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Toxicological basis data for the derivation of EU-LCI values for neopentyl glycol, diisobutyl succinate, diisobutyl glutarate, 1,2-dimethoxyethane and 1,2-diethoxyethane

Final report

by

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Abstract: Toxicological basis data for the derivation of EU-LCI values for neopentyl glycol, diisobutyl succinate, diisobutyl glutarate, 1,2-dimethoxyethane and 1,2-diethoxyethane

The objective of this study was the evaluation of toxicological data for five substances as basis for the derivation of EU-LCI values. EU-LCI values are used to characterise the toxicity of volatile organic compounds emitting from building products. They are defined as the concentration above which effects on human health in indoor environment can occur and are agreed by the EU-LCI Working Group. This group has also developed a harmonised procedure for the derivation of EU-LCI values from toxicological data.

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.

The substances evaluated and the draft EU-LCI values derived in this study were the following: neopentyl glycol (CAS No. 126-30-7), draft EU-LCI: 8700 µg/m³, based on the highest dose tested in repeated dose toxicity studies in rats (no treatment-related adverse effects were observed); diisobutyl succinate (CAS No. 925-06-4), draft EU-LCI: 35 µg/m³, derived by read across from dimethyl succinate, based on the degeneration of nasal mucosa in rats; diisobutyl glutarate (CAS No. 71195-64-7), draft EU-LCI: 35 µg/m³, derived by read across from dimethyl glutarate, based on the degeneration of nasal mucosa in rats; 1,2-dimethoxyethane (CAS No. 110-71-4), draft EU-LCI: 100 µg/m³, based on teratogenicity in rats; 1,2-diethoxyethane (CAS No. 629-14-1), EU-LCI: 150 µg/m³, based on teratogenicity in mice.

Kurzbeschreibung: Toxikologische Basisdaten für die Ableitung von EU-LCI Werten für Neopentylglykol, Bernsteinsäurediisobutylester, Glutarsäurediisobutylester, 1,2-Dimethoxyethan und 1,2-Diethoxyethan

Gegenstand dieser Studie war die Auswertung der toxikologischen Daten für fünf Substanzen als Grundlage für die Ableitung von EU-LCI Werten. EU-LCI Werte dienen der Charakterisierung der Toxizität leicht flüchtiger organischer Verbindungen, die aus Bauprodukten emittieren. Sie sind definiert als diejenige Konzentration, oberhalb derer im Innenraum Wirkungen auf die menschliche Gesundheit eintreten können und werden von der EU-LCI Arbeitsgruppe beschlossen. Diese Gruppe hat auch ein harmonisiertes Vorgehen für die Ableitung der EU-LCI Werte aus toxikologischen Daten entwickelt.

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 festgelegt.

Für folgende Substanzen wurden in dieser Studie toxikologische Evaluierungen durchgeführt und EU-LCI Werte abgeleitet: Neopentylglykol (CAS Nr. 126-30-7), EU-LCI: 8700 µg/m³, basierend auf der höchsten nach wiederholter Verabreichung in Ratten getesteten Konzentration (es wurden keine adversen Effekte beobachtet); Bernsteinsäurediisobutylester (CAS Nr. 925-06-4), EU-LCI: 35 µg/m³, abgeleitet durch Analogbetrachtung von Bernsteinsäuredimethylester, basierend auf der Schädigung der Nasenschleimhaut in Ratten; Glutarsäurediisobutylester (CAS Nr. 71195-64-7), EU-LCI: 35 µg/m³, abgeleitet durch Analogbetrachtung von Glutarsäuredimethylester, basierend auf der Schädigung der Nasenschleimhaut in Ratten; 1,2-Dimethoxyethan (CAS Nr. 110-71-4), EU-LCI: 100 µg/m³, basierend auf der Teratogenität in Ratten; 1,2-Diethoxyethan (CAS Nr. 629-14-1), EU-LCI: 150 µg/m³, basierend auf der Teratogenität in Mäusen.

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ADH	Alcohol Dehydrogenase
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 Limit Value)
ALDH	Aldehyde Dehydrogenase
ANSES	Agence nationale de sécurité sanitaire de l'alimentation, de l'environment et du travail (French Agency for Food, Environmental and Occupational Health and Safety)
BAuA	Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (Federal Institute for Occupational Safety and Health)
CAS	Chemical Abstracts Service
CLI	Concentration Limite d'Intérêt (Lowest concentration of interest)
CLP	Classification, labelling and packaging
DNEL	Derived No Effect Level
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECHA	European Chemicals Agency
EGDEE	Ethylene glycol diethyl ether
EGDME	Ethylene glycol dimethyl ether
EU	European Union
GD	Gestation Day
HPRT	Hypoxanthine-guanine Phosphoribosyl Transferase
LCI	Lowest Concentration of Interest
LD_{50}	Lethal Dose, 50 %
LOAEC/L	Lowest Observed Adverse Effect Concentration/Level
Log POW	Logarithm of the octanol/water partition coefficient
MAA	2-Methoxyacetic acid
MAK	Maximale Arbeitsplatzkonzentration (Maximum workplace concentration)
NIK	Niedrigste Interessierende Konzentration (Lowest concentration of interest)
NOAEC/L	No Observed Adverse Effect Concentration/Level
NPG	Neopentyl glycol
NTP	National Toxicology Program (of the USA)
OECD	Organisation for Economic Co-Operation and Development
POD	Point of Departure
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
SIDS	Screening Initial Data Set
SPIN	Substances in Preparations in Nordic Countries

TAF	Total Assessment Factor
TRGS 900	Technische Regeln für Gefahrstoffe (Technical Rules for Hazardous Substances)
VOC	Volatile Organic Compound

Summary

Buildings products are a potential source for emissions of hazardous chemicals into indoor air. In order to protect consumers from adverse health effects, limit values are defined for relevant chemicals to reflect the lowest concentration, above which some effects on human health can be expected. These so-called EU-LCI values (Lowest Concentration of Interest) are agreed by the EU-LCI working group based on the evaluation of toxicological data according to a harmonised procedure. The objective of this study was the toxicological evaluation of five substances as basis for the derivation of EU-LCI values.

Substance profile and EU-LCI value for neopentyl glycol

Neopentyl glycol is a colourless solid with a low vapour pressure at room temperature. It is a high production volume chemical that is manufactured in quantities of 100,000-1,000,000 t/a in the European Economic Area and employed for a variety of uses with potential relevance for consumer exposure via indoor air, such as paints, construction materials, furniture, textiles, fragrances and toys. Emissions from cement-based building materials can reach up to 1400 µg/m³ under standard testing conditions.

The toxicological database for neopentyl glycol is limited. It was included in the OECD programme for the evaluation of high production chemicals, but considered of low priority for further work, and no in-depth evaluation was performed. More data became available during registration under REACH. Reliable data on the toxicity of neopentyl glycol in animals are only available from studies using oral exposure. After inhalation, the substance is assumed to be absorbed and distributed rapidly. The acute systemic toxicity is very low. Local effects can be caused on the eyes, but not on the skin or respiratory tract. After repeated oral administration to rats, male animals showed signs of nephrotoxicity at a dose of 1000 mg/kg bw x d. No such effects were observed in females. Because of this as well as several characteristic histopathological findings, the kidney effects can be assumed to be caused by a mode of action dependent on α_{2u}-globulin, which is typical for male rats but has no relevance for humans who do not produce this protein. No other adverse effects were observed during sub-chronic exposure at doses levels up to 1000 mg/kg bw x d. *In vitro* genotoxicity tests provided no indication that neopentyl glycol has any mutagenic potential. Reproductive toxicity of neopentyl glycol was investigated after oral administration to rats, with no effects on fertility or prenatal development noted at the tested dose levels of up to 1000 mg/kg bw x d.

As no adverse effects were observed during toxicity testing that can be considered relevant for human health, the highest tested dose level of 1000 mg/kg bw x d is chosen as POD for the derivation of an EU-LCI value for neopentyl glycol and adjusted to 500 mg/kg bw x d to account for potential differences in absorption between the oral and inhalation route.

Standard assessment factors are chosen for study length (2), route-to-route extrapolation (1.15), interspecies differences (2.5) and intraspecies differences (10) to give a total assessment factor of 57.5. The calculated value of 8696 µg/m³ (2027 ppb) is rounded to a proposed EU-LCI value of 8700 µg/m³ for neopentyl glycol.

Substance profile and EU-LCI value for diisobutyl succinate

Diisobutyl succinate is not registered under REACH but some uses in consumer products such as paints and cleaning agents have been reported, and it has been detected in indoor air.

Because no toxicity data are available for diisobutyl succinate, read across from dimethyl succinate is performed. This read across is justified by the common metabolic pathway: In the nasal mucosa, both esters are converted by carboxylesterase to succinic acid and the respective

alcohol components. Succinic acid induces local cytotoxicity based on a decrease of pH. Dimethyl succinate is currently listed with an EU-LCI value of 50 µg/m³, but this is an ascribed value, and a new EU-LCI value needed to be derived based on toxicological evaluation before read across to diisobutyl succinate could be performed.

Toxicological data for dimethyl succinate show that its acute systemic toxicity is low, it acts irritant to the eyes, and it has no apparent mutagenic potential. Further investigations were only performed with dimethyl succinate as part of a mixture with dimethyl glutarate and dimethyl adipate. As all these esters are locally metabolised to their respective acids, which are of comparable chain length and acidity, read across from the ester mixture to dimethyl succinate seems justified. The leading health effect observed in subchronic inhalation toxicity studies with the ester mixture in rats is the degeneration of nasal olfactory epithelium. A NOAEC value could not be derived from the reported studies, the LOAEC was 20 mg/m³. Toxicity of the ester mixture to reproduction was not observed in a one-generation reproductive toxicity study and a developmental toxicity study with test concentrations up to 1000 mg/m³ administered to rats as an aerosol.

The LOAEC of 20 mg/m³ for local effects on the respiratory tract was chosen as POD. To account for exposure duration during testing (6 h/d, 5 d/week), an assessment factor of 5.6 was calculated. Standard assessment factors were chosen for study length (2), uncertainty of the dose-response (3), interspecies differences (2.5) and intraspecies differences (10). With a total assessment factor of 840 and the POD of 20 mg/m³, an initial value of 23.8 µg/m³ is calculated for the mixture of dibasic esters. Molar adjustment for the difference in molar mass between the mixture and the single substance dimethyl succinate gives 21.9 µg/m³, which is rounded to the proposed new EU-LCI value of 20 µg/m³ for dimethyl succinate.

For read across to diisobutyl succinate, molar adjustment is applied to the unrounded value of 21.9 µg/m³ to give an initial value of 34.5 µg/m³, which is rounded to the proposed EU-LCI value of 35 µg/m³ for diisobutyl succinate.

Substance profile and EU-LCI value for diisobutyl glutarate

The case of diisobutyl glutarate is quite similar to that of diisobutyl succinate described above: It is not registered under REACH but consumer uses and the occurrence in indoor air were reported.

Read across is performed, in this case from dimethyl glutarate to diisobutyl glutarate, again based on the common metabolic pathway through ester cleavage in the nasal mucosa, in this case to release glutaric acid as the responsible agent for local cytotoxicity. Dimethyl glutarate also has an ascribed EU-LCI value of 50 µg/m³. Therefore, a new EU-LCI value needed to be derived based on toxicological evaluation before read across to diisobutyl glutarate could be performed.

Toxicological data available for dimethyl glutarate indicates that its acute systemic toxicity is low, and there is no genotoxic potential. Investigations of repeated dose toxicity after inhalation exposure were performed both with dimethyl glutarate alone and with the dibasic ester mixture with somewhat different results. While the leading health effect observed for the ester mixture was the degeneration of nasal olfactory epithelium, with a LOAEC was 20 mg/m³ and no significant systemic toxicity, dimethyl glutarate alone led to decreased testosterone levels and increased epididymal sperm counts in rats, with a NOAEC of 10 mg/m³ for systemic toxicity. On the other hand, in the same study local effects on the upper airways were only observed at the highest dose, with a NOAEC for local toxicity of 50 mg/m³. Contrary to these results, effects on the male reproductive system were not observed during a one-generation reproductive toxicity

study with the mixture of dibasic esters. Investigations of developmental toxicity with both dimethyl glutarate alone and the ester mixture did not reveal any effects on prenatal development at the test concentrations up to 1000 mg/m³ administered as an aerosol to rabbits and rats.

