WG**
Risk value name	EU-LCI	EU-LCI
Risk value (µg/m³)	**1700**	**270, rounded to 300**
Reference period	Chronic	Chronic
Risk value (mg/m³) **Short term (15 min)**	-	-
Year	2016	2014
Key study	van Thriel et al. (2003a)	van Thriel et al. (2007)
Study type	acute inhalation, whole body, 0.1 and 6.4 ppm	acute inhalation, whole body, 1.5, 10.2, 20.2 ppm
Species	Human	Human
Duration of exposure in key study	**4 h**	**4 h**
Critical effect	Irritation (self-reported, eye and nose)	Eye irritation (self-reported)
Critical dose value	"Marginal LOAEC": 6.4 ppm	NOAEC 1.5 ppm ("self-reported symptoms were minimal" at this concentration)
Adjusted critical dose	LOAEC/2 = 3.2 ppm (NOAEC) No further adjustment	Adjusting 4 h/24 h => 1.5/6 = 0.25 ppm
Single assessment factors	UF_H 10 = 10	UF_H 5 = 5
Other effects		
Remarks	24 male students, 12 reported enhanced chemical sensitivity	46 male participants, 19 reported enhanced chemical sensitivity;

Sensory irritation of C_6 – C_{13} alkanols in humans and laboratory animals increases with increasing chain length (decreasing effect concentrations/RD50 values). At the same time, vapour pressure decreases markedly with increasing chain length.

Within this group of compounds, octan-1-ol and 2-ethylhexan-1-ol were studied in greater details as representatives of the unbranched and branched members, respectively. The data from these studies

also show that eye irritation can be observed at lower concentration than irritation of respiratory epithelia.

Clinical studies with well-characterised acute inhalation exposure of humans to vapours of these two compounds revealed that sensory irritation is the effect of concern when deriving health-based occupational exposure limits (OEL) or guidance values for indoor air. The already derived EU-LCI values for both these compounds are based on these data, using a POD of 6.4 ppm as a LOAEC for eye and nose irritation during exposure to octan-1-ol and a NOAEC of 1.5 ppm for eye irritation during exposure to 2-ethylhexan-1-ol (EU-LCI Working Group, 2021).

The derivation of the LCI values for 1-octanol and 2-ethyl-1hexanol are displayed in Table 28.

In the study with 1-octanol, only one “effective” concentration was used (the lower concentration served as “odour control”) and the described effects are based on subjective self-reported symptoms. The data for 2-ethyl-1-hexanol are based on studies with more than one exposure concentrations and the NOAEL is based on both objective measurements (eye-blinking frequency) and subjective reporting. The data for 2-ethyl-1-hexanol are based on a higher number of participants than those for 1-octanol. Regarding the derivation procedure, there are differences in the dose adjustment and the choice of extrapolation factors.

Comparison of both derivations suggests that the about sixfold difference between the two LCI values seems to be more driven by the experimental design and by differences in the used assessment factors and critical dose adjustments than by “real” differences in the potency of both compounds to induce sensory irritation.

No histological lesions of respiratory epithelia were observed in a subchronic inhalation study with 2-ethyl-hexan-1-ol in rats at 120 ppm (675 mg/m³), the highest concentration tested. It is concluded that the described sensory effects at acute exposure do not go along with histological lesions. Limited data for higher alkanols (> C_8) also provided no evidence for local (or systemic) effects at saturated vapour concentration.

It is proposed to perform the derivation of an EU-LCI value for C_6-C_{13} n- and iso-alkanols via read-across with 2-ethyl-hexan-1-ol. The EU-LCI value for this compound is based on a well-conducted clinical study with humans.

This represents a “conservative approach”. Inspection of the reported NOAEC/NOAEL derived for other substances of this group (see chapters 4.5.1 to 4.5.5) indicates that an EU-LCI value of 300 µg/m³ based on sensory irritation will also cover other adverse effects observed in studies with C_6-C_{13} n- and iso-alcohols:

The (by far) lowest NOAEL in these studies was 12 mg/(kg bw x d), reported in a combined repeated dose and reproductive/developmental toxicity study with oral exposure of rats to 3,5,5-trimethyl-1-hexanol. Maternal toxicity and foetoxicity were observed at 60 mg/(kg bw x d). Based on these data, the following derivation could be performed.

Toxicokinetic data for alcohols indicate that these compounds are well absorbed by oral and inhalation exposure. Thus, no additional factor is considered for differences in absorption, and the following assessment factors can be used:

- Route-to-route extrapolation: 1.15 m³/kg bw,
- Differences in absorption: 1 (assuming similar absorption by oral and inhalation exposure),

- Adjusted study length factor: 2 (conservative approach, assuming the effect is related to maternal toxicity. If the effect is considered related to fertility, the factor would be 1 since the exposure covered the sensitive time frame),
- Interspecies differences: 2.5
- Intraspecies differences: 10,
- Molar adjustment: 144.3/102.2 = 1.108 (considering the different molar masses of 3,5,5-trimethyl-1-hexanol and 2-ethyl-1-hexanol),
- leading to a calculated value of 12 mg/(kg bw x d) : (1.15 x 2 x 25) = 214 µg/m³ x 1.108 = 237 µg/m³. If the effect is considered related to fertility, the value would be 474 µg/m³).

It is concluded that the proposed EU-LCI value of 300 µg/m³ based on sensory irritation also covers other known (substance-specific) adverse health effects of other alcohols within this group.

For the derivation of an EU-LCI value for C_6-C_{13} n- and iso-alkanols read-across from 2 ethylhexan-1-ol is performed and an EU-LCI value of 300 µg/m³ is proposed for this group of substances[6].

No molar adjustment is recommended. Adjustment to lower members of this group (C_6 and C_7 alcohols) would lead to a lower mass-based value, which is not supported by the available data (the sensory irritation potency of 1-hexanol seems to be lower than that of 2-ethyl-1-hexanol). The data base for alcohols with a higher number of carbon atoms than 2-ethyl-1-hexanol is limited, but the above mentioned data calculation indicates that the derived value seems appropriate.

As far as data were available, the C_6-C_{13} n- and iso alcohols show very low odour thresholds. The lowest reported values for the individual compounds are in the range 5 µg/m³ for 1-decanol to 73 µg/m³ for 2-ethyl-1-hexanol (Nagata, 2003; Ruth, 1986). Therefore, olfactory perception must be expected at the proposed EU-LCI value.

Note: Since it does not seem to be justified to differentiate between n- and isoalkanols on the basis of the available data regarding sensory irritation, it should be discussed whether the published EU-LCI value for octan-1-ol should be withdrawn in case a group value for C_6-C_{13} n- and isoalkanols will be adopted.

[6] Note: The derivation of the EU-LCI value for 2-ethyl-1-hexanol is currently under re-evaluation. In case that this value will be changed, the rationale presented here for the group of C_6-C_{13} n- and isoalkanols should be reviewed and modified if necessary.

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D Appendix

D.1 Data collection and fact sheet for "other C_6-C_{13} n- and iso-alcohols"

This specification refers to **primary** alcohols with branched or non-branched alkyl chains.

Table 29: Data collection sheet for C_6-C_{16} "long-chain alcohols"

Compound	**C_6-C_{16} long-chain alcohols**	***Data collection sheet***
Nº CAS 1-Hexanol: 111-27-3; 1 ppm = 4.21 mg/m³ (23 °C) Octan-1-ol: 111-87-5; 1 ppm = 5.36 mg/m³ (23 °C) Decan-1-ol: 112-30-1; 1 ppm = 6.51 mg/m³ (23 °C) Dodecan-1-ol: 112-53-8; 1 ppm = 7.667 mg/m³ (23 °C)	1-Hexanol: Acute Tox. 4 (H302) - -	
EU-Classification **CLP, harmonised classification**		
Organisation name	**Ausschuss für Gefahrstoffe (Hazardous Substances Commission)**	
Risk value name	AGW (workers)	
Risk value (mg/m³)	1-Hexanol: 105 mg/m³ (25 ppm) Octan-1-ol: 54 mg/m³ (10 ppm) Decan-1-ol: 66 mg/m³ (10 ppm) Dodecan-1-ol: No value can be derived.	
Reference period	Chronic	
Risk value (mg/m³) **Short term (15 min)**	-	
Year	2021	
Key study	Van Thriel et al. (2007), supported by several studies on sensory irritation (see AGS, 2019)	
Study type	Acute exposure of humans in controlled study	
Species	Human	
Duration of exposure in key study	4 hours	
Critical effect	Sensory irritation (eye blinking frequeny)	
Critical dose value	BMDL 14.7 ppm (79 mg/m³) (derived by DFG, 2012)	
Adjusted critical dose		
Single assessment factors	Not explicitly stated	
Other effects		

Compound	**C_6-C_{16} long-chain alcohols**	***Data collection sheet***
Remarks	*"For 2-ethylhexanol, a TLV of 10 ml/m³ was derived … on the basis of detailed analyses and evaluations of the eyelid closure frequency as a surrogate for the sensory irritant effect in the test on volunteers… In analogy to 2-ethylhexanol, the AGW for octan-1-ol and decan-1-ol is set at 10 ml/m³ due to the comparable irritant effect on the eye and RD50 values."* *For 1-hexanol, the acute irritation and odour thresholds are 2-10 times higher than for the other long-chain alcohols, depending on the endpoint. Due to insufficient data, this range cannot be narrowed down further. Since the AGW for long-chain alcohols was reduced from 20 to 10 ppm…, the previous AGW of 1-hexanol is also halved to 25 ppm by analogy.*	

Table 30: Fact sheet for 2-ethyl-1-hexanol*

Compound	2-Ethyl-1-hexanol $C_8H_{17}OH$		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	
EU-LCI status	2	Draft/Final	Final
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2014
General information			
CLP-Index No.	4	INDEX	-
EC-No.	5	EINECS	203-234-3
CAS-No.	6	Chemical Abstract Service number	104-76-7
Harmonised CLP classification	7	Human health risk related classification	-
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	130.23 1 ppm = 5.35 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	Van Thriel, Kiesswetter et al., 2007
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.	
Exposure duration	14	h/d, d/w	4 hrs
Critical endpoint	15	Effect (s), site of	Eye irritation
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEL
POD value	17	[mg/m³] or ppm or [mg/kg_{BW}×d]	1.5 ppm
Assessment factors (AF)			
Adjustment for exposure duration	19	Study exposure h/d, d/w	1
Study length	20	sa→sc→c	6
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

Compound	2-Ethyl-1-hexanol $C_8H_{17}OH$		Fact sheet
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	1
	23b	Kinetic + dynamic	1
Intraspecies differences	24	Kinetic + dynamic General population	5
AF (sensitive population)	25		1
Other adjustment factors Quality of database	26	Completeness and consistency Reliability of alternative data *(R8-6 d, e)*	1
Results			
Summary of assessment factors	27	Total Assessment Factor	30
POD/TAF	28	Calculated value [µg/m³ and ppb]	1.5/30 = 50 ppb (270 µg/m³)
Molar adjustment factor	29		
Rounded value	30	[µg/m³]	300
Additional comments	31		No data available from studies with other animal species
Rationale selection	32		

*: (according to https://ec.europa.eu/docsroom/documents/49239)

In humans, toxicity endpoints associated with acute 2-ethylhexanol inhalation include irritation of the eyes and throat, headaches, cough, dizziness, and fatigue. No chronic systemic effects were reported in either animal or human studies. Animal studies have concluded that 2-ethylhexanol is neither genotoxic nor carcinogenic. In subchronic inhalation studies in rats, NOAELs of > 639 mg/m³ and > 850 mg/m³ were identified for systemic and developmental effects, respectively (Klimisch et al., 1998; Nelson, 1993). Subacute human exposure chamber studies by van Thriel and colleagues (2007) showed concentration-dependent increases in self-rated eye irritation, nasal irritation and annoyance. The effects were seen at all levels tested, 1.5, 10 and 20 ppm, with both constant and variable exposures. No objective effects were seen at 1.5 ppm and the self-reported irritation symptoms were minimal. A NOAEL for irritation of 1.5 ppm may be inferred from the study (SCOEL, 2011).

Since the NOAEL of 1.5 ppm is derived from a single exposure of 4 hours, an assessment factor of 6 is used to account for exposure duration and study length. An intraspecies AF of 5 is taken to extrapolate from healthy human volunteers to the general population.

Dividing the NOAEL by the combined AFs of 6 x 5 = 30 gives a value of 0.05 ppm or 270 µg/m³.

The rounded LCI of 300 µg/m³ is below the odour detection threshold of 0.08-0.13 ppm = 0.4-0.73 mg/m³ (Ruth, 1986).

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Table 31: Fact sheet for "other C_6-C_{13} n- and iso-alcohols"

Compound	"Other C6-C13 n- and iso-alcohols" $C_6H_{13}OH$ to $C_{13}H_{27}OH$		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	300
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2022
General information			
CLP-Index No.	4	INDEX	
EC-No.	5	EINECS	
CAS-No.	6	Chemical Abstract Service number	
Harmonised CLP classification	7	Human health risk related classification	
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	130.2 1 ppm = 5.4 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	2-Ethyl-1-hexanol
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]	EU-LCI value of 2-ethyl-1-hexanol
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	-	-
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	-
	22b	Severity of effect (R8 6d)	-

Compound	"Other C6-C13 n- and iso-alcohols" $C_6H_{13}OH$ to $C_{13}H_{27}OH$		Fact sheet
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]	
Molar adjustment factor	29	Used in read-across	Not performed (see rationale)
Rounded value	30	[µg/m³]	300
Additional comments	31		
Rationale selection	32		

Data compilation and evaluation is based on a project funded by the German Environment Agency (Voss et al., 2022).

Rationale for starting point

It is proposed to perform the derivation of an EU-LCI value for the group of C_6-C_{13} n- and iso-alkanols via read-across with 2-ethyl-hexan-1-ol. The EU-LCI value for this compound is based on a well-conducted clinical study with humans.

Evaluation of the available data for this group of alkanols shows that sensory irritation as observed in humans represents the critical endpoint for the derivation of health-based LCI values.

Sensory irritation of C_6 – C_{13} alkanols in humans and laboratory animals increases with increasing chain length (decreasing effect concentrations/RD50 values). At the same time, vapour pressure decreases markedly with increasing chain length.

Within this group of compounds, octan-1-ol and 2-ethylhexan-1-ol were studied in greater details as representatives of the unbranched and branched members, respectively. The data from these studies also show that eye irritation can be observed at lower concentrations than irritation of respiratory epithelia.

Clinical studies with well-characterised acute inhalation exposure of humans to vapours of these two compounds revealed that sensory irritation is the effect of concern when deriving health-based occupational exposure limits (OEL) or guidance values for indoor air. The already derived EU-LCI values for both these compounds are based on these data, using a POD of 6.4 ppm as a LOAEC for eye and nose irritation during exposure to octan-1-ol and a NOAEC of 1.5 ppm for eye irritation during exposure to 2-ethylhexan-1-ol (EU-LCI Working Group, 2021).

Comparison of both derivations suggests that the about sixfold difference between the two derived LCI values for 1-octanol and 2-ethyl-1-hexanol, respectively, seems to be more driven by the experimental design and by differences in the used assessment factors and critical dose adjustments than by "real" differences in the potency of both compounds to induce sensory irritation.

No histological lesions of respiratory epithelia were observed in a subchronic inhalation study with 2-ethylhexan-1-ol in rats at 120 ppm (675 mg/m³), the highest concentration tested. It is concluded that the described sensory effects at acute exposure do not go along with histological lesions. Limited data for higher alkanols (> C_8) also provided no evidence for local (or systemic) effects at saturated vapour concentration.

Performing read-across from 2-ethyl-1-hexanol represents a "conservative approach". Inspection of the reported NOAEC/NOAEL derived for other substances of this group indicates that an EU-LCI value of 300 µg/m³ based on sensory irritation will also cover other adverse effects observed in studies with C_6-C_{13} n- and iso-alcohols.

For the derivation of an EU-LCI value for C_6-C_{13} n- and iso-alkanols read-across from 2 ethylhexan-1-ol is performed and an EU-LCI value of 300 µg/m³ is proposed for this group of substances.

No molar adjustment is recommended. Adjustment to lower members of this group (C_6 and C_7 alcohols) would lead to a lower mass-based value, which is not supported by the available data (the sensory irritation potency of 1-hexanol seems to be lower than that of 2-ethyl-1-hexanol). The data base for alcohols with a higher number of carbon atoms than 2-ethyl-1-hexanol is limited, but the evaluation indicates that the derived value seems appropriate as a health-based EU-LCI for the group of C_6-C_{13} n- and iso-alcohols.

As far as data were available, the C_6-C_{13} n- and iso alcohols show very low odour thresholds. The lowest reported values for the individual compounds are in the range 5 µg/m³ for 1-decanol to 73 µg/m³ for 2-ethyl-1-hexanol (Nagata, 2003; Ruth, 1986). Therefore, olfactory perception must be expected at the proposed EU-LCI value.

Note: Since it does not seem to be justified to differentiate between n- and isoalkanols on the basis of the available data regarding sensory irritation, it should be discussed whether the published EU-LCI value for octan-1-ol should be withdrawn in case a group value for C_6-C_{13} n- and isoalkanols will be adopted.

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5 Toxicological evaluation of “other methacrylates” as basis for the derivation of an EU-LCI value

Methacrylate esters form a group with a common methacrylate moiety in all representatives and an alkyl chain differing in the number of carbon atoms and, in higher members (starting at C_3), possible branching of this chain. “Other methacrylates” refers to all esters of methacrylic acid other than methyl methacrylate containing unbranched or branched saturated alkyl groups, e. g., ethyl methacrylate.

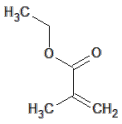
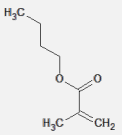
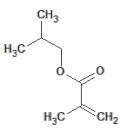
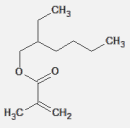
Compared to methyl methacrylate, the database for toxicological effects of other methacrylates is much more limited. The commercially most important alkyl methacrylates besides methyl methacrylate (MMA) are ethyl (EMA), n-butyl (BMA), isobutyl (iBMA) and 2-ethylhexyl methacrylate (2EHMA) (Gelbke et al., 2018; OECD SIDS, 2009). The available data have been summarised in several reviews (EFSA CEF, 2010; EFSA FAF et al., 2019; Gelbke et al., 2018; Greim et al., 1995; OECD SIDS, 2004; OECD SIDS, 2009). The genotoxic potential was reviewed by Albertini (2017). Registration dossiers according to REACH are also available for several alkyl methacrylates (see Table 35).

A category approach is justified for this group of “other methacrylates” due to trends observed in toxicokinetics and toxicity (Gelbke et al., 2018; OECD SIDS, 2004; OECD SIDS, 2009).

5.1 Substance identification

Substance identification data and physicochemical properties of relevant “other alkyl methacrylates” are shown in Table 32 and Table 33.

Table 32: Substance identification of selected “other methacrylates”

CAS-No. EU-No. CLP-Index-No.	Systematic name, common name	Sum formula	Structural formula
97-63-2 202-597-5 607-071-00-2	Ethyl methacrylate	$C_6H_{10}O_2$	
97-88-1 202-615-1 607-033-00-5	n-Butyl methacrylate	$C_8H_{14}O_2$	
97-86-9 202-613-0 607-113-00-X	Isobutyl methacrylate	$C_8H_{14}O_2$	
688-84-6 211-708-6 -	2-ethylhexyl methacrylate	$C_{12}H_{22}O_2$	

5.2 Substance properties and uses

Alkyl methacrylates are liquids at room temperatures with boiling points between 188 and 227 °C. Whereas EMA has a notable vapour pressure at room temperature, the vapour pressure of 2EHMA is low, considerably limiting the saturated vapour concentration at room temperature in air. The odour

of these compounds is reported as “sweet” or “fruity”, odour thresholds are not available (OECD SIDS, 2009).

These alkyl methacrylates are large-scale industrial products with a total tonnage band in the EU of ≥ 1 000 to < 10 000 t/a (EMA and 2EHMA) or ≥ 10 000 to 100 000 t/a (BMA and iBMA), respectively, (ECHA Dissemination, 2021a; ECHA Dissemination, 2021b; ECHA Dissemination, 2021c; ECHA Dissemination, 2022). These substances are used in a wide range of products, e. g. to make automotive coatings, paints, lacquers, enamels, adhesives, polishes and printing inks (OECD SIDS, 2009). n-Propyl methacrylate is reported to be used as monomer for methacrylic polymers/methacrylic acid esters and acrylic resins (HSDB, 2010) but no more detailed data are available.

Ethyl methacrylate was identified as a natural compound in certain fruits (litchi, mango, quince, and starfruit). Traces of iBMA were identified in beli, a tropical fruit, and in Roman chamomile (EFSA CEF, 2010; OECD SIDS, 2004).

Substances in the group of branched- and straight-chain unsaturated carboxylic acids and related esters with saturated and unsaturated aliphatic alcohols may occur as flavouring agents in foodstuffs (EFSA FAF et al., 2019).

Table 33: Physicochemical properties of commercial “other methacrylates” (Gelbke et al., 2018; OECD SIDS, 2009)

Alkyl group	Molar mass (g/mol)	Mp. (° C)	Boiling point (° C)	Vapour pressure (Pa) (at 20 °C)	Conversion 1 ppm = x mg/m³ (23 °C)	log kow	Solubility in water (mg/l) at 25 °C
Ethyl	114	< -75	118.2	20	4.69	1.87	4690
n-Butyl	142	-50	163	2.1	5.84	3.0	360
Isobutyl	142	-35	155	2.1	5.84	2.95	470
2-Ethyl-hexyl	198	< -50	227.6	0.065	8.15	4.95	1.6

5.3 Exposure

5.3.1 Indoor air

Since these alkyl methacrylates are almost exclusively used in the production of polymers, end-use consumer products contain only trace levels of these monomer compounds. Consumer exposure is likely to be very low (except possibly in the use of products for artificial nails and in the use in dental practices, both of which are not relevant in the context of this report). This is reflected by the low or missing number of determinations of ethyl methacrylate in indoor air (Table 34), data for higher methacrylates were not reported.

Table 34: Frequency of detection and concentrations in indoor air of methacrylates#

Substance (CAS No.)	No. of determinations	N > LoD (%)	Median (µg/m³)	P95 (µg/m³)	Maximum (µg/m³)
Methyl methacrylate	1828	13.5	0.5*	2.5	500
Ethyl methacrylate	42	0	2.5*	2.5*	2.5*

#: all values from (Hofmann and Plieninger, 2008); *: set to half the corresponding limit of determination

5.3.2 Other sources

From the amount added to food as flavour, EFSA FAF et al. (2019) made a rough estimate of a possible uptake of 0.12 µg EMA/d. Further data are not available.