The NOAEC of 10 mg/m³ for effects on male reproductive parameters is considered questionable: Firstly, the effects are contradictory in themselves. Decreased testosterone levels should be associated with decreases in sperm counts, not, as reported, with increases. Secondly, reproductive parameters were not affected in a dedicated reproduction study at much higher dose levels. Therefore, the local effects on the respiratory tract were still considered as decisive for the derivation of an EU-LCI value. For these effects, a NOAEC of 50 mg/m³ for dimethyl glutarate is reported from a study, for which not many details have been disclosed. On the other hand, the study reporting a LOAEC of 20 mg/m³ for the mixture of dibasic esters is fully published and all findings are described in detail. Therefore, the LOAEC of 20 mg/m³ from this study was chosen as POD.

To account for exposure duration during testing (6 h/d, 5 d/week), an assessment factor of 5.6 was calculated. Standard assessment factors were chosen for study length (2), uncertainty of the dose-response (3), interspecies differences (2.5) and intraspecies differences (10). With a total assessment factor of 840 and the POD of 20 mg/m³, an initial value of 23.8 µg/m³ is calculated for the mixture of dibasic esters. Molar adjustment for the difference in molar mass between the mixture and the single substance dimethyl glutarate gives 24.8 µg/m³, which is rounded to the proposed new EU-LCI value of 25 µg/m³ for dimethyl glutarate.

For read across to diisobutyl glutarate, molar adjustment is applied to the unrounded value of 24.8 µg/m³ to give an initial value of 36.8 µg/m³, which is rounded to the proposed EU-LCI value of 35 µg/m³ for diisobutyl glutarate.

Substance profile and EU-LCI value for 1,2-dimethoxyethane

1,2-Dimethoxyethane is a colourless liquid that is used as solvent and process chemical in industry and has been banned from most consumer uses due to its classification as reproductive toxicant. It may still be present in indoor air due to its previous use in paints and varnishes.

Toxicological data for 1,2-dimethoxyethane are available from its registration under REACH. Based on its harmonised classification as Repr. 1B (H360FD), the European Chemicals Agency published an Annex XV dossier for the identification as substance of very high concern. The critical toxicological properties of 1,2-dimethoxyethane are similar to other substances such as 2-methoxyethanol and are assumed to be caused by the main metabolite methoxyacetic acid. Acute systemic and local effects are not significant, although the substance can cause some irritation to skin. From genotoxicity studies *in vitro* and *in vivo* it can be concluded that 1,2-dimethoxyethane does not have any mutagenic potential. In subacute inhalation toxicity studies, the substance caused adverse effects on the male reproductive system in rabbits and rats (changes to the seminiferous epithelium, aspermia). The NOAEC was 187 mg/m³. In teratogenicity studies, inhalation exposure to 1,2-dimethoxyethane resulted in increased incidences of foetal malformations in rabbits and rats. The NOAEC values were 37 mg/m³ for rats (LOAEC 120 mg/m³) and 60 mg/m³ for rabbits.

The leading adverse health effect of 1,2-dimethoxyethane is its teratogenicity. This is in agreement with effects observed for similar compounds that are metabolised to methoxyacetic acid, the presumed responsible agent. From the available teratogenicity data, the NOAEC of 37 mg/m³ obtained from the rat study is chosen as POD for the derivation of an EU-LCI value because it is the lowest NOAEC reported for this endpoint.

To account for exposure duration during testing (6 h/d), an assessment factor of 4 was calculated. Standard assessment factors were chosen for the severity of the effect (3), interspecies differences (2.5) and intraspecies differences (10). An assessment factor for study length was not needed, as exposure was maintained throughout the relevant time window for the critical effect. With a total assessment factor of 300 and the POD of 37 mg/m³, a value of 123 µg/m³ (33.2) is calculated and rounded to 100 µg/m³ as the proposed EU-LCI value for 1,2-dimethoxyethane.

Substance profile and EU-LCI value for 1,2-diethoxyethane

1,2-Diethoxyethane is a colourless liquid. The available information on its uses is very limited. It is banned from most consumer uses due to its classification as reproductive toxicant but may still be present in indoor air due to previous uses as solvent in paints and varnishes.

There is only very little information regarding the toxicity of 1,2-diethoxyethane. It has been identified as a substance of very high concern by ECHA due to its classification as reproductive toxicant. Presumably, this effect is due to its metabolism to ethoxyacetic acid via ether cleavage and enzymatic oxidation. The acute systemic toxicity is very low. As part of the National Toxicology Program of the United States, the teratogenicity of 1,2-diethoxyethane was studied in mice and rabbits. Following oral administration during the relevant period of gestation, increased incidences of foetal malformations were found in both species. This occurred at dose levels well below maternal toxicity, which was limited to reduced body weight gains in the highest dose groups. In mice, the NOAEL was 50 mg/kg bw x d for developmental toxicity and 500 mg/kg bw x d for maternal toxicity. In rabbits, the NOAEL was 25 mg/kg bw x d for developmental toxicity and 100 mg/kg bw x d for maternal toxicity. No information regarding potential genotoxicity or carcinogenicity of 1,2-diethoxyethane could be found.

The leading adverse health effect of 1,2-diethoxyethane is its teratogenicity. This is in agreement with effects observed for similar glycol ether derivatives. From the available teratogenicity data, the NOAEL of 50 mg/kg bw x d in mice is chosen as POD for the derivation of an EU-LCI value because this approach leads to the lower LCI. This value is adjusted for route-to-route extrapolation by dividing by the human respiratory rate and the default factor to account for differences in absorption to give a POD of 87.5 mg/m³.

No assessment factor for study length was needed, as exposure was maintained throughout the relevant time window for the critical effect. Standard assessment factors were chosen for the severity of the effect (3), interspecies differences (7 x 2.5 = 6) and intraspecies differences (10). With a total assessment factor of 525 and the POD of 87.5 mg/m³, a value of 167 µg/m³ (34.4 ppb) was calculated. This was rounded to 150 µg/m³ as the proposed EU-LCI value for 1,2-diethoxyethane.

In an alternative procedure, the LCI value could be derived from the NOAEL of 25 mg/kg bw x d observed in rabbits. In this case, the POD after route-to-route extrapolation would be 44 mg/m³. Assessment factors for the severity of the effect (3), interspecies differences (2.4 x 2.5 = 6) and intraspecies differences (10) would result in a total assessment factor of only 180 and a calculated POD/TAF value of 244 µg/m³ (50.2 ppb), which is higher than the value calculated from the mouse study. The LCI value derived from the oral teratogenicity study in mice is therefore preferred because it can be considered to be more protective.

Zusammenfassung

Bauprodukte sind mögliche Quellen für Emissionen gefährlicher Chemikalien in die Innenraumluft. Zum Schutz von Verbraucherinnen und Verbrauchern vor schädlichen Wirkungen auf die Gesundheit werden für relevante Chemikalien Referenzwerte definiert, die die niedrigste Konzentration widerspiegeln, oberhalb derer Wirkungen auf die menschliche Gesundheit erwartet werden können. Diese sogenannten EU-LCI Werte (Lowest Concentration of Interest = niedrigste interessierende Konzentration) werden von der EU-LCI Arbeitsgruppe beschlossen. Grundlage ist die Auswertung toxikologischer Daten nach einem harmonisierten Vorgehen. Gegenstand dieser Studie war die toxikologische Evaluierung von fünf chemischen Stoffen als Grundlage für die Ableitung von EU-LCI Werten.

Stoffprofil und EU-LCI Wert für Neopentylglykol

Neopentylglykol ist ein farbloser Feststoff mit niedrigem Dampfdruck bei Raumtemperatur. Es wird in großen Mengen hergestellt, im Europäischen Wirtschaftsraum zwischen 100.000 und 1.000.000 t/a. Es hat ein breites Spektrum von Anwendungen mit möglicher Relevanz für die Exposition von Menschen über die Innenraumluft, zum Beispiel in Farben, Baustoffen, Möbeln, Textilien, Duftstoffen und Spielzeugen. Unter Standardtestbedingungen können die Emissionen von Neopentylglykol aus zementbasierten Baustoffen bis zu 1400 µg/m³ erreichen.

Die toxikologische Datenbasis für Neopentylglykol ist beschränkt. Zwar wurde es im Rahmen des OECD Programms zur Bewertung hochvolumiger Chemikalien evaluiert, aber die Priorität für weitere Arbeiten wurde als gering eingeschätzt, und eine vertiefte Bewertung fand nicht statt. Weitere Daten wurden durch die Registrierung unter REACH zugänglich. Verlässliche Daten zur Toxizität von Neopentylglykol in Versuchstieren sind nur aus Studien mit oraler Verabreichung verfügbar. Es wird angenommen, dass die Substanz nach Einatmen schnell aufgenommen und verteilt wird. Die akute systemische Toxizität ist sehr gering. Lokale Reizwirkungen werden auf die Augen ausgeübt, nicht aber auf die Haut oder die Atemwege. Nach wiederholter oraler Gabe zeigten männliche Ratten Anzeichen von Nierentoxizität bei einer Dosis von 1000 mg/kg bw x d. In weiblichen Ratten wurden diese Effekte nicht beobachtet. Aus diesem Grund sowie wie wegen bestimmter histologischer Befunde ist zu vermuten, dass die beobachtete Nierentoxizität auf einem durch α_{2u}-Globulin hervorgerufenen Wirkmechanismus beruht, der charakteristisch für männliche Ratten ist, aber keine Relevanz für den Menschen hat, der dieses Protein nicht produziert. Während der subchronischen Exposition in Dosierungen bis 1000 mg/kg bw x d wurden keine weiteren Schadwirkungen beobachtet. Studien zur Gentoxizität *in vitro* ergaben keinen Hinweis auf eine mögliche mutagene Wirkung von Neopentylglykol. Die Reproduktionstoxizität von Neopentylglykol nach oraler Verabreichung wurde in Ratten untersucht. Für die untersuchten Dosierungen bis zu 1000 mg/kg bw x d wurden keine Wirkungen auf Fortpflanzung oder Pränatalentwicklung festgestellt.

Da in den toxikologischen Studien keine schädlichen Wirkungen von Relevanz für die menschliche Gesundheit festgestellt wurden, wurde die höchste untersuchte Dosis von 1000 mg/kg bw x d als Ausgangspunkt für die Ableitung eines EU-LCI Wertes für Neopentylglykol ausgewählt. Berücksichtigung der möglicher Absorptionsunterschiede nach Inhalation verglichen mit oraler Aufnahme durch einen Korrekturfaktor von 2 ergab einen POD von 500 mg/kg bw x d.

Anwendung von Standardwerten für die Extrapolationsfaktoren zur Berücksichtigung der Studiendauer (2), der Extrapolation zwischen verschiedenen Aufnahmepfaden (1,15), der Interspeziesunterschiede 2,5) und der Intraspeziesunterschiede (10) ergab einen Gesamtfaktor

von 57,5. Der berechnete Wert von 8696 µg/m³ (2027 ppb) wurde gerundet auf 8700 µg/m³ als Vorschlag für einen EU-LCI Wert für Neopentylglykol.

Stoffprofil und EU-LCI Wert für Bernsteinsäurediisobutylester

Bernsteinsäurediisobutylester wurde nicht unter REACH registriert, aber einige Anwendungen in Verbraucherprodukten wie Farben und Reinigungsmitteln sind bekannt, und der Stoff wurde in der Innenraumluft nachgewiesen.