5.4 Toxicokinetics

Systemic effects after inhalation, oral and dermal exposure of experimental animals show that methyl methacrylate and higher alkyl methacrylates are absorbed via these pathways (OECD SIDS, 2004; Voss et al., 2017). For MMA, a deposition of 10 – 20 % in the upper respiratory tract of rats is reported after inhalation (Gelbke et al., 2018). No data are available for higher alkyl methacrylates.

The metabolism of alkyl methacrylate esters starts with hydrolysis by non-specific carboxylesterases to methacrylic acid and the structurally corresponding alcohol in several tissues, including the epithelium of the respiratory tract. At high concentrations with saturation of the hydrolysis capacity, a reaction of methacrylates with glutathione (GSH) and other reactive sulphydryl groups may occur (DFG, 2006; U.S.EPA, 1998b). In a study on the isolated respiratory tract of rats, however, the concentration of non-protein-bound SH groups in the tissue decreased by only 20 % even at 2355 mg MMA/m³ (U.S.EPA, 1998a). Further studies with MMA showed that up to 88 % of a [^{14}C]-labelled single dose of 5.7 mg MMA/kg bw (oral or i.v.) was exhaled as CO_2 by rats within 10 days, 65 % of which within 2 hours. Only traces (< 1 %) of unchanged MMA occur in exhaled air (U.S.EPA, 1998b). The hydrolysis of MMA by carboxylesterases in the blood proceeds rapidly with a half-life in the range of 20 - 40 min (U.S. EPA, 1998b). The resulting methacrylic acid can be detected in the urine of rats and humans, but most of it is further metabolised. Methacrylic acid is also formed as a physiological product during the degradation of the essential amino acid valine. It is introduced into the citrate cycle via several intermediate products and thus utilised in a central metabolic process (DFG, 1984).

Other studies have confirmed that alkyl-methacrylates in general are rapidly hydrolysed by ubiquitous carboxylesterases. First pass (local) hydrolysis of the parent ester has been shown to be significant for all routes of exposure, including the tissues of the upper respiratory tract, particularly the olfactory tissue. Systemically absorbed parent ester will be effectively removed during the first pass through the liver resulting in their relatively rapid elimination from the body (OECD SIDS, 2004).

5.5 Health effects

5.5.1 Acute toxicity, sensory irritation and local effects

The LD50 in rats and rabbits determined by oral and dermal exposure for the various alkyl methacrylates are greater than 2000 mg/kg bw. The toxicity via inhalation exposure is also low. The following LC50 values were obtained (OECD SIDS, 2004):

- ethyl methacrylate (4 h, rats): 55000 mg/m³,
- butyl methacrylate (approximate value, 4 h, rats): 29000 mg/m³,
- isobutyl methacrylate (4 h 50 min, mice): 29740 mg/m³ (OECD SIDS, 2004),
- 2-ethylhexyl methacrylate (6 h, rats): LC0 > 14 ppm (> 114 mg/m³) (ECHA Dissemination, 2022). Due to its low volatility the LC50 will be much higher than the saturated vapour concentration of 510 mg/m³ (64.5 ppm) (Gelbke et al., 2018).

Regarding irritation, EMA, BMA, iBMA, and 2EHMA were observed to be slight to moderate skin and moderate to severe eye irritants (ECHA Dissemination, 2021a; ECHA Dissemination, 2021b; ECHA Dissemination, 2021c; ECHA Dissemination, 2022), though the effects were variable depending on the experimental conditions (OECD SIDS, 2004).

In animal experiments on mice, exposure for 30 min to 3079 - 137280 mg MMA/m³ caused at most a reduction in the respiration rate of 25 %; an RD50 could therefore not be determined. In rats, 4 h exposure to 29800 mg/m³ already had a lethal effect on some of the animals (LC50) (DFG, 2006). These findings show that MMA has hardly any sensory irritation effect in animal experiments. However, this does not mean that there is no effect on the mucous membranes. In rats, damage to the olfactory epithelium of the nose with degeneration and atrophy already occurred after 6 hours of exposure to 200 ppm (about 830 mg/m³) (Mainwaring et al., 2001).

RD50 for other methacrylates are not available. However, studies with acute exposure of rats revealed that the potency of alkyl methacrylates to produce lesions of the olfactory epithelium decreases with increasing alkyl chain length. In these studies, rats were exposed to 200 ppm of MMA, EMA, BMA or iBMA, respectively, for 6 h. 2EHMA was not included because the low vapour pressure precluded such a high concentration. Histopathology of the nasal passages did not show any lesions in the respiratory epithelium, the nasal region of the first impact of methacrylate vapours. However, exposure of MMA (as described above) led to marked degeneration of the olfactory epithelium. Similar but slightly less severe effects were observed with 200 ppm EMA (about 950 mg/m³). No effect was observed in the olfactory epithelium of rats exposed to BMA and iBMA (Gelbke et al., 2018; OECD SIDS, 2004).

Methacrylate esters are generally regarded as skin sensitising (Gelbke et al., 2018; IOMC, 2001).

Methyl methacrylate has recently been evaluated regarding respiratory sensitisation. Based on diagnosed occupational asthma cases and epidemiological studies on human respiratory sensitisation, RAC concluded that the evidence is sufficient and MMA should be classified as respiratory sensitising (RAC, 2021). No data are available for higher alkyl methacrylates.

5.5.2 Repeated dose toxicity

Ethyl methacrylate

No repeated dose toxicity study with inhalation exposure is available.

A neurotoxicity study was conducted in male Sprague-Dawley rats (n = 8/group) (Abou-Donia et al., 2000). The animals received EMA in drinking water at concentrations of 0.1, 0.2 or 0.5 % for 60 days (equivalent to approximately 50, 100 and 250 mg/(kg bw x d)), controls received tap water. Alterations in clinical condition were observed at 0.2 % and 0.5 % EMA. At the lowest exposure level in the drinking water the animals “did not appear different from controls”, whereas at the next higher level (0.2 %) the rats were lethargic. The authors reported morphological alterations (spongiform alterations, axonal swellings, shrunken axons) in sections of brain, spinal cord and sciatic nerve from rats treated with 0.1 %, 0.2 % and 0.5 % EMA in drinking water.

Concern has been expressed by EFSA committees on the quality and interpretation of data from this and other similar neurotoxicity studies performed by the same authors. The morphological changes observed in the described study were not considered to be a reliable indication of neurotoxicity. Only images of the highest dose group and no images of tissues from control animals were presented. This and the low quality of the presented slides prohibit adequate evaluation of the suggested findings and it cannot be excluded that these findings are mere artefacts. The Panel concluded that the indications for this effect were not sufficiently underpinned (EFSA CEF, 2010).A peer-review performed by a group of pathologist concluded that no treatment-related lesions in the sections of peripheral nerve and brain were observed and the spinal cord vacuolation was most consistent with foci of myelin artifacts (OECD SIDS, 2004).

n-Butyl and isobutyl methacrylate

There were only studies available with n-butyl methacrylate (BMA).

In a subacute inhalation study according to OECD TG 412, Sprague-Dawley rats (5 M + 5 F/group) were exposed “whole body” against 0, 310, 952 or 1891 ppm BMA (0, 1832, 5626, 11175 mg/m³) for 6 h/d, 5 d/week for 4 weeks. Irritation of eyes (lacrimation, eye squinting) and laboured breathing were observed at ≥ 952 ppm. Histopathological, a treatment-related localised bilateral degeneration of the olfactory epithelium lining the dorsal meatus of the nasal cavity was noted in both sexes at ≥ 952 (≥ 5626 mg/m³). No deaths and no treatment-related effects on body weight, feed consumption, haematological and clinical chemistry values were reported except for a slight increase in serum BUN at the highest concentration. This was accompanied by an increased relative kidney weight in both sexes without histopathological changes (ECHA Dissemination, 2021a) . A NOAEC of 310 ppm (1832 mg/m³) can be derived from this study.

Lethargy, increased urine output, loss in weight-gain, and congestion of blood vessels in livers, lungs and kidneys but no cellar injury was reported in an older unpublished study (report date 1959) after exposure of rats (n = 3, no details available) against an atmosphere saturated with BMA on 6 h/day for 20 days. No further details of the study are available. A concentration of about 11800 mg n-butyl methacrylate/m³ is reported in the dossier to correspond to a saturated vapour atmosphere in this study (ECHA Dissemination, 2021a). However, calculation from the vapour pressure reported for n-butyl methacrylate of 2.1 hPa (at 20 °C) leads to a saturated vapour concentration of 11760 mg/m³ (Gelbke et al., 2018), a value very close to the highest concentration of 11175 mg/m³ used in the subacute inhalation study mentioned above.

In a subchronic oral toxicity study according to OECD TG 408, Wistar rats (10 M + 10 F/group, additionally 5 M + 5 F/high dose and control for recovery) were exposed by gavage to 0, 60, 120 or 360 mg/(kg bw x d) for 90 days. At the highest dose, body weight gain in males was lower during the final week of the study. Effects on organs were also observed at 360 mg/(kg bw x d), limited to effects on the liver (increased liver weight, prolonged prothrombin time, lower serum globulin and triglyceride levels in males and/or females) and kidneys (increased absolute weight in females) without histopathological changes. Multifocal degenerative and regenerative olfactory epithelium of the nasal cavity was observed at ≥ 120 mg/(kg bw x d). The effect was completely reversible within

the 28-day recovery phase. The registration dossier noted that, considering the short half-life of n-BMA in blood (99.7 % removed in first pass by the liver), these effects were not of systemic origin but local effects related to the dosing procedure. This substance-related effect was completely reversible, as no animal of the recovery group showed any finding in the nose after 28 days after cessation of exposure. Thus, based on the toxicologically relevant signs of systemic toxicity at the highest dose, a NOAEL of 120 mg/(kg bw x d) (LOAEL: 360 mg/(kg bw x d)) is obtained in this study (ECHA Dissemination, 2021a).

2-Ethylhexyl methacrylate

The registration dossier for 2-ethylhexyl methacrylate (2EHMA) summarises the data of an unpublished subacute inhalation toxicity study in which Alderley Park rats (4 M + 4 F/group) were exposed to 0, 25 and 60 ppm (0, 203 and 486 mg/m³) 2EHMA 6 h/day, 5 d/week for three weeks. There were no signs of toxicity at autopsy; blood and urine tests were normal. Gross examination of the major organs revealed no adverse effects, however, histology showed increased cellularity in the lungs (ECHA Dissemination, 2022). The higher concentration is very close to the saturated vapour concentration for 2EHMA (64.5 ppm or 510 mg/m³) (Gelbke et al., 2018) so the possibility of aerosol formation cannot be excluded.

A subchronic oral toxicity study according to OECD TG 408 was performed in which Wistar rats (10 M + 10 F/group, additionally 5 M + 5 F/high dose and control for 28-day recovery) received 0, 60, 120 or 360 mg/(kg bw x d) by gavage for 90 days. At the highest dose, the following treatment-related effects were noted: lower weight, weight gain and food intake in females, transient changes of blood chemical parameters and increased relative organ weights of liver and kidney in both sexes. The NOAEL was considered to be 120 mg/(kg bw x d) (ECHA Dissemination, 2022).