Da für Bernsteinsäurediisobutylester keinerlei Toxizitätsdaten vorliegen, wurde eine Analogbetrachtung mit Bernsteinsäuredimethylester durchgeführt. Dieses Vorgehen ist gerechtfertigt durch den gemeinsamen Stoffwechselweg: Die Ester werden in der Nasenschleimhaut durch Carboxylesterase zu Bernsteinsäure und dem jeweiligen Esteralkohol umgesetzt. Bernsteinsäure verursacht durch Senkung des pH-Wertes Zytotoxizität im umliegenden Gewebe. Für Bernsteinsäuredimethylester ist derzeit ein EU-LCI Wert von 50 µg/m³ vermerkt. Hierbei handelt es sich aber um einen zugeschriebenen Wert (‚ascribed value'). Für eine Analogbetrachtung mit Bernsteinsäurediisobutylester muss daher zunächst ein neuer EU-LCI Wert für Bernsteinsäuredimethylester auf der Basis toxikologischer Daten abgeleitet werden.

Die toxikologischen Daten für Bernsteinsäuredimethylester zeigen geringe akute systemische Toxizität. Es wirkt reizend auf die Augen. Hinweise auf mutagenes Potential wurden nicht festgestellt. Weitere Untersuchungen wurden mit Bernsteinsäuredimethylester nur als Teil eines Gemisches zusammen mit Glutarsäuredimethylester und Adipinsäuredimethylester durchgeführt. Da diese Ester alle lokal in der Nase zu ihren jeweiligen Säuren umgesetzt werden, und diese von vergleichbarer Kettenlänge und Säurestärke sind, scheinen Analogschlüsse zwischen dem Estergemisch und Bernsteinsäuredimethylester als Einzelstoff gerechtfertigt. Die maßgebliche Gesundheitswirkung, die für das Estergemisch in einer subchronischen Inhalationsstudie in Ratten festgestellt wurde, ist eine degenerative Veränderung des olfaktorischen Epithels in der Nase. Aus den durchgeführten Studien konnte kein NOAEC-Wert abgeleitet werden, der LOAEC-Wert war 20 mg/m³. Studien zur Reproduktionstoxizität und zur Teratogenität des Estergemisches in Ratten ergaben keine Hinweise auf schädigende Wirkungen im untersuchten Dosisbereich bis 1000 mg/m³.

Der LOAEC-Wert von 20 mg/m³ für die lokale Wirkung auf die Atemwege wurde als POD ausgewählt. Für die Berücksichtigung der experimentellen Expositionsdauer von 6 h/d, 5 d/Woche wurde ein Korrekturfaktor von 5,6 angewendet. Zusammen mit Standardfaktoren für die Studiendauer (2), die Unsicherheit hinsichtlich der Dosis-Wirkungs-Beziehung (3), die Interspeziesunterschiede (2,5) und die Intraspeziesunterschiede (10) resultierte ein Gesamtfaktor von 840. Der errechnete Wert von 23,8 µg/m³ für das Estergemisch führte nach Korrektur für die unterschiedlichen Molmassen zu einem Wert von 21,9 µg/m³ für Bernsteinsäuredimethylester. Der gerundete Wert von 20 µg/m³ ist der Vorschlag für einen neuen EU-LCI Wert für Bernsteinsäuredimethylester.

Für die Analogbetrachtung mit Bernsteinsäurediisobutylester wurde der ungerundete Wert von 21,9 µg/m³ zugrunde gelegt, der nach Korrektur für die unterschiedlichen Molmassen einen Wert von 34,5 µg/m³ ergab. Der gerundete Wert von 35 µg/m³ ist der Vorschlag für einen EU-LCI Wert für Bernsteinsäurediisobutylester.

Stoffprofil und EU-LCI Wert für Glutarsäurediisobutylester

Die Sachlage für Glutarsäurediisobutylester ist der für Bernsteinsäurediisobutylester beschriebenen sehr ähnlich. Der Stoff ist nicht unter REACH registriert, aber Anwendungen in Verbraucherprodukten und Vorkommen in der Innenraumluft wurden berichtet.

Wieder wurde eine Analogbetrachtung durchgeführt, in diesem Fall zwischen Glutarsäurediisobutylester und Glutarsäuredimethylester. Grundlage ist abermals der gemeinsame Stoffwechselweg über die Esterspaltung in der Nasenschleimhaut, in diesem Fall unter Freisetzung von Glutarsäure, die Zytotoxizität im umliegenden Gewebe verursacht. Auch für Glutarsäuredimethylester ist derzeit ein EU-LCI Wert von 50 µg/m³ als zugeschriebener Wert vermerkt. Für eine Analogbetrachtung mit Glutarsäurediisobutylester muss daher zunächst ein neuer EU-LCI Wert für Glutarsäuredimethylester auf der Basis toxikologischer Daten abgeleitet werden.

Die toxikologischen Daten für Glutarsäuredimethylester zeigen geringe akute systemische Toxizität. Hinweise auf mutagenes Potential wurden nicht festgestellt. Untersuchungen zur Inhalationstoxizität nach wiederholter Verabreichung wurden mit Glutarsäuredimethylester sowohl als Einzelstoff als auch als Teil des Estergemisches wie oben beschrieben durchgeführt. Die Ergebnisse wichen zum Teil voneinander ab. Während für das Estergemisch als maßgebliche Gesundheitswirkung die Veränderung der Nasenschleimhaut mit dem LOAEC-Wert von 20 mg/m³, aber keinerlei systemische Toxizität beobachtet wurde, führte Glutarsäuredimethylester als Einzelstoff zu verminderten Testosteronspiegeln und erhöhter Spermienproduktion in den Nebenhoden, mit einem NOAEC-Wert von 10 mg/m³ für die systemische Toxizität. Lokale Wirkungen auf die oberen Atemwege wurden dagegen in dieser Studie nur mit der Höchstdosis beobachtet, so dass für die lokale Toxizität ein NOAEC-Wert von 50 mg/m³ abgeleitet wurde. Im Gegensatz zu diesen Beobachtungen wurden in einer Fortpflanzungsstudie mit dem Estergemisch keine Wirkungen auf das männliche Fortpflanzungssystem festgestellt. Teratogenitätsstudien mit Glutarsäuredimethylester als Einzelstoff sowie als Teil des Estergemisches ergaben im untersuchten Dosisbereich bis 1000 mg/m³ keine Anzeichen für eine Wirkung auf die Pränatalentwicklung von Ratten und Kaninchen.

Der NOAEC-Wert von 10 mg/m³ für die Wirkung auf männliche Fortpflanzungsparameter erscheint fragwürdig: Zum einen sind die beobachteten Effekte widersprüchlich in sich selbst. Verminderte Testosteronspiegel sollten mit einer verminderten Spermienproduktion einhergehen und nicht, wie beschrieben, mit einer gesteigerten. Zum zweiten wurden in einer speziell auf Fortpflanzungstoxizität ausgelegten Studie mit weitaus höheren Dosierungen keinerlei Wirkungen auf das männliche Reproduktionssystem erzielt. Daher wird nach wie vor die lokale Toxizität auf die Atemwege als maßgebliche Gesundheitswirkung für die Ableitung eines EU-LCI Wertes betrachtet. Hinsichtlich dieser Wirkung wurde für Glutarsäuredimethylester ein NOAEC-Wert von 50 mg/m³ aus einer Studie abgeleitet, für die nur wenige Einzelheiten veröffentlicht wurden. Auf der anderen Seite ist die Studie, die einen LOAEC-Wert von 20 mg/m³ für das Estergemisch gefunden hat, vollständig publiziert, und die Befunde wurden sehr detailliert beschrieben. Daher wird der LOAEC-Wert von 20 mg/m³ aus dieser Studie als POD gewählt.

Für die Berücksichtigung der experimentellen Expositionsdauer von 6 h/d, 5 d/Woche wurde ein Korrekturfaktor von 5.6 angewendet. Zusammen mit Standardfaktoren für die Studiendauer (2), die Unsicherheit hinsichtlich der Dosis-Wirkungs-Beziehung (3), die Interspeziesunterschiede (2,5) und die Intraspeziesunterschiede (10) resultierte ein Gesamtfaktor von 840. Der errechnete Wert von 23,8 µg/m³ für das Estergemisch führte nach Korrektur für die unterschiedlichen Molmassen zu einem Wert von 24,8 µg/m³ für Glutarsäuredimethylester. Der gerundete Wert von 25 µg/m³ ist der Vorschlag für einen neuen EU-LCI Wert für Glutarsäuredimethylester.

Für die Analogbetrachtung mit Glutarsäurediisobutylester wurde der ungerundete Wert von 24,8 µg/m³ zugrunde gelegt, der nach Korrektur für die unterschiedlichen Molmassen einen

Wert von 36,8 µg/m³ ergab. Der gerundete Wert von 35 µg/m³ ist der Vorschlag für einen EU-LCI Wert für Glutarsäurediisobutylester.

Stoffprofil und EU-LCI Wert für 1,2-Dimethoxyethan

1,2-Dimethoxyethan ist eine farblose Flüssigkeit, die im industriellen Rahmen als Lösungsmittel und Prozesschemikalie eingesetzt wird. Verbraucheranwendungen sind aufgrund der Einstufung als reproduktionstoxisch durch rechtliche Bestimmungen weitgehend untersagt, aber aus früheren Verwendungen in Farben und Lacken kann der Stoff noch in der Innenraumluft vorkommen.

Toxikologische Daten für 1,2-Dimethoxyethan stehen durch die Registrierung unter REACH zur Verfügung. Basierend auf der harmonisierten Einstufung als Repr. 1B (H360FD) veröffentlichte die Europäische Chemikalienagentur ein Annex XV-Dossier zur Identifizierung von 1,2-Dimethoxyethan als besonders besorgniserregender Stoff. Die kritischen toxikologischen Eigenschaften von 1,2-Dimethoxyethan ähneln denen bestimmter anderer Stoffe wie etwa 2-Methoxyethanol und werden auf das Stoffwechselprodukt Methoxyessigsäure zurückgeführt. Bis auf leichte Hautreizungen liegen keine akuten systemischen oder lokalen Schadwirkungen vor. Gentoxizitätsstudien *in vitro* und *in vivo* führten zu dem Schluss, dass 1,2-Dimethoxyethan kein mutagenes Potential besitzt. In subakuten Studien zur Inhalationstoxizität in Kaninchen und Ratten verursachte 1,2-Dimethoxyethan Beeinträchtigungen von männlichen Reproduktionsparametern (Veränderung des Keimepithels, Aspermie) mit einem NOAEC-Wert von 187 mg/m³. In Teratogenitätsstudien führte Inhalation von 1,2-Dimethoxyethan in Kaninchen und Ratten zu einem vermehrten Auftreten missgebildeter Föten. Der NOAEC-Wert war 37 mg/m³ in Ratten (mit einem LOAEC-Wert von 120 mg/m³) und 60 mg/m³ in Kaninchen.

Die maßgebliche Schadwirkung von 1,2-Dimethoxyethan ist seine Teratogenität. Dies stimmt auch mit Befunden für ähnliche Stoffe überein, die metabolisch zu Methoxyessigsäure umgewandelt werden, welche als eigentlich wirksames Agens angesehen wird. Aus den vorliegenden Daten zur Teratogenität von 1,2-Dimethoxyethan wurde der NOAEC-Wert von 37 mg/m³ in Ratten als POD ausgewählt, da dies der niedrigste vorliegende NOAEC-Wert für den kritischen Effekt ist.

Mit einem Korrekturfaktor von 4 für die experimentelle Expositionsdauer von 6 h/d und Standardfaktoren für den Schweregrad der Wirkung (3), die Interspeziesunterschiede (2,5) und die Intraspeziesunterschiede (10) resultierte ein Gesamtfaktor von 300. Ein Extrapolationsfaktor für die Studienlänge wird nicht benötigt, da das für die Wirkung relevante Zeitfenster vollständig experimentell erfasst wurde. Der errechnete Wert von 123 µg/m³ (33,2 ppb) wurde gerundet auf 200 µg/m³ als Vorschlag für einen EU-LCI Wert für 1,2-Dimethoxyethan.