In a combined repeat dose and reproductive/developmental toxicity screening test (OECD TG 422), Sprague-Dawley rats (12 M + 12 F/group) were treated by gavage with 0, 30, 100, 300 or 1000 mg 2EHMA/(kg bw x d) for 49 days (M) or from 14 days before mating, throughout mating and pregnancy until day 4 of lactation (F). One high-dose female died during the study (no further information presented). Treatment-related microscopic changes were observed in the liver and spleen of high dose males and in the thymus, spleen and brain of high dose females. These changes consisted of mild focal necrosis of the liver, mild decreased extramedullary haematopoiesis in the spleen, mild atrophy of the thymus, and a softened lesion of the medulla oblongata. 300 mg/(kg bw x d) was considered a LOAEL for males, based on increased absolute and relative weights of the kidneys, and relative weight of liver and pituitary gland. Corresponding changes at the high dose were noted in serum BUN (kidney); protein, enzymes and A/G ratio (liver), and haematology (spleen and pituitary). Blood samples were not taken from the pregnant females. In high dose females, increased absolute kidney and relative weights of thyroid gland, liver and brain were observed. Relative kidney weight was also increased at 100 and 300 mg/(kg bw x d), but the effect at 100 mg/(kg bw x d) was considered biologically insignificant based on the magnitude of the change compared to controls. The LOAEL for females is therefore considered to be 300 mg/(kg bw x d), as in males, based on organ weight changes. The NOAEL for males and females in this study is thus 100 mg/(kg bw x d) (ECHA Dissemination, 2022).

5.5.3 Genotoxicity and carcinogenicity

Genotoxicity

As explained by (Gelbke et al., 2018), the electrophilicity is considered an alert for Michael addition to DNA, however, electrophilicity of all methacrylate esters is regarded as being low. Furthermore, ester cleavage to methacrylic acid (MAA) (and the alcohol) is a detoxification step resulting in metabolic products without expected mutagenic activity.

The genotoxic profile of alkyl methacrylates was evaluated in detail by Albertini (2017). The evaluation included MMA, EMA, hydroxyethyl methacrylate, BMA, iBMA, and 2EHMA, as well as methacrylic acid itself. The author concluded that, as a class, the lower alkyl methacrylates are universally negative for gene mutations in prokaryotes but do exhibit high dose clastogenicity in mammalian cells *in vitro.* The high dose clastogenicity in mammalian cells *in vitro* can be explained by potential intermediates generated under these conditions, or, alternatively, by the acidity caused by metabolic formation of MAA (Albertini, 2017). It has been shown that cell culture conditions at low pH may lead to clastogenicity (Gelbke et al., 2018). Overall, there was no convincing evidence that these compounds induce genotoxic effects *in vivo* in either submammalian or mammalian species. This dichotomy of effects can be explained by the potential genotoxic intermediates generated *in vitro* (Albertini, 2017).

Carcinogenicity

No carcinogenicity studies are available with alkyl methacrylates except methyl methacrylate. MMA was not carcinogenic in an older 2-year drinking water study with rats and dogs (Borzelleca et al., 1964). In 2-year inhalation studies with rats, mice, and hamsters MMA caused non-neoplastic lesions in the olfactory epithelium of rats and mice, but there was no evidence of local or systemic carcinogenicity in any species (Lomax, 1992; Lomax et al., 1997; NTP, 1986; Rohm and Haas, 1979a; 1979b)

The genotoxicity profile for the lower methacrylates as evaluated by Albertini (2017) was consistent with the earlier findings of long term carcinogenicity bioassays in animals, i.e. MMA as example of the group as not carcinogenic.

5.5.4 Toxicity to reproduction

Ethyl methacrylate

In a developmental toxicity study comparable to OECD TG 414, pregnant Sprague-Dawley rats (19 – 25/group) were exposed by whole-body inhalation exposure against 0, 600, 1200, 1800 or 2400 ppm EMA (0, 2820, 5640, 8460, 11280 mg/m³), 6 h/day on GD 6 to 20. No maternal deaths were observed, but maternal toxicity (decreased weight gain) was noted at ≥ 1200 ppm. Food consumption was already reduced at 600 ppm, but only slightly (< 5 %) and during the first half of exposure. Foetal body weight was lower at exposure concentrations ≥ 1200 ppm, but no substance-related embryo- or foetal lethality or malformations were observed at any EMA concentration. Also, there were no significant differences between the control and treated groups for external, visceral, or skeletal variations (Saillenfait et al., 1999). The NOAEC for maternal toxicity and embryo-/foeto-toxicity in this study was 600 ppm (LOAEC: 1200 ppm).

No histopathological evaluation of the respiratory tract was performed in the developmental toxicity study; therefore, no conclusion can be drawn regarding local effects on the nasal epithelia which have been observed in other studies with methacrylates after repeated inhalation.

n-Butyl and isobutyl methacrylate

In a developmental toxicity study comparable to OECD TG 414, pregnant Sprague-Dawley rats (22 – 25/group) were exposed by inhalation against 0, 100, 300, 600 or 1200 ppm (0, 590, 1770, 3540, 7080 mg/m³) n-BMA, 6 h/day on GD 6 to 20. No maternal deaths were observed. Maternal decreased weight gain was noted at ≥ 300 ppm during GD 6 – 13, but overall weight gain was only reduced 1200 ppm. Food consumption was also reduced at 1200 ppm. Foetal body weight was significantly but marginally lower (< 4 %) at 600 ppm in females and at 1200 ppm in males or both sexes combined (about 6 %). A slight increase in skeletal variations per litter was noted at 1200 ppm, but no substance-related embryo- or foetal lethality or malformations were observed at any BMA

concentration (Saillenfait et al., 1999). In this study, the NOAEC for maternal toxicity was 600 ppm (LOAEC 1200 ppm), based on reduced weight gain over the whole course of exposure. 600 ppm is also regarded as NOAEC for embryo-/foetoxicity, based on reduced foetal body weight in both sexes (thus, regarding the slight effect in females at 300 ppm as not adverse).

In a combined repeat dose and reproductive/developmental toxicity screening test (OECD TG 422), Sprague-Dawley rats (10 M + 10 F/group) were treated by gavage with 0, 30, 100, 300 or 1000 mg/(kg bw x d) for 44 days (M) or from 14 days before mating, throughout mating and pregnancy until day 3 of lactation (F). At the highest dose, in males weight gain depression, reduced food intake and increased relative kidney weights were noted and also alterations in urine analysis (increases in ketone bodies and occult blood), haematology and blood chemistry (increases in prothrombin time and BUN). Decreased absolute and relative spleen weight and splenic atrophy were observed at ≥ 100 mg/(kg bw x d). In females, weight gain depression, decreased food consumption, and splenic atrophy were observed at 1000 mg/(kg bw x d). An independently conducted review concluded that, based on published historical control data from the same test laboratory, effects seen at 100 and 300 mg/(kg bw x d) were not statistically significant when compared with historical controls. Thus, the NOAEL of this study is reported to be 300 mg/(kg bw x d) (ECHA Dissemination, 2021a).

2-Ethylhexyl methacrylate

Regarding toxicity to reproduction, the NOAEL in the OECD TG 422 study described above is considered as 1000 mg/(kg bw x d) for males (no effect on copulation and fertility) and 300 mg/(kg bw x d) for females (low number of corpora lutea and implantation sites at 1000 mg/(kg bw x d)). At 1000 mg/(kg bw x d), body weights of male and female neonates on Day 0 of lactation were significantly lower compared to controls. The neonates from three dams died during the lactation period at the highest dose. There was also a significantly lower number of total offspring in the high dose group, and at 300 mg/(kg bw x d), the number of neonates on Day 0 of lactation was lower compared with the control group. However, the difference was no longer significant on day 4 (due to reduced survival of neonates in control), and the observed number of neonates was within the historical control range of other OECD TG 422 in the same lab. No gross abnormalities were observed in neonates at any dose level (ECHA Dissemination, 2022).

A developmental toxicity study (OECD TG 414) was carried out with pregnant New Zealand rabbits (25 F/group). The animals received 0, 30, 100 or 300 mg 2EHMA/(kg bw x d) by gavage on GD6-28. Pregnancy was aborted for unknown reasons in two females at 100 mg/(kg bw x d) and one female at 300 mg/(kg bw x d). Food consumption was reduced in the high-dose group over the last week of the study, and mean absolute weight gain was non-significantly lower during the first week compared to the controls. However, mean body weight gain and terminal body weight were not reduced. Necropsy indicated a slightly increased incidence of red discoloured fundic mucosa of the stomach in high-dose animals, but histological examination did not reveal any treatment-related changes. The incidence of post-implantation losses was non-significantly increased at 300 mg/(kg bw x d), but the number of viable foetuses was not reduced. No other developmental or teratogenic effects were observed (ECHA Dissemination, 2022).

5.5.5 Odour perception

An odour threshold of 0.21 ppm (860 µg/m³) was determined by the “triangle bag method” for methyl methacrylate (MMA) (Nagata, 2003). No odour thresholds are available for higher alkyl methacrylates.

5.6 Evaluation

5.6.1 Existing regulations and classifications

There is a harmonised classification for the following C_2 to C_8 alkyl methacrylates with respect to toxicity (ECHA C&L Inventory, 2021):

- Ethyl methacrylate: skin irrit. 2 (H315), eye irrit. 2 (H319), STOT SE 3 (H335), skin sens. 1 (H317),
- n-butyl methacrylate: skin irrit. 2 (H315), eye irrit. 2 (H319), STOT SE 3 (H335), skin sens. 1 (H317),
- isobutyl methacrylate: skin irrit. 2 (H315), STOT SE 3 (H335), skin sens. 1B (H317),

As can be seen in the overview presented in Table 35, DNEL were derived on substance-specific data only for n-butyl and 2-ethylhexyl methacrylate.

Table 35: Overview of registration dossiers and DNEL derivation (inhalation route) for alkyl methacrylates[1]

Alkyl moiety	CAS No.	Dossier online	DNEL (mg/m³) general population	DNEL (mg/m³) workers	Route-to-route extra-polation	Read-across compound considered
Ethyl	97-63-2	Yes	76	370.5	No	Yes (methyl and butyl)
Propyl	2210-28-8	No	-	-		
Isopropyl	225-094-2	No	-	-		
Butyl	97-88-1	Yes	66.5 (local: 366.4)	415.9	No	No
Sec-butyl	2998-18-7	No	-	-		
Isobutyl	97-86-9	Yes	66.5 (local: 366.4)	415.9	No	Yes (n-butyl)
t-Butyl	585-07-9	Yes	-[2]	416 (local: 409)	No	Yes (n-butyl)
Pentyl	2849-98-1	No	-	-		
Isopentyl	7336-27-8	No	-	-		
Hexyl	142-09-6	Yes	-[5]	-	-	-
Heptyl	5459-37-0	No	-	-		
Isoheptyl	94247-07-1	No	-	-		
2-Methylhexyl	60250-80-8	No	-	-		
2-Ethylhexyl	688-84-6	Yes	-[3]	2.5	Yes	No
2-Propylheptyl	149855-64-1	Yes	-[2]	17.6	Yes	Yes (2-ethyl-hexyl)
Octyl	2157-01-9	Yes	-[3]	2.5	Yes	Yes (2-ethylhexyl)
Isooctyl	28675-80-1	No	-	-		
Octadecyl	32360-05-7	Yes	-[4]	-[4]	Yes	Yes (2-ethyl-hexyl)

1: Source: REACH registration dossiers (available at https://echa.europa.eu), only data for esters of methacrylic acid (MMA) with C_2 to C_8 mono-alkanols evaluated (no higher alkanols, alkandiols or higher polyols, no cyclo-, unsaturated, aromatic or non-HC-substituted alkyl methacrylates), 2: No consumer use intended, 3: only professional and industrial uses. For the general population the only known uses are all with (co-)polymers only. 4: Due to the extremely low vapour pressure of dodecyl methacrylate and the long-chain alkyl methacrylate esters (C12 – C22), inhalation exposure is not considered as relevant; 5: no toxicological summary provided in the dossier.