Stoffprofil und EU-LCI Wert für 1,2-Diethoxyethan

1,2-Diethoxyethan ist eine farblose Flüssigkeit. Die vorliegenden Informationen zur Verwendung sind sehr begrenzt. Verbraucheranwendungen sind aufgrund der Einstufung als reproduktionstoxisch rechtlich weitgehend untersagt, aber aus früheren Verwendungen in Farben und Lacken kann der Stoff in der Innenraumluft vorkommen.

Zur Toxizität von 1,2-Diethoxyethan liegen nur sehr wenige Angaben vor. Aufgrund seiner Einstufung als reproduktionstoxisch wurde es von der ECHA als besonders besorgniserregender Stoff identifiziert. Vermutlich geht die toxische Wirkung auf die metabolische Umsetzung zu Ethoxyessigsäure zurück. Die akute systemische Toxizität ist sehr gering. Im Rahmen des National Toxicology Program der USA wurde die Teratogenität von 1,2-Diethoxyethan in Kaninchen und Mäusen untersucht. Nach oraler Verabreichung während der relevanten Phase

der Tragzeit wurde in beiden Tierarten ein gehäuftes Auftreten missgebildeter Föten festgestellt. Dies geschah bereits weit unterhalb der für die Muttertiere toxischen Dosis. Nur für die Höchstdosis wurde in den Muttertieren eine verminderte Gewichtszunahme beobachtet. In Mäusen wurde ein NOAEL von 50 mg/kg bw x d für die Teratogenität und 500 mg/kg bw x d für die mütterliche Toxizität festgestellt. In Kaninchen betrug der NOAEL 25 mg/kg bw x d für die Teratogenität und 100 mg/kg bw x d für die mütterliche Toxizität. Bezüglich möglicher Gentoxizität oder Karzinogenität von 1,2-Diethoxyethan liegen keine Informationen vor.

Die maßgebliche Schadwirkung von 1,2-Diethoxyethan ist seine Teratogenität. Dies stimmt auch mit Befunden für ähnliche Stoffe überein, die metabolisch zu Ethoxyessigsäure umgewandelt werden, welche als eigentlich wirksames Agens angesehen wird. Aus den vorliegenden Daten zur Teratogenität von 1,2-Diethoxyethan wurde der NOAEL von 50 mg/kg bw x d in Mäusen als POD ausgewählt, da dieses Vorgehen zu dem niedrigsten LCI Wert führte. Für die Extrapolation von oraler zu inhalativer Aufnahme wurde der NOAEL-Wert durch die menschliche Atemfrequenz und den Standardfaktor von 2 für etwaige Absorptionsunterschiede dividiert. Der erhaltene POD war 87,5 µg/m³.

Ein Extrapolationsfaktor für die Studienlänge wird nicht benötigt, da das für die Wirkung relevante Zeitfenster vollständig experimentell erfasst wurde. Mit den Standardfaktoren für den Schweregrad der Wirkung (3), die Interspeziesunterschiede (7 x 2,5 = 6) und die Intraspeziesunterschiede (10) resultierte ein Gesamtfaktor von 525. Der errechnete Wert von 167 µg/m³ (34,4 ppb) wurde gerundet auf 150 µg/m³ als Vorschlag für einen EU-LCI Wert für 1,2-Diethoxyethan.

Wenn alternative dazu der LCI Wert auf der Grundlage der Kaninchenstudie mit dem NOAEL von 25 mg/kg bw x d abgeleitet würde, wäre der POD, nach Extrapolation von oraler zu inhalativer Aufnahme, 44 mg/m³. Die Extrapolationsfaktoren für den Schweregrad der Wirkung (3), die Interspeziesunterschiede (2,4 x 2,5 = 6) und die Intraspeziesunterschiede (10) würden in einem Gesamtfaktor von nur 180 resultieren und damit in einem errechneten Wert für POD/TAF von 244 µg/m³ (50,2 ppb), welcher höher wäre als der mit den Mausdaten erhaltene. Der LCI Wert durch Ableitung aus der oralen Teratogenitätsstudie in Mäusen wird daher bevorzugt.

1 Introduction

Emissions of volatile organic compounds from building products are a relevant source for the exposure to chemicals from indoor air. Many of these chemicals can cause adverse health effects in humans. In order to minimise exposure to hazardous chemicals, voluntary and mandatory labelling schemes for construction materials can be used to indicate that emissions of chemicals are kept below levels of potential relevance to human health. For this purpose, the European Commission publishes health-related limit values, the so-called Lowest Concentration of Interest (LCI), for chemicals that are frequently emitted from building products. LCI is defined as "the lowest concentration above which, according to best professional judgement, the pollutant may have some effect on people in the indoor environment".

EU-LCI values are agreed by the EU-LCI working group. Several substances were given 'ascribed' EU-LCI values that correspond to values assigned to them by the national authorities in Germany or France in earlier years. In contrast, 'derived' EU-LCI values are based on the evaluation of toxicological data according to a harmonised framework developed by the EU-LCI working group (ECA, 2013). The procedure follows general toxicological and risk assessment principles and in particular the REACH guidance on information requirements and chemical safety assessment (ECHA, 2012a; 2017). It involves the compilation and evaluation of all available toxicological data, the identification of the critical health effect, the choice of the appropriate point of departure, and the application of assessment factors to account for route-to-route extrapolation, exposure duration, study length, interspecies and intraspecies differences, the severity of the effect, the uncertainty of the dose-response, sensitive population groups etc as applicable.

The objective of this study was the derivation of draft EU-LCI values for five substances:

- Neopentyl glycol (CAS No. 126-30-7)
- Diisobutyl succinate (CAS No. 925-06-4)
- Diisobutyl glutarate (CAS No. 71195-64-7)
- 1,2-Dimethoxyethane (CAS No. 110-71-4)
- 1,2-Diethoxyethane (CAS No. 629-14-1)

Existing risk assessment reports or evaluations from the following institutions were taken into account as far as they were available: European Commission, European Chemicals Agency, National Institute for Occupational Safety and Health (USA), World Health Organization, Organization for Economic Co-Operation and Development, Agency of Toxic Substances and Disease Registry (USA), US Environmental Protection Agency, German Environment Agency, and occupational limit values issued by individual countries. Further, the following sources were consulted for additional chemical and toxicological information: European Chemicals Agency dissemination site, eChemPortal maintained by OECD, Hazardous Substances Data Bank and TOXNET maintained by the U.S. National Library of Medicine, ChemIDplus and PubMed.

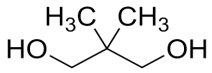
The draft EU-LCI values for the five substances were presented at a meeting of the EU-LCI working group in Berlin on 4/5 November 2019 and amended according to the received comments.

2 Toxicological evaluation of neopentyl glycol as basis for the derivation of an EU-LCI value

2.1 Substance identification

Substance identification data and physicochemical properties of neopentyl glycol are shown in Table 1 and Table 2.

Table 1 Substance identification of neopentyl glycol

CAS No. EC No.	Systematic name; common names	Summary formula	Structural formula
126-30-7 204-781-0	2,2-Dimethylpropane-1,3-diol; 1,3-dihydroxy-2,2-dimethylpropane; neopentyl glycol (NPG)	$C_5H_{12}O_2$	

2.2 Substance properties and uses

Neopentyl glycol is at room temperature a colourless solid with a very low vapour pressure. It is freely miscible with water and organic solvents.

Table 2 Physicochemical properties of neopentyl glycol

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa)	Conversion 1 ppm = x mg/m³	Log P_{OW}	Solubility in water (g/L)
104.15	123-130	209	$3.3\ 10^{-3}$ (25 °C)	4.29 (23 °C)	-0.15 (25 °C)	830 (20 °C)

Source: ECHA Dissemination (2020a).

As a high production chemical, neopentyl glycol is manufactured and/or imported in the European Economic Area in quantities of 100,000 – 1,000,000 t/a. It is used in a large variety of applications for industrial activities as well as in consumer products. The most relevant uses with regard to indoor air are in paints, coatings, adhesives, plasters, construction materials, fragrances, air refreshers, flooring, furniture, textiles, leather products, footwear, toys, paper/cardboard products and electronic equipment.

2.3 Exposure

2.3.1 Indoor air

There are no reports about measured concentrations of neopentyl glycol in indoor environments. However, an emission chamber test on different cement- and lime-based building materials found high emissions of neopentyl glycol from cement-based materials (Katsoyiannis et al., 2012). After 72 h it was found in concentrations as high as 1,400 µg/m³, accounting for up to 93 % of total VOCs. The concentrations were not considerably changed between 24 and 72 h. Test conditions included a temperature of 23 °C, a relative humidity of 50 % and an air exchange rate of 0.5/h.

2.3.2 Other sources

No information could be found.

2.4 Toxicokinetics

There is no information available regarding toxicokinetics of neopentyl glycol after inhalation. Metabolism after oral exposure was studied in rabbits (Gessner et al., 1960). After dosing four animals per gavage with 1000-1500 mg/kg bw x d, excretion in urine was determined over a period of 24 h. In the pooled samples, 62 % (range 53-67 %) of the applied dose was found as the glucuronic acid conjugate, indicating rapid absorption. The only other compounds detected were the metabolite 3-hydroxy-2,2-dimethylpropionic acid (1.9 % of the applied dose) and a small amount of the unchanged test substance (0.7 % of the applied dose).

2.5 Health effects

2.5.1 Acute toxicity, sensory irritation and local effects

Neopentyl glycol shows very low acute systemic toxicity after inhalation or oral exposure (ECHA Dissemination, 2020a):

Acute toxicity of neopentyl glycol after inhalation was studied in rats in a test design similar to that described in the Annex to OECD test guideline 403. After 8h-exposure to a vapour-saturated atmosphere (calculated nominal concentration of neopentyl glycol: 140 mg/m³), animals were observed over a period of 7 days. No mortality, clinical signs, body weight changes, or gross pathological findings after necropsy were observed.

Three rats exposed for 6 h to 39400 ppm (168 g/m³) showed symptoms of irritation of the respiratory tract, laboured and/or accelerated respiration, loss of coordination and prostration during the exposure period. One out of three rats died within 24 h, the other two survived the post exposure observation period of 14 days. Body weight of the survivors was increased. Necropsy was not performed.

Acute oral toxicity was studied in a test set-up similar to OECD test guideline 401 in rats and in mice. In rats, doses between 200 and 12000 mg/kg bw were administered per gavage. The LD_{50} value was determined as 6920 mg/kg bw. In surviving animals, clinical signs such as atony, apathy, and narcosis were reversible. In mice, the administered doses were between 1600 and 6400 mg/kg bw, and the LD_{50} value was determined as 3200 mg/kg bw.

As described above, local effects on the respiratory tract were only observed during exposure to the extremely high concentration of 168 g/m³, but not with the lower, but still considerably high concentration of 140 mg/m³.

Skin irritation studies with neopentyl glycol using rabbits gave inconsistent results (ECHA Dissemination, 2020a). In an earlier study not conforming to current test guidelines, animals showed no effect after 1-15 minutes, but slight irritant effects after 20 h. Later, two skin irritation studies according to OECD test guideline 404 were performed. After 4 h of exposure, slight irritant effects were observed in one study, but not in the other.

During a study according to OECD test guideline 405, neopentyl glycol caused serious eye damage in rabbits (ECHA Dissemination, 2020a). After 100 mg of the test substance was instilled into the conjunctival sac, necrosis occurred within 72 h. After 21 days, the damage was irreversible.

In a Murine Local Lymph Node Assay according to OECD test guideline 429, neopentyl glycol did not show any skin sensitising potential (ECHA Dissemination, 2020a). After application of the test substance (60 % in propylene glycol) to CBA/J mice, no increases in 3H-thymidine

incorporation, auricular nymph node cell counts, lymph node weights or ear weights were observed.