The DNEL for ethyl methacrylate was obtained by interpolation between the respective DNELs for MMA and n-BMA, weighed by the difference in molecular weight (ECHA Dissemination, 2021b).

The “local” DNEL for n-butyl methacrylate (BMA) is based on a NOAEC for olfactory epithelium lesions obtained in subacute inhalation study with rats (see 5.5.2). No time-extrapolation was performed for derivation of local DNEL because “As demonstrated with MMA once the olfactory

lesion is formed there is little or no increase in sensitivity with sub-acute to chronic exposure. No adjustment for studies of longer duration is required.". Also, the known mode of action involving ubiquitous and non-specific enzyme systems was considered to justify an intraspecies extrapolation factor of five for the general population (ECHA Dissemination, 2021a).

The DNEL for 2-ethylhexyl methacrylate (2EHMA) was only derived for workers as no consumer exposure is intended. The DNEL is based on a NOAEL of 120 mg/(kg bw x d) for effects on body weight and clinical parameters obtained in a subchronic oral toxicity with rats (see 5.5.2). Route-to-route extrapolation was performed including a standard factor of two to account for possible differences between oral and inhalation uptake. A standard factor of two was used for time extrapolation (ECHA Dissemination, 2022).

Besides the DNELs summarised in Table 35, a NIK (Lowest Concentration of Interest) value of 750 µg/m³ is reported for "other methacrylates" (AGBB, 2021). This value is based on the NIK value of 750 µg/m³ value for methyl methacrylate (read-across substance). The toxicologically critical endpoint for methyl methacrylate, as well as for butyl methacrylate, is the lesion of the olfactory epithelium. For deriving the NIK value, no molar adjustment was performed but derived NIK value for MMA was adopted for "other alkyl methacrylates".

5.6.2 Derivation of EU-LCI values for "other methacrylates"

Methacrylate esters form a group with a common methacrylate moiety in all representatives and an alkyl chain differing in the number of carbon atoms and, in higher members (starting at C_3), possible branching of this chain. "Other methacrylates" refers to all esters of methacrylic acid other than methyl methacrylate containing unbranched or branched saturated alkyl groups.

Compared to methyl methacrylate, the database for toxicological effects of other methacrylates is more limited. The available data have been summarised in several reviews (EFSA CEF, 2010; Gelbke et al., 2018; OECD SIDS, 2004; OECD SIDS, 2009). For several of these compounds, registration dossiers according to REACH are also available (see Table 35).

In case of **methyl methacrylate (MMA),** a concentration-dependent increase in the incidence and severity of olfactory epithelial lesions was observed in a chronic inhalation study with rats (NOAEC: 104 mg/m³ or 25 ppm, LOAEC: 416 mg/m³ or 100 ppm) (ECHA Dissemination, 2022b; Lomax, 1992; Lomax et al., 1997; U.S.EPA, 1998).

Similar lesions of the olfactory epithelium as produced by MMA have also been observed following inhalation exposure of rats to aliphatic esters of other saturated and unsaturated carboxylic acids and alcohols, e.g., methyl and ethyl acetate (ECB, 2003; Hardisty et al., 1999). The lesion is associated with the formation of the carboxylic acid by hydrolysis of the corresponding ester, which, after exceeding the specific buffer capacity of the cells, leads to acidification and consequently cytotoxic damage. Similar lesions are also caused by methyl acrylate (U.S.EPA, 1990), which, however, is more active than MMA and for which additional effects as reaction with sulfhydryl groups contribute to the toxic effect (OECD SIDS, 2003). The latter only plays a minor role in case of MMA, possibly at very high tissue concentrations, when metabolism by carboxyl esterases becomes saturated (Gelbke et al., 2018).

The OCED SIDS concluded that acute inhalation studies with rats have shown that EMA also produces olfactory lesions comparable to MMA following acute exposure at 200 ppm (948 mg/m³), but that alkyl-methacrylate esters with longer alkyl chains than EMA do not elicit a toxic response at this dose level after acute exposure, mainly because their physicochemical characteristics prevent significant local uptake of the vapours. Based upon the available data a clear trend exists across the short-chain alkyl methacrylate category such that the NOAEC/LOAEC for olfactory nasal lesions increases with increasing ester size (OECD, 2009).

Similar local lesions as caused by MMA were also observed in a subacute inhalation study with **n-butyl methacrylate (MBA)** (ECHA Dissemination, 2021a). The data base for alkyl methacrylates other than the two mentioned (MMA and BMA) is much more limited; especially, no sufficient toxicity data from inhalation studies with repeated exposure are available.

Generally, it can be assumed that the described local toxicity of alkyl methacrylates after inhalation is driven by the hydrolytic production of methacrylic acid from the corresponding ester and not by the toxicity of the alcohol produced at the same time. However, the systemic toxicity of the alkyl methacrylate itself or of the alcohol formed by hydrolysis may not be negligible. Therefore, in performing read-across for alkyl methacrylates, data from studies with oral exposure are taken into account and the derivation of EU-LCI values for data-deficient alkyl methacrylates will take into account two aspects:

- local toxicity in the nasal epithelium, usually by read-across using data for MMA or BMA,
- systemic toxicity (including toxicity to reproduction) using substance-specific or read—across data from oral toxicity studies.

5.6.2.1 EU-LCI value for ethyl methacrylate

The data base regarding the toxicity of ethyl methacrylate (EMA) is very limited.

No repeated dose toxicity study with inhalation exposure is available. A NOAEC for maternal toxicity and embryo-/foetoxicity of 600 ppm (2820 mg/m³) was obtained in a developmental toxicity study with rats (Saillenfait et al., 1999). However, no histopathological evaluation of the respiratory tract was performed in this study.

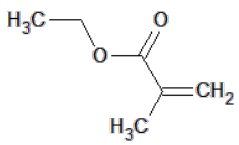
The EU-LCI derivation for ethyl methacrylate (EMA) was conducted via read-across with methyl methacrylate (MMA).

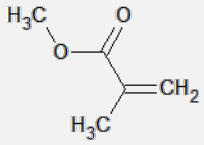
The rationale for read-across with methyl methacrylate are:

- Data poor compound: insufficient toxicological data for EMA; *de novo* derivation of EU-LCI for EMA is not possible.
- Read-across from MMA: within the chemical class of “alkyl methacrylates”, MMA is the closest homologue compound with an adequate data base. One additional CH_2 group in the aliphatic chain of EMA is the only difference between the two substances.
- Toxicological critical endpoint for MMA: nasal irritation (olfactory damage).

The key assumption underlying the read-across of the EU-LCI value from MMA to EMA is that both compounds have the same critical endpoint (lesions of the olfactory epithelium) and this is caused by the common methacrylate group (and not by the additional CH_2 group of the alkyl chain).

Table 36: Comparison of the structure and molar mass of methyl and ethyl methacrylate

Compound	Structure	Molar mass (g/mol)	EU-LCI value
Ethyl methacrylate (EMA)		114.14	Read-across Proposed: 850 µg/m³

Compound	Structure	Molar mass (g/mol)	EU-LCI value
Methyl methacrylate (MMA)		100.12	Derived: 750 µg/m³ (rounded value) Unrounded value 743 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,
- Using the derived unrounded EU-LCI value for methyl methacrylate of 743 µg/m³ and performing MW conversion at 23 °C and 1013 hPa leads to an EU-LCI for ethyl methacrylate of 743 µg/m³ x 1.14= 847 µg/m³, rounded to 850 µg/m³.

For the derivation of an EU-LCI value for ethyl methacrylate, it is suggested to perform the read-across from methyl methacrylate.

An EU-LCI value of 850 µg/m³ is proposed for ethyl methacrylate.

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

5.6.2.2 EU-LCI value for n- and isobutyl methacrylate

The lesions of the olfactory nasal epithelium of rats observed after inhalation exposure against butyl methacrylate (BMA) are considered as the critical effect. Similar lesions have been observed in rats after inhalation exposure against methyl methacrylate (MMA).

The NOAEC of 1832 mg/m³ obtained in a subacute inhalation study is used as the POD for the derivation of the EU-LCI.

The following assessment factors are used:

- Adjustment for exposure duration: 5.6
- Study length (subacute to chronic): 6
- Interspecies differences: 2.5
- Intraspecies differences: 10

Total assessment factor: 840,

leading to a calculated value of 2181 µg/m³ (rounded value: 2200 µg/m³).

An EU-LCI value of 2200 µg/m³ is proposed for n-butyl methacrylate.

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

For comparison: Derivation of the EU-LCI for BMA by read-across using the EU-LCI of 750 µg/m³ for MMA, performing molar adjustment and considering the “cut-off rule” (EC, 2013) with cut-off to propyl methacrylate would lead to a value of 2000 µg/m³, similar to the proposed value.

Derivation of the EU-LCI for BMA by route-to-route extrapolation using the NOAEL of 300 mg/(kg bw x d) from the combined repeated dose and reproductive/developmental toxicity screening test and

assuming no differences in oral and inhalation absorption would lead to a value of 300 : 2 : 1.15 : 2.5 : 10 = 5217 µg/m³.)

The data base for the derivation of sec-butyl, isobutyl, and t-butyl methacrylate from substance-specific data is insufficient. EU-LCI values for these isomers of n-butyl methacrylate may be derived by read-across from n-butyl methacrylate.

It is proposed to adopt the proposed EU-LCI value of 2200 µg/m³ for all isomers of butyl methacrylate.

Since no odour thresholds are available for butyl methacrylates, no conclusions can be drawn regarding olfactory perception at the proposed EU-LCI.

5.6.2.3 EU-LCI value for 2-ethylhexyl methacrylate

The registration dossier for 2-ethylhexyl methacrylate (2EHMA) summarises the data of an unpublished subacute inhalation toxicity study with rats exposed to 0, 25 and 60 ppm (0, 203 and 486 mg/m³). There were no overt signs of toxicity at autopsy; however, histology showed increased cellularity in the lungs (ECHA Dissemination, 2022). The higher concentration is very close to the saturated vapour concentration for 2EHMA (64.5 ppm or 510 mg/m³) (Gelbke et al., 2018) so the possibility of aerosol formation cannot be excluded.

Because of incomplete reporting and the possible aerosol exposure, these data cannot be used for the derivation of an EU-LCI value but only as supportive information.

The NOAEL of 120 mg/(kg bw x d) (based on lower weight, weight gain and food intake, transient changes of blood chemical parameters and increased relative organ weights of liver and kidney) obtained in a subchronic oral toxicity study (OECD TG 408) with rats is used as the POD for the derivation of the EU-LCI. Toxicokinetic data for alkyl methacrylates indicate that these compounds are well absorbed by oral and inhalation exposure. Thus, no additional factor is considered for differences in absorption, and the following assessment factors are used:

- Route-to-route extrapolation: 1.15 m³/(kg bw x d)
- Differences in absorption: 1 (assuming similar absorption by oral and inhalation exposure)
- Adjusted study length factor: 2
- Interspecies differences: 2.5
- Intraspecies differences: 10,

leading to a calculated value of 120 mg/(kg bw x d) : (1.15 x 2 x 25) = 2087 µg/m³ (rounded value: 2100 µg/m³).

An EU-LCI value of 2100 µg/m³ is proposed for 2-ethylhexyl methacrylate.

Since no odour threshold is available for 2EHMA, no conclusions can be drawn regarding olfactory perception of EMA at the proposed EU-LCI.