2.5.2 Repeated dose toxicity

Inhalation toxicity of neopentyl glycol after repeated exposure was only investigated in a short-term study not according to current standards, for which only fragmentary information is available. Over a period of 10 days, rats were exposed to an atmosphere containing neopentyl glycol in a mean concentration of 17 g/m³ (range: 7.7-57.5 g/m³) during 6 h/d. Symptoms of respiratory irritation and vasodilation of the skin were reported. No evidence of toxic effects on internal organs was found at necropsy.

A subchronic oral toxicity study according to OECD test guideline 408 was performed by BASF and included in the REACH registration dossier for neopentyl glycol (ECHA Dissemination, 2020a). Wistar rats were dosed with 50, 250 and 1000 mg/kg bw x d neopentyl glycol in drinking water for a period of 91 days (females) and 92 days (males), respectively. The performed examinations included clinical signs, body weight, food and water consumption, ophthalmoscopic examination, haematology, clinical chemistry, urinalysis, neurobehavioural examination, oestrous cycle determination, sperm parameters, gross pathology, and histopathology of all organs. No treatment-related adverse effects were observed in any dose group. Observed changes such as increases in haematocrit and urine volume in high dose females as well as increase in cholesterol and decrease in urine pH in high dose males were judged as possibly treatment-related but not adverse. Increases in relative kidney weights in males of the two highest dose groups and in relative liver weights in high dose males were regarded as adaptive rather than adverse, because there were no concurrent histopathological changes. Thus, the NOAEL derived from this study is ≥ 1000 mg/kg bw x d.

The REACH registration dossier of neopentyl glycol also reports an earlier short-term oral toxicity study similar to OECD test guideline 407 (ECHA Dissemination, 2020a). Albino rats received the test substance in doses of either 100 or 1000 mg/kg bw x d in their diet for a period of 36 days. Examinations included clinical signs, body weight, food consumption, functional observations (not specified), limited clinical chemistry and haematology parameters, urinalysis, gross pathology, and limited histopathological parameters. In high dose animals, reduced food consumption and a concomitant decrease in body weight gain was observed. In males, this was also reflected in increased relative testes weights. The findings were judged to be of no toxicological relevance. The NOAEL was concluded to be 1000 mg/kg bw x d.

A combined repeated dose toxicity study with reproductive/developmental toxicity screening test according to OECD test method 422 was performed in Japan and is reported in a Screening Information Data Set (SIDS) prepared under the OECD programme on high production volume chemicals (OECD, 2002). Sprague-Dawley rats received 100, 300, or 1000 mg/kg bw x d neopentyl glycol in water per gavage over 45 days (males) and from 14 d premating until day 4 of lactation (females), respectively. No treatment-related effects were observed in maternal animals and in offspring. In male animals of the parent generation, elevated levels of total protein, albumin and bilirubin were measured in the two higher dose groups. At these doses, absolute and relative liver weights were also increased. However, as histopathological examination revealed no lesions of the liver, the observed changes are considered an adaptive reaction rather than an adverse effect. Male animals dosed with 1000 mg/kg bw d also had increased absolute and relative kidney weights and histopathological changes in the kidneys such as basophilic alteration of the renal tubular epithelium and increased incidences in hyaline droplets and protein casts. These changes are considered treatment-related adverse effects; the NOAEL is 300 mg/kg bw d.

2.5.3 Genotoxicity and carcinogenicity

Several *in vitro* studies were performed to evaluate the mutagenic potential of neopentyl glycol (ECHA Dissemination, 2020a; OECD, 2002):

In bacterial reverse mutation tests in *Salmonella typhimurium* (TA 98, TA 100, TA 1535, TA 1537, TA 1538) and in *Escherichia coli* WP2 uvrA with and without metabolic activation neopentyl glycol did not show any mutagenic activity at the tested dose levels of up to 5000 µg/plate. The tests were comparable to OECD guideline 471 (Ames test).

Two independent studies were carried out according to OECD test guideline 476 to investigate the potential of neopentyl glycol to induce gene mutations at the hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus in Chinese hamster ovary cells, both with and without exogenous metabolic activation. In the tested concentrations up to 1100 µg/mL, neopentyl glycol did not cause any mutagenicity or cytotoxicity.

Potential cytogenic effects were studied using a test design similar to OECD guideline 473 (chromosome aberration test). Numerical and structural aberration were measured in Chinese hamster cells exposed to dose levels of 0, 0.25, 0.5 and 1.0 mg/mL with and without metabolic activation. Negative results and no cytotoxic effects were reported at all dose levels.

In view of the negative results observed *in vitro*, no *in vivo* genotoxicity or carcinogenicity studies with neopentyl glycol were performed.

2.5.4 Toxicity to reproduction

2.5.4.1 Fertility

As mentioned above, a combined repeated dose toxicity study with reproductive/developmental toxicity screening test according to OECD test method 422 was performed (OECD, 2002). Sprague-Dawley rats received 100, 300, or 1000 mg/kg bw x d neopentyl glycol per gavage in water over 45 days (males) and from 14 d premating until day 4 of lactation (females), respectively. At the highest dose group, the oestrous cycle was slightly but significantly prolonged. However, reproductive performance as determined by copulation, fertility, gestation, implantation, and delivery indices was not affected. The NOAEL was ≥1000 mg/kg bw x d.

2.5.4.2 Development

The above-mentioned combined repeated dose toxicity study with reproductive/developmental toxicity screening test (OECD, 2002) showed no adverse effect on development of the F1 generation. Examinations included birth index, viability index, sex ratio, litter and pup weight at birth and at day 4, and external examinations at termination on lactation day 4. The NOAEL for developmental toxicity was ≥1000 mg/kg bw x d.

A prenatal developmental toxicity study was performed by BASF and included in the REACH registration dossier for neopentyl glycol (ECHA Dissemination, 2020a). After administration of neopentyl glycol by gavage to pregnant Wistar rats in doses of 100, 300 and 1000 mg/kg bw x d on gestation days 6-19, no maternal or developmental toxicity was observed. Examinations included clinical signs, body weight, food consumption, conception rate, pre-implantation loss, post-implantation loss, post-mortem examinations of uteri and ovaries of the maternal animals, viability and external, soft tissue and skeletal examinations of the foetuses. The NOAEL for both maternal and developmental toxicity was ≥1000 mg/kg bw x d.

2.5.5 Odour perception

Neopentyl glycol is reported to have a sweetish odour. No information regarding the odour perception threshold could be found.

2.6 Evaluation

2.6.1 Existing regulations and classifications

A harmonised classification of neopentyl glycol according to the CLP Regulation is not available. Notifications submitted to ECHA by industry predominantly classify neopentyl glycol as Eye Dam. 1 (H318), some only as Eye Irrit. 2 (H319). In addition, some notifications included classification as Skin Irrit. 2 (H315) and very few also as STOT SE 3 (H335).

Only few limit values for the concentration of neopentyl glycol in air could be found (Table 3).

Table 3 Limit values for neopentyl glycol in air

Organisation	AgBB	REACH registrants	REACH registrants
Year	2012	Not reported (≥2013)	
Risk value name	NIK	DNEL (general)	DNEL (worker)
Risk value	1 mg/m³	8.7 mg/m³	35 mg/m³
Reference period	Chronic	Chronic	Chronic (worker)
Key study	Biosafety Research, 1993 (cited in OECD, 2002)	BASF, 2013 (cited in ECHA Dissemination, 2020a)	
Study type	Combined repeated dose toxicity study with reproductive /developmental screening test	Repeated dose toxicity study	
Species	Rat (Sprague-Dawley)	Rat (Wistar)	
Duration	45 d (males)/ca. 60 d (fem.)	90 d	
Critical effect	Increased kidney weights and tubular nephropathy in males	No treatment-related adverse effects observed	
Critical dose value	NOAEL = 300 mg/kg bw x d	NOAEL ≥ 1000 mg/kg bw x d	
Adjusted critical dose value	130.4 mg/m³	434.8 mg/m³	881.6 mg/m³
Assessment factor(s)	6 (study length) x 2 (interspecies) x 10 (intraspecies) = 120	2 (study length) x 2.5 (interspecies) x 10 (intraspecies) = 50	2 (study length) x 2.5 (interspecies) x 5 (intraspecies) = 25

The German AgBB (Committee for Health-related Evaluation of Building Products) issued a NIK (Lowest Concentration of Interest) value of 1 mg/m³, based on kidney effects observed in male rats in a combined repeated dose toxicity study with reproductive/developmental toxicity screening test (OECD, 2002). As the study involved oral exposure, route-to-route extrapolation was performed: the NOAEL of 300 mg/kg bw x d was divided by 1.15 m³/kg bw x d, reflecting the respiratory volume of the rat and including allometric scaling, and a default factor of 2 to account for possible differences in absorption after oral uptake and inhalation, respectively. The resulting adjusted critical dose value of 130.4 mg/m³ was divided by a total assessment factor of

120 (factor 6 for study length x factor 2 for remaining interspecies differences x factor 10 for intraspecies differences) to give 1.08 mg/m³, rounded to the NIK value of 1 mg/m³.

The REACH registration dossier of neopentyl glycol (ECHA Dissemination, 2020a) includes Derived No Effect Levels (DNELs) for inhalation exposure to neopentyl glycol, differentiated for workers and the general population. Both DNEL values are based on an oral repeated dose toxicity study in rats that had not revealed any treatment-related adverse effects at the tested dose range up to 1000 mg/kg bw x d. For the general population, route-to-route extrapolation was performed as described above. Division of the NOAEL of 1000 mg/kg bw x d by the composite factor of 2.3 m³/kg bw x d gave an adjusted critical dose value of 434.8 mg/m³. Division by the total assessment factor of 50 (factor 2 for study length x factor 2.5 for remaining interspecies differences x factor 10 for intraspecies differences) resulted in the DNEL value of 8.7 mg/m³ for the general population. For workers, some additional considerations were taken into account: 1) the factor used for route-to-route extrapolation was 0.38 instead of 1.15, assuming only 8 h exposure instead of 24 h; 2) a correction factor of 0.67 was applied to account for increased respiration during light work; 3) an assessment factor of 5 was used for intraspecies differences among the worker population as opposed to 10 for the general population. Thus, the adjusted critical dose value was calculated as 881.6 mg/m³, the total assessment factor was 25, and the resulting DNEL value for workers was 35 mg/m³.

2.6.2 Derivation of an EU-LCI value

Neopentyl glycol is a high production volume chemical with a wide variety of uses relevant for exposure of the general population through indoor air. While its low vapour pressure at room temperature may indicate a low concern for elevated indoor air concentrations, an emission chamber test with different building materials demonstrated that emissions of neopentyl glycol from some materials can be substantial (Katsoyiannis et al., 2012).

The toxicological database for neopentyl glycol is limited. Although it was included in the OECD programme for the evaluation of high production chemicals, the initial screening of available data lead to the conclusion that the substance was of low priority for further work, and no in-depth evaluation was performed (OECD, 2002). More data became available from toxicity testing performed in the context of registration under REACH (ECHA Dissemination, 2020a). Reliable data on the toxicity of neopentyl glycol in animals are only available from studies using oral exposure. Data on the inhalation toxicity in animals or the toxicity in humans are not available.

Considering the limited available information regarding toxicokinetics (Gessner et al., 1960), neopentyl glycol can be assumed to be rapidly absorbed, distributed and excreted, predominantly in the urine. There is no indication that potentially toxic or accumulating metabolites are formed.

While the substance can cause irreversible damage to the eyes, no significant irritation of the skin or the respiratory tract was observed (ECHA Dissemination, 2020a).

Two studies are available regarding repeated dose oral toxicity in rats: A combined repeated dose toxicity study with reproductive/developmental toxicity screening test, conducted in the early 1990s and reported in the OECD SIDS and a 90-day oral toxicity study performed in 2012 and reported in the REACH registration dossier of neopentyl glycol. For both studies, the original full report is not publicly available. Relevant information is provided in OECD, 2002, and ECHA Dissemination, 2020a. For the earlier study, some relevant information is lacking, for instance on historical control data. The two studies come to different conclusions: In the earlier study, the NOAEL was concluded to be 300 mg/kg bw x d based on nephrotoxicity observed in male animals at the highest test dose of 1000 mg/kg bw x d. No other treatment-related adverse

effects were reported. In the more recent study, no treatment-related adverse effects were observed at all, and the NOAEL was therefore defined as ≥ 1000 mg/kg bw x d.

Experimental data from a number of genotoxicity tests *in vitro* provided no indication that neopentyl glycol has any mutagenic potential (OECD, 2002; ECHA Dissemination, 2020a).

The potential reproductive toxicity of neopentyl glycol was investigated after oral exposure in two studies following current test guidelines (OECD, 2002; ECHA Dissemination, 2020a). In two different strains of rat, no effects on fertility or prenatal development were noted at the tested dose levels of up to 1000 mg/kg bw x d.

The only existing limit value for neopentyl glycol in air that was issued by a public institution is the AgBB NIK value, which is based on the NOAEL of 300 mg/kg bw x d due to nephrotoxicity in male rats. However, at the time when this value was adopted no other long-term toxicity data were available. The more recent NOAEL of ≥1000 mg/kg bw x d was reported after that.

The reported findings regarding the observed kidney effects indicate that nephrotoxicity in this case is likely to be caused by α_{2u}-globin via a mode of action that is specific for male rats. Typical signs include the absence of nephrotoxicity in females, the formation of hyaline droplets and an increased number of granular casts, as they are reported from this study. Since humans, like female rats, do not produce a protein like α_{2u}-globulin, such effects are not considered relevant for human health risk assessment (Hard et al., 1993; Swenberg, 1993). Therefore, it seems appropriate to choose the NOAEL of 1000 mg/kg bw x d as POD for the derivation of an EU-LCI value for neopentyl glycol. This value is adjusted by a default factor of 2 to account for potential differences in absorption between the oral and inhalation route, respectively, to give a POD value of 500 mg/kg bw x d.

Assessment factors are chosen as follows:

- Study length: 2 (standard value for sub-chronic to chronic extrapolation)
- Route-to-route extrapolation: 1.15 (standard factor for rats, including allometric scaling)
- Interspecies differences: 2.5 (standard value for remaining kinetic and dynamic differences)
- Intraspecies difference: 10 (standard value for the general population)

With a total assessment factor of 57.5 and a POD of 500 mg/kg bw x d, an initial value of 8696 µg/m³ (2027 ppb) is calculated. A rounded value of 8700 µg/m³ is proposed as the EU-LCI value for neopentyl glycol.

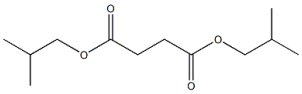
3 Toxicological evaluation of diisobutyl succinate as basis for the derivation of an EU-LCI value

Diisobutyl succinate is an extremely data poor compound. The derivation of an EU-LCI value is based on read across from dimethyl succinate. According to the EU-LCI framework, read across can start from an existing EU-LCI value. However, the EU-LCI value of 50 µg/m³ published for dimethyl succinate is an 'ascribed value'. Therefore, first a new EU-LCI value for dimethyl succinate needs to be derived based on toxicological evaluation before read across to diisobutyl succinate can be performed.

3.1 Substance identification

Substance identification data and physicochemical properties of diisobutyl succinate are shown in Table 4 and Table 5.

Table 4 Substance identification of diisobutyl succinate

CAS No. EC No.	Systematic name; common names	Summary formula	Structural formula
925-06-4 213-113-7	Bis(2-methylpropyl) butanedioate; diisobutyl succinate	$C_{12}H_{22}O_4$	

3.2 Substance properties and uses

Diisobutyl succinate is liquid at room temperature. Experimental data for physicochemical properties are not available. All values shown in Table 5 are predictions derived from computational models (U.S. EPA, 2020a).

Table 5 Physicochemical properties of diisobutyl succinate

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa)	Conversion 1 ppm = x mg/m³	Log P_{OW}	Solubility in water (g/L)
230.30	-20.5	252	1.0×10^{-2}	9.48 (23 °C)	2.87	0.5

Source: U.S. EPA, 2020a.

No EU-wide information regarding the use of diisobutyl succinate is available. In the ECHA database of chemicals, diisobutyl succinate is listed as 'pre-registered'. According to the database on Substances in Preparations in Nordic Countries (SPIN), diisobutyl succinate was used in these countries in yearly quantities of 10-38 t during the period 2000-2017. Reported use categories with consumer relevance include paints, laqueurs and varnishes, cleaning and washing agents, and surface treatment.

3.3 Exposure

3.3.1 Indoor air

Diisobutyl succinate was detected in 4 of 369 samples of indoor air from offices, homes, schools and pre-schools analysed between 2000 and 2006 (Hofmann and Plieninger, 2008). The maximum concentration found was 360 µg/m³, the arithmetic mean was 1.7 µg/m³. In another

evaluation of 855 samples, both the 50th and the 90th percentile of diisobutyl succinate concentrations are reported as <2 µg/m³ (AGÖF, 2013).

3.3.2 Other sources

No relevant information could be found.

3.4 Toxicokinetics

Diisobutyl succinate

Substance-specific information regarding the toxicokinetics of diisobutyl succinate is not available. Generally, metabolism of carboxylic esters after inhalation starts with deposition in the nasal mucosa and conversion by carboxylesterase expressed in the olfactory and, to a lesser extent, in the respiratory epithelium (Olson et al., 1993). Thus, diisobutyl succinate is metabolised to succinic acid (butanedioic acid) and isobutanol (2-methylpropanol).

Dimethyl succinate

In surgically isolated upper respiratory tracts of male and female rats, deposition of dimethyl succinate alone and in a mixture with other dibasic esters occurred with efficiency rates around 98 % (Morris et al., 1991). Enzyme kinetics of carboxylesterase-mediated metabolism of dibasic esters was studied *in vitro* using homogenised nasal epithelial cells from rats (Bogdanffy et al., 1991). Substrate conversion was about 6 times higher in olfactory epithelial cells than in respiratory epithelial cells and about twice as high in preparations obtained from males as compared to females. Substrate inhibition of enzymatic activity only occurred at concentrations > 25 mM, which are unlikely to be attainable *in vivo*. Using nasal explants obtained from female rats it could be demonstrated that ester cleavage by carboxylesterase was directly linked to cytotoxicity as indicated by acid phosphatase release (Trela and Bogdanffy, 1991). This cytotoxicity is presumably related to the pH decrease caused by the released carboxylic acids.

3.5 Health effects

3.5.1 Acute toxicity, sensory irritation and local effects

Diisobutyl succinate

No information regarding acute systemic or local effects of diisobutyl succinate could be found.

Dimethyl succinate

The systemic toxicity of dimethyl succinate is low, as evidenced by an oral toxicity limit test in rats that resulted in an LD_{50} value of 6892 mg/kg bw x d (ECHA Dissemination, 2020b).

For the investigation of local effects on the upper respiratory tract, rats were exposed, nose-only, to an aerosol/vapour mixture of dibasic esters (16.5 % dimethyl succinate, 66 % dimethyl glutarate, 17 % dimethyl adipate) at a concentration of 5900 mg/m³ for 4 h and subsequently killed at 1, 4, 7, 14, 21, and 42 days after exposure (Lee et al., 1992). Nasal lesions were distributed along major inspiratory airflow routes. Widespread epithelial abrasions occurred in the anterior nasal cavity but were markedly less severe in the posterior nasal cavity. The damaged cuboidal non-ciliated and respiratory epithelium regained a normal structure by 4 and 7 days post exposure, respectively. The regeneration of damaged olfactory epithelium was related to the severity of initial tissue damage. Slightly damaged epithelium regained a normal appearance within 1-2 weeks, but more extensively damaged epithelium failed to regain a normal structure by 6 weeks.

Two dermal irritation/corrosion studies according to OECD test guideline 404 were carried out with dimethyl succinate in New Zealand White rabbits (ECHA Dissemination, 2020b). No effects were observed.

Effects of dimethyl succinate on the eyes were investigated in two studies according to OECD test guideline 405 in New Zealand White rabbits (ECHA Dissemination, 2020b). In one study, slightly irritant effects were noted that did not fulfill the criteria for hazard classification. However, in the other study the observed effects were more severe, and resulted in the conclusion that dimethyl succinate is irritating to the eye (Cat. 2).

No skin sensitisation potential was observed in a Local Lymph Node Assay in CBA mice according to OECD test guideline 429 (ECHA Dissemination, 2020b).

3.5.2 Repeated dose toxicity

Diisobutyl succinate

No information regarding the toxicity of diisobutyl succinate after repeated exposure could be found.

Dimethyl succinate

Investigations of repeated dose toxicity were not carried out for dimethyl succinate alone, but only as part of a mixture with other dibasic esters (16.9-17.8 % dimethyl succinate, 65.1-66.5 % dimethyl glutarate, 16.5-16.8 % dimethyl adipate).

In a subchronic inhalation toxicity study according to OECD test guideline 413 Sprague-Dawley rats were exposed to an aerosol (mean particle size 5.6 µm) of the dibasic ester mixture during 6 h/d on 5 days per week over a treatment period of 14 weeks (ECHA Dissemination, 2020b). The investigated concentrations were 160, 400 and 1000 mg/m³. In the highest dose group, animals showed reduced body weight gains and a slight decrease in serum sodium concentrations. Reduced absolute and relative liver weight was observed in females of all dose groups as well as in high dose males. These observations were not accompanied by any histopathological tissue changes. Histopathological examination of the nasal areas revealed degeneration of the olfactory epithelium in all dose groups. In particular, squamous metaplasia was noted in 3/20 animals exposed at 160 mg/m³, in 17/20 animals exposed at 400 mg/m³ and in 19/20 animals exposed at 1000 mg/m³. Due to these effects, a NOAEC value could not be derived. The LOAEC in this study was 160 mg/m³, based on the degeneration of olfactory epithelium and the reduced liver weight.

Another, similar study investigated lower concentrations of dibasic esters (Keenan et al., 1990). Sprague-Dawley rats were exposed during 6 hours per day on 5 days per week over a treatment period of 13 weeks to test substance vapours at 20 mg/m³, 76 mg/m³ and 390 mg/m³. In each dose group, 10 animals of each sex were euthanised and examined already after 7 weeks of exposure, 20 animals were euthanised and examined at the end of the 13-week exposure period, and 10 animals were kept for a 6-week recovery phase. In the highest dose group, females showed reduced body weight gain and decreased liver weights. Both effects disappeared during recovery. Histopathological evidence of nasal tissue degeneration was observed in animals of all dose groups. The effects were more pronounced in the higher dose groups and after the longer exposure time. Females appeared to be more sensitive than males. More details regarding the observed nasal cavity changes are summarised in Table 6 and Table 7. Due to these effects a NOAEC value could not be derived from this study. The LOAEC was 20 mg/m³, based on the degeneration of olfactory epithelium.

Table 6 Incidences of nasal cavity lesions following exposure to dibasic esters: male rats

	0 mg/m³	20 mg/m³	76 mg/m³	390 mg/m³
Degeneration of olfactory epithelium:				
after 7 weeks exposure	0/10	1/10	2/11	8/10
after 13 weeks exposure	0/20	0/20	5/19	18/20
Changes observed in olfactory epithelium following 6 weeks recovery after 13 weeks exposure:				
Disorganisation of epithelium	0/10	0/10	1/10	2/10
Respiratory metaplasia	0/10	1/10	0/10	4/10
Decrease of neuronal cells	0/10	0/10	2/10	1/10

Source: Keenan et al., 1990.