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E Appendix

E.1 Data collection and fact sheet for ethyl methacrylate

Table 37: Data collection sheet for ethyl methacrylate and "other methacrylates"

Compound	Ethyl methacrylate	"Other methacrylates"
Nº CAS 1 ppm = x mg/m³ (23 °C)	**97-63-2** 4.7	- **Depending on substance-specific molar mass**
EU-Classification **CLP, harmonised classification**		-
Organisation name	**REACH Registrants**	**AGBB**
Risk value name	DNEL (general population)	NIK ('Lowest Concentration of Interest')
Risk value (mg/m³)	76 (systemic) 189.8 (local)	0.75
Reference period	Chronic	Chronic
Risk value (mg/m³) **Short term (15 min)**	-	-
Year	2021	2021
Key study	See below	Lomax LG (1992); U.S.EPA (1998a)
Study type		Inhalation study with methyl methacrylate (MMA)
Species		Rat
Duration of exposure in key study		6 h/d, 5 d/week
Critical effect		Lesions of olfactory epithelium
Critical dose value	NAEC: 189.8 mg/m³	NOAEC: 104 mg/m³
Adjusted critical dose		104 : 5.6 = 18.6 mg/m³
Single assessment factors	Not reported	UF_A x UF_H = 2,5 x 10
Other effects		
Remarks	DNEL obtained by interpolation between the respective DNELs for MMA and n-BMA, weighed by the difference in molecular weight.	Read-across was applied and methyl methacrylate (MMA) was used as test item instead of ethyl methacrylate. The derived NIK value for MMA was adopted for other alkyl methacrylates.

Table 38: Fact sheet for methyl methacrylate*

Compound	Methyl methacrylate (MMA) C5H8O2		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	750
EU-LCI status	2	Draft/Final	Final
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2016
General information			
CLP-Index No.	4	INDEX	607-035-00-6
EC-No.	5	EINECS	201-297-1
CAS-No.	6	Chemical Abstract Service number	80-62-6
Harmonised CLP classification	7	Human health risk related classification	Skin Irrit. 2, Skin Sens. 1, STOT SE3
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	100.12 1 ppm = 4.16 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	F344 rats
Route / type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic, etc.	Chronic
Exposure duration	14	h/d, d/w	6 h/d, 5 d/w
Critical endpoint	15	Effect (s), site of	Lesions of olfactory epithelium
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEC
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	104 mg/m³
Assessment factors (AF)			
Adjustment for exposure duration	19	Study exposure h/d, d/w	5.6
Study length	20	sa→sc→c	1
Route-to-route extrapolation factor	21	-	1

Compound	Methyl methacrylate (MMA) C5H8O2		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	140
POD/TAF	28	Calculated value [µg/m³ and ppb]	743 µg/m³ and 178.6 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	750
Additional comments	31		
Rationale selection	32		

*: according to https://ec.europa.eu/docsroom/documents/49239

Data compilation and evaluation is based on a project funded by the German Environment Agency (Voss et al., 2017).

Methyl methacrylate (MMA) is a colourless liquid with an acrid fruity odour. No natural sources of MMA are known. MMA is a large-scale technical product. It is mainly used for the production of high molecular polymers, e. g. acrylic glass. In indoor air of homes, schools, nursery schools and offices, MMA is usually not detectable. However, very high concentrations of up to 13000 µg/m³ have been measured following improper renovation works in buildings. Similarly, high concentrations of about the same level can occur in nail and beauty salons.

No human or animal data on resorption of MMA following inhalation are available. In the isolated respiratory tract of rats, an uptake of about 20 % has been determined. Distribution and metabolism of MMA parallels that of other aliphatic esters, i.e. hydrolysis in nasal epithelia with the formation of the corresponding acid and alcohol. In this case, methacrylic acid and methanol MMA taken up into the bloodstream is also rapidly hydrolysed. The metabolites are further oxidised, with no accumulation in the body. Only small amounts of MMA are excreted in urine. The main elimination is by carbon dioxide in exhaled air.

Rationale for critical effect

The derivation of the EU-LCI is based on animal toxicity studies. Epidemiological studies of workers with occupational exposure to MMA may be used as supportive evidence but are considered insufficient as basis for the derivation.

The lesions of the olfactory epithelium in the nose of rats are considered as the critical effect. In a chronic inhalation study male and female F344 rats were exposed to MMA concentrations of 0, 104, 416 or 1664 mg/m³ for 6 h/d, 5 d/week for two years. A detailed histologic examination of animals in all exposure groups revealed a concentration-dependent increase in the incidence and severity of olfactory epithelial lesions. This study gave a NOAEC of 104 mg/m³ (Lomax, 1992; Lomax et al., 1997; U.S.EPA, 1998).

Similar lesions of the olfactory epithelium as produced by MMA have also been observed following inhalation exposure of rats to aliphatic esters of other saturated and unsaturated carboxylic acids and alcohols, e.g., methyl and ethyl acetate (ECB, 2003; Hardisty et al., 1999). The lesion was associated with the formation of the carboxylic acid by hydrolysis of the corresponding ester, which, after exceeding the specific buffer capacity of the cells, led to acidification and consequently cytotoxic damage. Similar lesions were also caused by methyl acrylate (U.S. EPA, 1990), which, however, was more active than MMA and for which additional effects as reaction with sulfhydryl groups contribute to the toxic effect (OECD SIDS, 2003). The latter only plays a minor role in case of MMA.

The chronic inhalation toxicity study with rats (Lomax, 1992; Lomax et al., 1997; U.S.EPA, 1998) was taken as the basis for the derivation of the EU-LCI. A benchmark calculation (using BMDS version 2.6.0.1 of U.S. EPA) has been performed for the incidence of minimal to severe degeneration/atrophy of the olfactory epithelium in male rats. The best-fitted model gave a BMDL05 of 120 mg/m³ which was only slightly above the reported NOAEC of 104 mg/m³. Thus, the conventional NOAEC approach may be used as well.

Rationale for starting point

The NOAEC of 104 mg/m³ for olfactory epithelial lesions in rats is used as the POD for the derivation of the EU-LCI.

Rationale for extrapolation factors

- Adjustment for exposure duration: 5.6
- Interspecies differences: 2.5
- Intraspecies differences: 10

Total extrapolation factor is 140, leading to a rounded value of 750 µg/m³.

A slightly higher value of 850 µg/m³ would be obtained by using the BMDL05 of 120 mg/m³ as POD. The EU-LCI is in the range of the absolute odour threshold (0.21 ppm = 0.86 mg/m³) determined by Nagata (2003).

Table 39: Fact sheet for ethyl methacrylate

Compound	Ethyl methacrylate (EMA) C6H10O2		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	850
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2022
General information			
CLP-Index No.	4	INDEX	607-071-00-2
EC-No.	5	EINECS	202-597-5
CAS-No.	6	Chemical Abstract Service number	97-63-2
Harmonised CLP classification	7	Human health risk related classification	Skin Irrit. 2 (H315), Eye Irrit. 2 (H319), STOT SE 3 (H335), Skin Sens. 1 (H317)
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	114.14 1 ppm = 4.7 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	Methyl methacrylate (MMA)
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/TAF in EU-LCI factsheet for MMA
POD value	17	[mg/m³] or ppm or [mg/kg_{BW}×d]	0.74 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	Ethyl methacrylate (EMA) C6H10O2		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]	743 µg/m³ and 178.6 ppb
Molar adjustment factor	29	Used in read-across (114.14/100.12)	1.14
Rounded value	30	[µg/m³] (743 µg/m³ x 1.14 = 847 µg/m³)	850
Additional comments	31		
Rationale selection	32		

Data compilation and evaluation is based on a project funded by the German Environment Agency (Voss et al., 2022).

Rationale for starting point

The data base regarding the toxicity of ethyl methacrylate (EMA) is very limited.

No repeated dose toxicity study with inhalation exposure is available.

In a developmental toxicity study comparable to OECD TG 414, pregnant Sprague-Dawley rats (19 – 23/group) were exposed by inhalation against 0, 600, 1200, 1800 or 2400 ppm EMA (0, 2820, 5640, 8460, 11280 mg/m³), 6 h/day on GD 6 to 20. No maternal deaths were observed, but maternal toxicity (decreased weight gain) was noted at ≥ 1200 ppm. Food consumption was already reduced at 600 ppm, but only slightly (< 5 %) and during the first half of exposure. Foetal body weight was lower at exposure concentrations ≥ 1200 ppm, but no substance-related embryo- or foetal lethality or malformations were observed at any EMA concentration (Saillenfait et al., 1999). The NOAEC for maternal toxicity and embryo-/foetoxicity in this study was 600 ppm (LOAEC: 1200 ppm).

No histopathological evaluation of the respiratory tract was performed in the developmental toxicity study; therefore, no conclusion can be drawn regarding local effects on the nasal epithelia which have been observed in other studies with methacrylates after repeated inhalation.

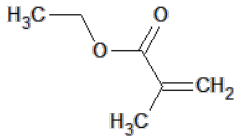
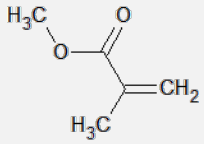
Rationale for read-across

The EU-LCI derivation for ethyl methacrylate (EMA) was conducted via read-across with methyl methacrylate (MMA). The key assumption is that MMA is the closest homologue with sufficient existing toxicological data and an already published EU-LCI value:

- Data poor compound: insufficient toxicological data for EMA; *de novo* derivation of EU-LCI for EMA is not possible.
- Read-across from MMA: within the chemical class of "alkyl methacrylates", MMA is the closest homologue compound with an adequate data base. One additional CH_2 group in the aliphatic chain of EMA is the only difference between the two substances.
- Toxicological critical endpoint for MMA: nasal irritation (olfactory damage).

The key assumption underlying the read-across of the EU-LCI value from MMA to EMA is that both compounds have the same critical endpoint (lesions of the olfactory epithelium) and this is caused by the common methacrylate group (and not by the additional CH_2 group of the alkyl chain).

Table 40: Comparison of the structure and molar mass of methyl and ethyl methacrylate

Compound	Structure	Molar mass (g/mol)	EU-LCI value
Ethyl methacrylate (EMA)		114.14	Read-across Proposed: 850 µg/m³
Methyl methacrylate (MMA)		100.12	Derived: 750 µg/m³ (rounded value) Unrounded value: 743 µg/m³

- No cut-off rule in place: difference in chain length between the two homologue compounds is no more than two CH_2 groups per aliphatic chain,
- Using the derived unrounded EU-LCI value for methyl methacrylate of 743 µg/m³ and performing MW conversion at 23 °C and 1013 hPa leads to an EU-LCI for ethyl methacrylate of 743 µg/m³ x 1.14= 847 µg/m³, rounded to 850 µg/m³.

For the derivation of an EU-LCI value for ethyl methacrylate, it is suggested to perform the read-across from methyl methacrylate.

An EU-LCI value of 850 µg/m³ is proposed for ethyl methacrylate.

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

E.1.1 Data collection and fact sheet for n- and iso-propyl methacrylate

Table 41: Data collection sheet for n- and isopropyl methacrylates

Compound	"Other methacrylates"
N° CAS 1 ppm = x mg/m³ (23 °C)	- **Depending on substance-specific molar mass**
EU-Classification **CLP, harmonised classification**	-
Organisation name	**AGBB**
Risk value name	NIK ('Lowest Concentration of Interest')
Risk value (mg/m³)	0.75
Reference period	Chronic
Risk value (mg/m³) **Short term (15 min)**	-
Year	2021
Key study	Lomax LG (1992); U.S.EPA (1998a)
Study type	Inhalation study with methyl methacrylate (MMA)
Species	Rat
Duration of exposure in key study	6 h/d, 5 d/week
Critical effect	Lesions of olfactory epithelium
Critical dose value	NOAEC: 104 mg/m³
Adjusted critical dose	104 : 5.6 = 18.6 mg/m³
Single assessment factors	UF_A x UF_H = 2,5 x 10
Other effects	
Remarks	Read-across was applied and methyl methacrylate (MMA) was used as test item instead of ethyl methacrylate. The derived NIK value for MMA was adopted for other alkyl methacrylates.