Table 7 Incidences of nasal cavity lesions following exposure to dibasic esters: female rats

	0 mg/m³	20 mg/m³	76 mg/m³	390 mg/m³
Degeneration of olfactory epithelium:				
after 7 weeks exposure	1/10	0/10	2/11	9/10
after 13 weeks exposure	1/20	5/20	7/19	19/20
Changes observed in olfactory epithelium after 6 weeks recovery following 13 weeks exposure:				
Disorganisation of epithelium	0/10	1/10	1/10	8/10
Respiratory metaplasia	0/10	2/10	3/10	3/10
Decrease of neuronal cells	0/10	4/10	2/10	3/10

Source: Keenan et al., 1990.

3.5.3 Genotoxicity and carcinogenicity

Diisobutyl succinate

No information regarding genotoxicity or carcinogenicity of diisobutyl succinate could be found.

Dimethyl succinate

Several *in vitro* studies were performed to evaluate the mutagenic potential of dimethyl succinate (ECHA Dissemination, 2020b):

In bacterial reverse mutation tests in *Salmonella typhimurium* (TA 97a, TA 98, TA 100, TA 102, TA 1535) with and without metabolic activation dimethyl succinate did not show any mutagenic activity at the tested dose levels of up to 5000 µg/plate. The tests were performed according to OECD guideline 471 (Ames test).

An *in vitro* mammalian cell gene mutation test according to OECD test guideline 476 was carried out in mouse lymphoma L5178Y cells with and without metabolic activation. Test durations were 3 h and 24 h, respectively. Without metabolic activation, no statistically significant increases in mutant frequency were observed. With metabolic activation, a significant increase in mutation frequency was observed at the highest test concentration of 1460 µg/mL. As the observed effects were within the historical control range, they were considered to be of no biological relevance.

Potential cytogenic effects were studied according to OECD guideline 473 (chromosome aberration test) in human lymphocytes obtained from healthy male volunteers. Two independent assays were performed, investigating dose levels up to 10.0 mM (1460 µg/ml), in the absence or presence of S9 metabolism. No increase in the incidence of structural chromosomal aberrations was noted. A low incidence of observed numerical changes was judged to be of no biological significance.

Further investigations on genotoxicity were carried out with dimethyl succinate as part of a mixture of dibasic esters. The overall conclusion was negative. For detail see chapter 4.5.3.

In view of the negative results observed *in vitro*, no *in vivo* genotoxicity or carcinogenicity studies with dimethyl succinate were performed.

3.5.4 Toxicity to reproduction

Diisobutyl succinate

No information regarding reproduction toxicity of diisobutyl succinate could be found.

Dimethyl succinate

Investigation of reproduction toxicity was not carried out for dimethyl succinate alone, but only as part of a mixture with other dibasic esters (16.5-17.8 % dimethyl succinate, 65.1-66.0 % dimethyl glutarate, 16.8-17 % dimethyl adipate).

3.5.4.1 Fertility

A one-generation reproduction toxicity study according to OECD test guideline 415 was performed with Sprague-Dawley rats (Kelly et al., 1998). The mixture of dibasic esters was administered as an aerosol (mass median aerodynamic diameter 6.2 µm) at concentrations of 160, 400 and 1000 mg/m³. Exposure was maintained for 6 h/d on 5 days per week over a period of 14 weeks pre-mating and for 6 h/d daily over a period of 8 weeks throughout mating, gestation and lactation (exposure in female animals was interrupted from gestation day 19 to post-partem day 3). In parental animals, decreases in food consumption and in body weight were observed in the two highest dose groups, and degenerative changes in the olfactory epithelium occurred in all dose groups. Reproductive performance, as documented by mating and fertility indices, length of gestation, number of pups, pup anomalies and viability, was not affected by exposure to the test substance. In offspring, the only noted effect was a reduced body weight at birth and after 21 days post-partem in animals with parents in the highest dose group. The authors concluded on a LOAEC of 160 mg/m³ for parental toxicity, based on degeneration of the nasal mucosa, and a NOAEC of ≥1000 mg/m³ for developmental toxicity.

3.5.4.2 Development

A developmental toxicity study similar to OECD test guideline 414 was performed in pregnant Sprague-Dawley rats (Alvarez et al., 1995). The mixture of dibasic esters was administered as an aerosol (mass median aerodynamic diameter 5.3-5.4 µm) at concentrations of 160, 400 and 1000 mg/m³. Exposure was maintained for 6 h/d on gestation days 7-16 before animals were sacrificed on gestation day 21. In maternal animals, reduced food consumption and body weight gain was observed in the high and mid dose groups, as well as reduced liver weights. No effects on the development of foetuses were observed. Investigated parameters included the number of live offspring, litter size and weight, and the incidence of external, visceral or skeletal malformations. The NOAEC for developmental toxicity was ≥1000 mg/m³.

3.5.5 Odour perception

No information regarding odour perception of diisobutyl succinate could be found.

3.6 Evaluation

3.6.1 Existing regulations and classifications

Diisobutyl succinate

Because of lacking data, diisobutyl succinate has not been classified according to the CLP Regulation.

The only limit value that could be found is a NIK value of 100 µg/m³ assigned by the German AgBB, which was derived by read across from the NIK value of 50 µg/m³ for dimethyl succinate (see below) by molar adjustment.

Dimethyl succinate

A harmonised classification of dimethyl succinate according to the CLP Regulation is not available. Notifications submitted to ECHA by industry predominantly conclude on "not classified" or Eye Irrit. 2 (H319).

Only few limit values for the concentration of dimethyl succinate in air could be found (Table 8).

Table 8 Limit values for dimethyl succinate in air

Organisation	AgBB	BAuA-Ausschuss für Gefahrstoffe	REACH registrants	REACH registrants
Year	2010	2006	Not reported	
Risk value name	NIK	AGW TRGS 900	DNEL (general)	DNEL (worker)
Risk value	50 µg/m³	8 mg/m³	1.2 mg/m³	6.7 mg/m³
Reference period	Chronic	Chronic (worker)	Chronic	Chronic (worker)
Key study	Read across from mixture of dibasic esters (see text for details)	Read across from dimethyl glutarate (see chapter 4.6.1 for details)	Alvarez et al., 1995	
Study type			Prenatal developmental toxicity study	
Species			Rat (Sprague-Dawley)	
Duration			21 days (exposure on GD 7-16)	
Critical effect			No treatment-related adverse effects observed	
Critical dose value			NOAEC: 1000 mg/m³	
Adjusted critical dose value			179 mg/m³	503 mg/m³
Assessment factor(s)			6 (study length) x 2.5 (interspecies) x 10 (intraspecies) = 150	6 (study length) x 2.5 (interspecies) x 5 (intraspecies) = 75

The German AgBB issued a NIK value of 50 µg/m³ for dimethyl succinate, which was derived by applying a default assessment factor of 100 to the MAK value (Maximum Workplace

Concentration) of 5 mg/m³ for the mixture of dibasic esters (16.9 % dimethyl succinate, 66.6 % dimethyl glutarate, 16.5 % dimethyl adipate). The MAK value for the ester mixture is based on the LOAEC of 20 mg/m³ for the degeneration of olfactory epithelium in rats as reported by Keenan et al., 1990.

Another limit value for dimethyl succinate in Germany is the AGW (occupational limit value) of 8 mg/m³ listed in the Technical Rules for Hazardous Substances (TRGS 900). This value was issued by the Committee of Hazardous Substances, an expert committee associated with the Federal Institute for Occupational Safety and Health (BAuA) and was derived by read across from dimethyl glutarate (for details see chapter 4.6.1).

The REACH registration dossier for dimethyl succinate includes DNEL values of 1.2 mg/m³ and 6.7 mg/m³ for the general public and for workers, respectively. Both values are based on the NOAEC value of 1000 mg/m³ for developmental toxicity, based on no adverse effects observed in rats. There is no explanation for the choice of this POD as opposed to the local effects on the upper respiratory tract that were observed in subchronic inhalation toxicity studies. Likewise, no rationale is provided for the calculation of the adjusted NOAEC values or the choice of assessment factors (according to REACH guidance documents AF 1 for study length would be more appropriate for a prenatal development study since the study covers the critical time frame in its entirety). These DNEL values were derived by registrants and are not approved by ECHA or any other public institution.

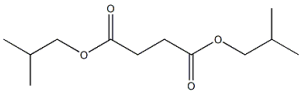
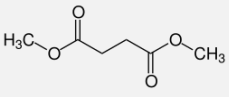
3.6.2 Derivation of an EU-LCI value

Diisobutyl succinate is an extremely data poor compound. The production volume is considered to be low. However, some uses in products of relevance for consumer exposure via indoor air have been reported and the substance was detected during investigations of indoor air quality.

No toxicity data have been published. Diisobutyl succinate has been 'pre-registered' under REACH, but a full registration dossier is not available.

The metabolic pathway of carboxyl esters after inhalation starts with deposition in the nasal mucosa and cleavage by carboxylesterase to release the respective acid and alcohol components (Olson et al., 1993; Bogdanffy et al., 1991). The deposition rate for dibasic esters is about 98 % (Morris et al., 1991). The enzymatic release of the acid is directly linked to the induction of cytotoxicity, presumably due to the pH reduction (Trela and Bogdanffy, 1991). Thus, diisobutyl succinate is converted to isobutanol and succinic acid, which can be assumed to determine the main health effects of diisobutyl succinate after inhalation by its local effects on the upper respiratory tract. Therefore, it seems appropriate to consider read across from dimethyl succinate for the derivation of an EU-LCI value for diisobutyl succinate. A comparison of the two compounds is shown in Table 9.

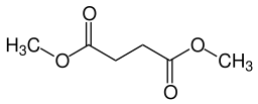
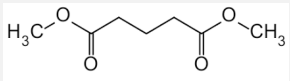
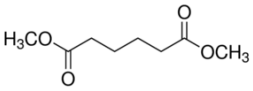
Table 9 Comparison of diisobutyl succinate and dimethyl succinate

Compound	CAS No.	Structural formula	Molar mass [g/mol]
Diisobutyl succinate	925-06-4		230.3
Dimethyl succinate	106-65-0		146.14

Dimethyl succinate has an ascribed EU-LCI value of 50 µg/m³. Therefore, it is necessary to derive a new EU-LCI value for dimethyl succinate based on toxicological evaluation before read across to diisobutyl succinate can be performed.

Dimethyl succinate has been registered under REACH and a full registration dossier is available (ECHA Dissemination, 2020b). A few toxicity studies were performed with the compound as such, but most investigations were carried out with a mixture of dibasic esters containing dimethyl succinate, dimethyl glutarate and dimethyl adipate. The toxicity of these three substances is determined by the respective acid components through pH reduction. As the acidity of the acids is very similar and the difference in chain length is not larger than two CH_2 groups, read across from toxicity data of the ester mixture to dimethyl succinate is considered justified. A comparison of the three dibasic esters is shown in Table 10.

Table 10 Comparison of dimethyl succinate, dimethyl glutarate and dimethyl adipate

Compound	Structural formula	Molar mass	pK_{A1} of free acid	pK_{A2} of free acid
Dimethyl succinate		146.16 g/mol	4.16	5.61
Dimethyl glutarate		160.17 g/mol	4.32	5.42
Dimethyl adipate		174.20 g/mol	4.43	5.42

The acute systemic toxicity of dimethyl succinate is low. It is irritating to eyes, but not to skin. Single exposure to an aerosol of the dibasic ester mixture (5900 mg/m³ over 4 h) caused nasal lesions, which were to some extent reversible, depending on their severity (Lee et al., 1992).

Two subchronic inhalation toxicity studies were carried out with the mixture of dibasic esters in rats. After exposure to concentrations of 160, 400 and 100 mg/m³ for 6 h/d on 5 days per weeks over 14 weeks, degeneration of the olfactory epithelium was found in all dose groups (ECHA Dissemination, 2020b). Slight reductions in body weight gains and liver weights observed in high dose animals were not considered biologically relevant. The LOAEC was 160 mg/m³, a NOAEC could not be derived from this study. A similar study (Keenan et al., 1990) applied lower concentrations of dibasic esters – 20, 76 and 390 mg/m³ – over 13 weeks (6 h/d, 5 d/week). In female rats, all test concentrations caused lesions of the olfactory epithelium. In male rats, this was only observed in the two higher dose groups. After a six-week recovery period, signs of tissue repair and regenerative processes were noted. Animals exposed to 390 mg/m³ showed slight reductions in body weight gain. Thus, the NOAEC for systemic toxicity was 76 mg/m³. For local effects, the LOAEC was 20 mg/m³.