Table 42: Fact sheet for n-propyl methacrylate

Compound	Propyl methacrylate (PMA) C6H10O2		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	950
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2022
General information			
CLP-Index No.	4	INDEX	
EC-No.	5	EINECS	218-639-0
CAS-No.	6	Chemical Abstract Service number	2210-28-8
Harmonised CLP classification	7	Human health risk related classification	
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	128.17 1 ppm = 5.3 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	Methyl methacrylate (MMA)
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/TAF in EU-LCI factsheet for MMA
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	0.74 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	-	-
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	-

Compound	Propyl methacrylate (PMA) C6H10O2		Fact sheet
	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]	743 µg/m³ and 178.6 ppb
Molar adjustment factor	29	Used in read-across (128.17/100.12)	1.28
Rounded value	30	[µg/m³] (743 µg/m³ x 1.28 = 951 µg/m³)	950
Additional comments	31		
Rationale selection	32		

Table 43: Fact sheet for isopropyl methacrylate

Compound	Isopropyl methacrylate (iPMA) C6H10O2		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	950
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2022
General information			
CLP-Index No.	4	INDEX	
EC-No.	5	EINECS	225-094-2
CAS-No.	6	Chemical Abstract Service number	4655-34-9
Harmonised CLP classification	7	Human health risk related classification	
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	128.17 1 ppm = 5.3 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	Methyl methacrylate (MMA)
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/TAF in EU-LCI factsheet for MMA
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	0.74 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	-	-
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	-

Compound	Isopropyl methacrylate (iPMA) C6H10O2		Fact sheet
	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]	743 µg/m³ and 178.6 ppb
Molar adjustment factor	29	Used in read-across (128.17/100.12)	1.28
Rounded value	30	[µg/m³] (743 µg/m³ x 1.28 = 951 µg/m³)	950
Additional comments	31		
Rationale selection	32		

Data compilation and evaluation is based on a project funded by the German Environment Agency (Voss et al., 2022).

Rationale for starting point

No registration dossier and no data from reviews are available for propyl methacrylates, except for an LD50 (i. p.) of 1000 mg/kg bw in mice and a negative result in an Ames test with and without metabolic activation system (HSDB, 2010).

n-Propyl methacrylate is reported to be used as monomer for methacrylic polymers/methacrylic acid esters and acrylic resins (HSDB, 2010) but no more detailed data are available.

Rationale for read-across

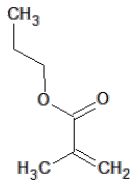
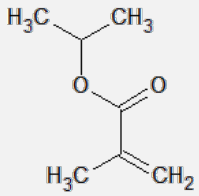
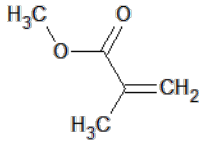
Principally, an EU-LCI value for both propyl methacrylates may be derived analogue to ethyl methacrylate by read-across using data for methyl methacrylate (see above):

- No cut-off rule in place: difference in chain length between the two homologue compounds is no more than two CH_2 groups per aliphatic chain,
- Using the derived unrounded EU-LCI value for methyl methacrylate of 743 µg/m³, considering the molar mass of MMA (104.12 g/mol) and of the propyl methacrylates (128.17 g/mol), and performing MW conversion at 23 °C and 1013 hPa leads to an EU-LCI of 743 µg/m³ x 128.17/100.12= 951 µg/m³, rounded to 950 µg/m³.

Alternatively, the derivation could be based on read-across using data for n-butyl methacrylate (see below):

- No cut-off rule in place: difference in chain length between the two homologue compounds is no more than two CH_2 groups per aliphatic chain,
- Using the derived unrounded EU-LCI value for n-butyl methacrylate (BMA) of 2181 µg/m³, considering the molar mass of BMA (142.2 g/mol) and of the propyl methacrylates (128.17 g/mol), and performing MW conversion at 23 °C and 1013 hPa leads to an EU-LCI of 2181 µg/m³ x 128.17/142.2 = 1962.9 µg/m³ rounded to 2000 µg/m³.

Table 44: Comparison of the structure and molar mass of methyl and n-propyl methacrylate

Compound	Structure	Molar mass (g/mol)	EU-LCI value
n-Propyl methacrylate (PMA)		128.17	Read-across Proposed: 950 µg/m³
Isopropyl methacrylate (iPMA)		128.17	Read-across Proposed: 950 µg/m³
Methyl methacrylate (MMA)		100.12	Derived: 750 µg/m³ (rounded value) Unrounded value: 743 µg/m³

Considering the almost complete lack of available data for propyl methacrylates, the more conservative approach based on read-across from methyl methacrylate is preferred.

An EU-LCI value of 950 µg/m³ may be proposed for n- and isopropyl methacrylate.

Since no odour threshold is available for both compounds, no conclusions can be drawn regarding olfactory perception of n-and isopropyl methacrylate at the proposed EU-LCI.

E.1.2 Data collection and fact sheet for butyl methacrylates

Table 45: Data collection sheet for n-butyl methacrylate

Compound	**n-Butyl methacrylate**	
Nº CAS 1 ppm = x mg/m³ (23 °C)	**97-88-1** 5.9	
EU-Classification **CLP, harmonised classification**		
Organisation name	**REACH registrants**	**AGBB**
Risk value name	DNEL (general population)	NIK ('Lowest Concentration of Interest')
Risk value (mg/m³)	66.5 (systemic) 366.4 (local)	0.75
Reference period	Chronic	Chronic
Risk value (mg/m³) **Short term (15 min)**	-	-
Year	2021	2021
Key study	OECD 413 as reported in the dossier	Lomax LG (1992); U.S.EPA (1998a)
Study type	Subacute inhalation study	Inhalation study with methyl methacrylate (MMA)
Species	Sprague-Dawley rat (n = 10 M + 10 F/group)	Rat
Duration of exposure in key study	6 h/d, 5 d/week, 4 weeks	6 h/d, 5 d/week
Critical effect	Degeneration of olfactory epithelium	Lesions of olfactory epithelium
Critical dose value	NOAEC: 11175 mg/m³	NOAEC: 104 mg/m³
Adjusted critical dose	11175 x 6/24 x 5/7 = 1995.5 mg/m³	104 : 5.6 = 18.6 mg/m³
Single assessment factors	UF_S 6 (local: 1), UF_A 1, UF_H 5 = 30 (local: 5)	UF_A x UF_H = 2,5 x 10
Other effects		
Remarks	Interspecies factor: 1; intraspecies factor: 5	Read-across was applied and methyl methacrylate (MMA) was used as test item instead of butyl methacrylate. The derived NIK value for MMA was adopted for other alkyl methacrylates.

Compound	n-Butyl methacrylate	
	No time extrapolation factor for derivation of local DNEL because "As demonstrated with MMA once the olfactory lesion is formed there is little or no increase in sensitivity with sub-acute to chronic exposure. No adjustment for studies of longer duration is required."	

Table 46: Fact sheet for butyl methacrylate

Compound	Butyl methacrylate (BMA) C8H14O2		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	2200
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2022
General information			
CLP-Index No.	4	INDEX	607-033-00-5
EC-No.	5	EINECS	202-615-1
CAS-No.	6	Chemical Abstract Service number	97-88-1
Harmonised CLP classification	7	Human health risk related classification	Skin Irrit. 2 (H315), Eye Irrit. 2 (H319), STOT SE 3 (H335), Skin Sens. 1 (H317)
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	142.2 1 ppm = 5.9 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	ECHA (2021) Subacute inhalation toxicity study with rats (OECD TG 421)
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	Rat, Sprague-Dawley (10 M, 10 F/group)
Route / type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic, etc.	Subacute (28 d)
Exposure duration	14	h/d, d/w	6 h/d, 5 d/week
Critical endpoint	15	Effect (s), site of	Lesions of olfactory epithelium
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEC
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	1832 mg/m³ (310 ppm)
Assessment factors (AF)			
Adjustment for exposure duration	19	Study exposure h/d, d/w	5.6
Study length	20	sa→sc→c	6
Route-to-route extrapolation factor	21	-	1

Compound	Butyl methacrylate (BMA) C8H14O2		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	840
POD/TAF	28	Calculated value [µg/m³ and ppb]	2181 µg/m³ (370 ppb)
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	2200
Additional comments	31		
Rationale selection	32		

Data compilation and evaluation is based on a project funded by the German Environment Agency (Voss et al., 2022).

Rationale for starting point

Studies with n-butyl methacrylate

In a subacute inhalation study according to OECD TG 412, Sprague-Dawley rats (5 M + 5 F/group) were exposed “whole body” against 0, 310, 952 or 1891 ppm BMA (0, 1832, 5626, 11175 mg/m³) for 6 h/d, 5 d/week for 4 weeks. Irritation of eyes (lacrimation, eye squinting) and laboured breathing were observed at ≥ 952 ppm. Histopathological, a treatment-related localised bilateral degeneration of the olfactory epithelium lining the dorsal meatus of the nasal cavity was noted in both sexes at ≥ 952 ppm (≥ 5626 mg/m³). No deaths and no treatment-related effects on body weight, feed consumption, haematological and clinical chemistry values were reported except for a slight increase in serum BUN at the highest concentration. This was accompanied by an increased relative kidney weight in both sexes without histopathological changes (ECHA Dissemination, 2021). A NOAEC of 310 ppm (1832 mg/m³) can be derived from this study.

Lethargy, increased urine output, loss in weight-gain, and congestion of blood vessels in livers, lungs and kidneys but no cellar injury was reported in an older unpublished study (report date 1959) after exposure of rats (n = 3, no details available) against an atmosphere saturated with BMA on 6 h/day for 20 days. No further details of the study are available. A concentration of about 11800 mg n-butyl

methacrylate/m³ is reported in the dossier to correspond to a saturated vapour atmosphere in this study (ECHA Dissemination, 2021). However, calculation from the vapour pressure reported for n-butyl methacrylate of 2.1 hPa (at 20 °C) leads to a saturated vapour concentration of 11760 mg/m³ (Gelbke et al., 2018), a value very close to the highest concentration of 11175 mg/m³ used in the subacute inhalation study mentioned above.

Rationale for key study/POD

The lesions of the olfactory nasal epithelium of rats observed after inhalation exposure against butyl methacrylate (BMA) are considered as the critical effect (ECHA Dissemination, 2021). Similar lesions have been observed in rats after inhalation exposure against methyl methacrylate (MMA).

The NOAEC of 1832 mg/m³ obtained in a subacute inhalation study is used as the POD for the derivation of the EU-LCI.

Rationale for extrapolation factors

- Adjustment for exposure duration: 5.6
- Study length (subacute to chronic): 6
- Interspecies differences: 2.5
- Intraspecies differences: 10

Total assessment factor: 840,

leading to a calculated value of 2181 µg/m³ (rounded value: 2200 µg/m³).

An EU-LCI value of 2200 µg/m³ is proposed for n-butyl methacrylate.

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

For comparison:

Derivation of the EU-LCI for BMA by read-across using the EU-LCI of 750 µg/m³ for MMA, performing molar adjustment and considering the “cut-off rule” (EC, 2013) with cut-off to propyl methacrylate would lead to a value of 2000 µg/m³, similar to the proposed value.

Studies with sec-butyl, isobutyl, and t-butyl methacrylate: The database is insufficient for the derivation of EU-LCI values based on substance-specific data.

Rationale for read-across

The EU-LCI derivation for butyl methacrylates other than n-butyl methacrylate may be conducted via read-across with n-butyl methacrylate. The key assumption is that n-butyl methacrylate is the closest homologue with sufficient existing toxicological data and a proposed EU-LCI value:

- Data poor compounds: no adequate toxicological data for other butyl methacrylates; *de novo* derivation of EU-LCI is not possible.
- Read-across from n-butyl methacrylate: within the chemical class ‘alkyl methacrylates’, n-butyl methacrylate is the closest homologue compound with an adequate data base. The only difference between the n-butyl and other butyl methacrylates is the structure of the butyl chain.
- Toxicological critical endpoint for n-butyl methacrylate: nasal irritation (olfactory damage).

- The key assumption underlying the read-across of the proposed EU-LCI value from n-butyl to other butyl methacrylates is that these compounds have the same critical endpoint (lesions of the olfactory epithelium) and this is caused by the common methacrylate group (and not by the structure of the butyl chain).
- No cut-off rule in place: no difference in chain length between the isomeric butyl methacrylates.

For the derivation of an EU-LCI value for butyl methacrylates other than n-butyl methacrylate, it is suggested to perform the read-across from n-butyl methacrylate and thus an EU-LCI value of 2200 µg/m³ is proposed for all butyl methacrylates.

Since no odour thresholds are available for butyl methacrylates, no conclusions can be drawn regarding olfactory perception at the proposed EU-LCI.

E.1.3 Data collection and fact sheet for 2-ethylhexyl methacrylates

Table 47: Data collection sheet for 2-ethylhexyl methacrylate

Compound	**2-Ethylhexyl methacrylate**		
No. CAS 1 ppm = x mg/m³ (23 °C)	**688-84-6** 8.2		
EU-Classification CLP, harmonised classification			
Organisation name	**REACH registrants**	**REACH registrants**	**AGBB**
Risk value name	DNEL (general population)	DNEL (workers)	NIK ('Lowest Concentration of Interest')
Risk value (mg/m³)	No hazard identified	2.5	0.75
Reference period	Chronic	Chronic	Chronic
Risk value (mg/m³) Short term (15 min)	-	-	-
Year	2021	2021	2021
Key study		OECD 408 as reported in the dossier	Lomax LG (1992); U.S.EPA (1998a)
Study type		Subchronic oral (gavage) study	Inhalation study with methyl methacrylate (MMA)
Species		Wistar rat (n = 10 or 15 M + 10 or 15 F/group)	Rat
Duration of exposure in key study		90 d	6 h/d, 5 d/week
Critical effect		Decreased body weight, changes in clinical-chemical parameters	Lesions of olfactory epithelium
Critical dose value		NOAEL: 120 mg/(kg bw x d)	NOAEC: 104 mg/m³
Adjusted critical dose		15.28 mg/m³	104 : 5.6 = 18.6 mg/m³

Compound	**2-Ethylhexyl methacrylate**		
Single assessment factors		Route-to-route: 2 0.38 m^3/kg (standard breathing volume rats); 10 m^3/6.7 m^3 (Correction for activity driven differences of respiratory volumes in workers compared to workers in rest) UF_S 2, UF_A 1, UF_H 3 = 6	UF_A x UF_H = 2.5 x 10
Other effects			
Remarks	Only professional and industrial uses; for the general population only known uses are all with (co-) polymers only		Read-across was applied and methyl methacrylate (MMA) was used as test item instead of 2-ethylhexyl methacrylate. The derived NIK value for MMA was adopted for other alkyl methacrylates.

Table 48: Fact sheet for 2-ethylhexyl methacrylate

Compound	2-Ethylhexyl methacrylate (2EHMA) C12H22O2		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2022
General information			
CLP-Index No.	4	INDEX	
EC-No.	5	EINECS	211-708-6
CAS-No.	6	Chemical Abstract Service number	688-84-6
Harmonised CLP classification	7	Human health risk related classification	-
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	198.3 1 ppm = 8.2 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	ECHA (2021) Subchronic oral toxicity study with rats (OECD TG 408)
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	Rat, Sprague-Dawley (10 M, 10 F/group)
Route / type of study	12	Inhalation, oral feed, etc.	Oral
Study length	13	Days, subchronic, chronic, etc.	Subchronic
Exposure duration	14	h/d, d/w	Daily
Critical endpoint	15	Effect (s), site of	
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEL
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	120 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)

Compound	2-Ethylhexyl methacrylate (2EHMA) C12H22O2		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)	Included in route-to-route extrapolation factor
	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]	2087 µg/m³ (255 ppb)
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	2100
Additional comments	31		
Rationale selection	32		

Data compilation and evaluation is based on a project funded by the German Environment Agency (Voss et al., 2022).

Rationale for starting point

The registration dossier for 2-ethylhexyl methacrylate (2EHMA) summarises the data of an unpublished subacute inhalation toxicity study in which Alderley Park rats (4 M + 4 F/group) were exposed to 0, 25 and 60 ppm (0, 203 and 486 mg/m³) 2EHMA 6 h/day, 5 d/week for three weeks. There were no signs of toxicity at autopsy; blood and urine tests were normal. Gross examination of the major organs revealed no adverse effects, however, histology showed increased cellularity in the lungs (ECHA Dissemination, 2021). The higher concentration is very close to the saturated vapour concentration for 2EHMA (64.5 ppm or 510 mg/m³) (Gelbke et al., 2018) so the possibility of aerosol formation cannot be excluded.

A subchronic oral toxicity study according to OECD TG 408 was performed in which Wistar rats (10 M + 10 F/group, additionally 5 M + 5 F/high dose and control for 28-day recovery) received 0, 60, 120 or 360 mg/(kg bw x d) by gavage for 90 days. At the highest dose, the following treatment-related effects were noted: lower weight, weight gain and food intake in females, transient changes of blood chemical parameters and increased relative organ weights of liver and kidney in both sexes. The NOAEL was considered to be 120 mg/(kg bw x d) (ECHA Dissemination, 2021).

In a combined repeated dose and reproductive/developmental toxicity screening test (OECD TG 422), Sprague-Dawley rats (12 M + 12 F/group) were treated by gavage with 0, 30, 100, 300 or 1000 mg 2EHMA/(kg bw x d) for 49 days (M) or from 14 days before mating, throughout mating and pregnancy until day 4 of lactation (F). One high-dose female died during the study (no further information presented). Treatment-related microscopic changes were observed in the liver and spleen of high dose males and in the thymus, spleen and brain of high dose females. These changes consisted of mild focal necrosis of the liver, mild decreased extramedullary haematopoiesis in the spleen, mild atrophy of the thymus, and a softened lesion of the medulla oblongata. 300 mg/(kg bw x d) was considered a LOAEL for males, based on increased absolute and relative weights of the kidneys, and relative weight of liver and pituitary gland. Corresponding changes at the high dose were noted in serum BUN (kidney); protein, enzymes and A/G ratio (liver), and haematology (spleen and pituitary). Blood samples were not taken from the pregnant females. In high dose females, increased absolute kidney and relative weights of thyroid gland, liver and brain were observed. Relative kidney weight was also increased at 100 and 300 mg/(kg bw x d), but the effect at 100 mg/(kg bw x d) was considered biologically insignificant based on the magnitude of the change compared to controls. The LOAEL for females is therefore considered to be 300 mg/(kg bw x d), as in males, based on organ weight changes. The NOAEL for males and females in this study is thus 100 mg/(kg bw x d) (ECHA Dissemination, 2021).

Regarding toxicity to reproduction, the NOAEL in the OECD TG 422 study described above is considered as 1000 mg/(kg bw x d) for males (no effect on copulation and fertility) and 300 mg/(kg bw x d) for females (low number of corpora lutea and implantation sites at 1000 mg/(kg bw x d)). At 1000 mg/(kg bw x d), body weights of male and female neonates on Day 0 of lactation were significantly lower compared to controls. The neonates from three dams died during the lactation period at the highest dose. There was also a significantly lower number of total offspring in the high dose group, and at 300 mg/(kg bw x d), the number of neonates on Day 0 of lactation was lower compared with the control group. However, the difference was no longer significant on day 4 (due to reduced survival of neonates in control), and the observed number of neonates was within the historical control range of other OECD TG 422 in the same lab. No gross abnormalities were observed in neonates at any dose level (ECHA Dissemination, 2021).

A developmental toxicity study (OECD TG 414) was carried out with pregnant New Zealand rabbits (25 F/group). The animals received 0, 30, 100 or 300 mg 2EHMA/(kg bw x d) by gavage on GD6-28. Pregnancy was aborted for unknown reasons in two females at 100 mg/(kg bw x d) and one female at 300 mg/(kg bw x d). Food consumption was reduced in the high-dose group over the last week of the study, and mean absolute weight gain was non-significantly lower during the first week compared to the controls. However, mean body weight gain and terminal body weight were not reduced. Necropsy indicated a slightly increased incidence of red discoloured fundic mucosa of the stomach in high-dose animals, but histological examination did not reveal any treatment-related changes. The incidence of post-implantation losses was non-significantly increased at 300 mg/(kg bw x d), but the number of viable foetuses was not reduced. No other developmental or teratogenic effects were observed (ECHA Dissemination, 2021).

Rationale for key study/POD

Because of incomplete reporting, the data from the only available study with inhalation exposure to 2EHMA cannot be used for the derivation of an EU-LCI value but only as supportive information.

The NOAEL of 120 mg/(kg bw x d) obtained in a subchronic oral toxicity study (OECD TG 408) with rats is used as the POD for the derivation of the EU-LCI.

Rationale for extrapolation factors

- Route-to-route extrapolation factor: 1.15 m³/(kg bw x d)
- Differences in absorption: 1 (assuming similar absorption by oral and inhalation exposure)
- Adjusted study length factor: 2
- Interspecies differences: 2.5
- Intraspecies differences: 10,

leading to a calculated value of 120 mg/(kg bw x d) : (1.15 x 2 x 25) = 2087 µg/m³ (rounded value: 2100 µg/m³).

An EU-LCI value of 2100 µg/m³ is proposed for 2-ethylhexyl methacrylate.

Since no odour threshold is available for 2EHMA, no conclusions can be drawn regarding olfactory perception of EMA at the proposed EU-LCI.

E.1.4 Further alkyl methacrylates

EU-LCI values for alkyl methacrylates other than methyl methacrylate (for which a final EU-LCI is published) have been proposed for n-butyl and 2-ethylhexyl methacrylate (2EHMA) on the basis of substance-specific data. The proposed EU-LCI values of 2200 µg/m³ for n-butyl methacrylate and of 2100 µg/m³ for 2EHMA are very similar. Considering the uncertainties of these derivations due to the limited data base (e. g., subacute study for n-butyl methacrylate, route-to-route extrapolation for 2EHMA), a common EU-LCI value of 2100 µg/m³ for both substances may be considered (using the lower value for a conservative approach). Additionally, this common value could also be proposed for other C_4 to C_8-alkyl methacrylates.

A NOAEL of 1000 mg/(kg bw x d), the highest dose applied, is available for dodecyl methacrylate from an OECD TG 422 study with oral exposure of rats (ECHA Dissemination, 2021). Otherwise, the data base becomes extremely limited for methacrylates with alkyl chains longer than 2-ethylhexyl. At the same time, no data are available regarding use of these compounds in products for consumers, and no data on indoor air concentrations or other data indicating inhalation exposure of consumers are available. Therefore, EU-LCI values are not derived for these alkyl methacrylates.

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