Genotoxicity tests with dimethyl succinate *in vitro* showed no indication of mutagenic potential.

Administration of an aerosol (160, 400 and 1000 mg/m³) of the dibasic ester mixture to rats in a one-generation reproduction toxicity study (Kelly et al., 1998) and a developmental toxicity study (Alvarez et al., 1995) did not reveal any effects on reproductive parameters or prenatal development.

The only published limit value for diisobutyl glutarate in air is the AgBB NIK value of 100 µg/m³, which was derived by read across from the NIK value of 50 µg/m³ for dimethyl glutarate. The NIK value for dimethyl glutarate was derived from the MAK value of 5 mg/m³, which is based on the LOAEC of 20 mg/m³ for the mixture of dibasic esters reported by Keenan et al., 1990.

The leading health effect of dibasic esters after inhalation is the degeneration of nasal mucosa. The study reported by Keenan et al., 1990, provides the most detailed evaluation of this effect at the lowest test concentrations. The LOAEC of 20 mg/m³ from this study is therefore considered an adequate POD for the derivation an EU-LCI value for dimethyl succinate.

Assessment factors are chosen as follows:

- Exposure duration: 5.6 (from 6 h/d on 5 d/week)
- Study length: 2 (standard value for subchronic to chronic extrapolation)
- Uncertainty of the dose-response: 3 (standard value for using a LOAEC instead of a NOAEC)
- Interspecies differences: 2.5 (standard value for remaining kinetic and dynamic differences)
- Intraspecies difference: 10 (standard value for the general population)

The total assessment factor of 840 and the POD of 20 mg/m³ gave an initial value of 23.8 µg/m³ (3.61 ppb) for the mixture of dibasic esters.

A molar adjustment factor for read across from the mixture to dimethyl succinate was calculated by dividing the molar mass of dimethyl succinate (146.16 g/mol) by the molar mass determined for the tested mixture based on the reported quantitative composition [(0.169 x 146.14 g/mol) + (0.655 x 160.17 g/mol) + (0.165 x 174.20 g/mol) = 158.35 g/mol]. Application of the resulting molar adjustment factor of 0.922 to the unrounded value of 23.8 µg/m³ resulted in an initial value of 21.9 µg/m³, which is rounded to the proposed new EU-LCI value of 20 µg/m³ for dimethyl succinate. This value is lower than the current ascribed value of 50 µg/m³. It may be considered conservative as it is based on local effects that have been characterised as predominantly mild and may be presumed to be reversible.

For read across to diisobutyl succinate, the unrounded value of 21.9 µg/m³ calculated for dimethyl succinate is used. Application of the molar adjustment factor of 1.576 (from 230.3 g/mol divided by 146.14 g/mol) leads to an initial value of 34.5 µg/m³, which is rounded to the proposed EU-LCI value of 35 µg/m³ for diisobutyl succinate.

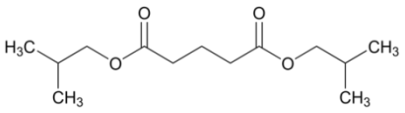
4 Toxicological evaluation of diisobutyl glutarate as basis for the derivation of an EU-LCI value

Like the previously discussed diisobutyl succinate, diisobutyl glutarate is also an extremely data poor compound. Again, the derivation of an EU-LCI value is based on read across, in this case from dimethyl glutarate. As discussed before for dimethyl succinate, the EU-LCI value of 50 µg/m³ published for dimethyl glutarate is an ascribed value. Therefore, at first a new EU-LCI value for dimethyl glutarate needs to be derived based on toxicological evaluation before read across to diisobutyl glutarate can be performed.

4.1 Substance identification

Substance identification data and physicochemical properties of diisobutyl glutarate are shown in Table 11 and Table 12.

Table 11 Substance identification of diisobutyl glutarate

CAS No. EC No.	Systematic name; common names	Summary formula	Structural formula
71195-64-7 275-257-7	Bis(2-methylpropyl) pentanedioate; diisobutyl glutarate	$C_{13}H_{24}O_4$	

4.2 Substance properties and uses

Diisobutyl glutarate is liquid at room temperature. Experimental data for physicochemical properties are not available. All values shown in Table 12 are predictions derived from computational models (U.S. EPA, 2020b).

Table 12 Physicochemical properties of diisobutyl glutarate

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa)	Conversion 1 ppm = x mg/m³	Log Pow	Solubility in water (g/L)
244.33	-26.8	272	7.0×10^{-3} (25 °C)	10.06 (23 °C)	3.37	1.7

Source: U.S. EPA, 2020b.

No EU-wide information regarding the use of diisobutyl glutarate is available. In the ECHA database of chemicals, diisobutyl glutarate is listed as 'pre-registered'. According to the SPIN database, diisobutyl succinate was used in Nordic countries in yearly quantities of 24-109 t during the period 2000-2017. Reported use categories with consumer relevance include paints, laqueurs and varnishes, cleaning and washing agents, surface treatment, and solvents.

4.3 Exposure

4.3.1 Indoor air

Diisobutyl glutarate was detected in 4 of 369 samples of indoor air from offices, homes, schools and pre-schools analysed between 2000 and 2006 (Hofmann and Plieninger, 2008). The maximum concentration found was 710 µg/m³, the arithmetic mean was 3.4 µg/m³. In another

evaluation of 898 samples, both the 50th and the 90th percentile of diisobutyl glutarate concentrations are reported as <2 µg/m³ (AGÖF, 2013).

4.3.2 Other sources

No relevant information could be found.

4.4 Toxicokinetics

Diisobutyl glutarate

Substance-specific information regarding the toxicokinetics of diisobutyl glutarate is not available. As discussed previously (chapter 3.4), diisobutyl glutarate can be assumed to be converted to glutaric acid (pentanedioic acid) and isobutanol (2-methylpropanol) by carboxylesterase in the nasal epithelium.

Dimethyl succinate

In surgically isolated upper respiratory tracts of male and female rats, deposition of dimethyl glutarate alone and in a mixture with other dibasic esters occurred with efficiency rates around 98 % (Morris et al., 1991). Enzyme kinetics of carboxylesterase mediated metabolism of dibasic esters was studied *in vitro* using homogenised nasal epithelial cells from rats (Bogdanffy et al., 1991). Substrate conversion was about 10 times higher in olfactory epithelial cells than in respiratory epithelial cells, but only marginally higher in preparations obtained from males as compared to females. Substrate inhibition of enzymatic activity only occurred at concentrations > 25 mM, which are unlikely to be attainable *in vivo*. Using nasal explants obtained from female rats it could be demonstrated that ester cleavage by carboxylesterase was directly linked to cytotoxicity as indicated by acid phosphatase release (Trela and Bogdanffy, 1991).

4.5 Health effects

4.5.1 Acute toxicity, sensory irritation and local effects

Diisobutyl glutarate

No information regarding acute systemic or local effects of diisobutyl glutarate could be found.

Dimethyl glutarate

The systemic toxicity of dimethyl glutarate is low, as evidenced by an oral toxicity limit test in Sprague-Dawley rats according to OECD test guideline 423 (acute toxic class method). At the tested dose of 5000 mg/kg bw, no mortality was observed, and no abnormalities were noted at necropsy (ECHA Dissemination, 2020c).

For the investigation of local effects on the upper respiratory tract, rats were exposed, nose-only, to an aerosol/vapour mixture of dibasic esters (16.5 % dimethyl succinate, 66 % dimethyl glutarate, 17 % dimethyl adipate) at a concentration of 5900 mg/m³ for 4 h and subsequently killed at 1, 4, 7, 14, 21, and 42 days after exposure (Lee et al., 1992). Nasal lesions were distributed along major inspiratory airflow routes. Widespread epithelial abrasions occurred in the anterior nasal cavity but were markedly less severe in the posterior nasal cavity. The damaged cuboidal non-ciliated and respiratory epithelium regained a normal structure by 4 and 7 days post exposure, respectively. The regeneration of damaged olfactory epithelium was related to the severity of initial tissue damage. Slightly damaged epithelium regained a normal appearance within 1-2 weeks, but more extensively damaged epithelium failed to regain a normal structure by 6 weeks.

Investigations regarding skin irritation/corrosion were not carried out for dimethyl glutarate alone, but only as part of a mixture with dimethyl succinate and dimethyl adipate (quantitative composition undisclosed). In one study, no irritant effects were observed after 4 h exposure. In another study with prolonged exposure over 24 h moderate to severe erythema were induced in New Zealand White rabbits (ECHA Dissemination, 2020c).

Only slightly irritating effects on eyes, which did not fulfill classification criteria, were observed in several studies with a dibasic ester mixture containing dimethyl succinate, dimethyl glutarate and dimethyl adipate in undisclosed quantities (ECHA Dissemination, 2020c). Dimethyl glutarate alone was not investigated regarding its effects on eyes.

4.5.2 Repeated dose toxicity

Diisobutyl glutarate

No information regarding the toxicity of diisobutyl glutarate after repeated exposure could be found.

Dimethyl glutarate

Dimethyl glutarate was tested at three concentrations (10, 50 and 400 mg/m³) in a subchronic inhalation toxicity study with rats (ECHA Dissemination, 2020c). Exposure was maintained for 6 h/d on 5 days per week over a 90-day period and followed by a 1-month recovery phase. Reduced body weight gains were observed in male animals of the 400 mg/m³ dose group during the exposure period, and lower mean body weights in the recovery phase. Males of the two highest dose groups showed decreased serum testosterone concentrations and increased epididymal sperm counts. No associated changes in organ weights or histopathology of the male reproductive organs were noted. Degeneration of the nasal olfactory epithelium was found in females of the highest dose group, and animals of both sexes showed increased nasal cell proliferation at this dose. The authors of the study concluded on a NOAEC of 10 mg/m³ for systemic toxicity, based on decreased testosterone levels and increased epididymal sperm counts, and a NOAEC of 50 mg/m³ for local respiratory toxicity based on degeneration of olfactory mucosa.

As discussed in chapter 3.5.2, subchronic inhalation toxicity studies were also performed with dimethyl glutarate as part of a mixture with other dibasic esters, in which dimethyl glutarate was the main component (65.1-66.5 %). From these studies, a NOAEC could not be derived. The LOAEC was 20 mg/m³ based on observed degeneration of olfactory epithelium (Keenan et al., 1990).

4.5.3 Genotoxicity and carcinogenicity

Diisobutyl glutarate

No information regarding genotoxicity or carcinogenicity of diisobutyl glutarate could be found.

Dimethyl glutarate

Two studies were performed to evaluate the mutagenic potential of dimethyl glutarate (ECHA Dissemination, 2020c):

In an *in vitro* mammalian cell mutation assay in Chinese hamster ovary cells according to OECD test guideline 476, dimethyl glutarate did not cause gene mutations at the HPRT locus in the presence and absence of metabolic activation.

An *in vivo* mammalian erythrocyte micronucleus test according to OECD test guideline 474 was performed in Fischer 344 rats. Dose levels of 500, 1000 and 2000 mg/m³ were administered by inhalation for 6 hours per day on two consecutive days. Examination of bone marrow smears obtained 24 h after exposure showed no evidence of induced chromosomal damage or bone marrow cell toxicity.

Genotoxicity studies were also performed with dimethyl glutarate as the main component (65.1-66.5 %) in a mixture with other dibasic esters (ECHA Dissemination, 2020c):

In two independent bacterial reverse mutation tests comparable to OECD guideline 471 in *Salmonella typhimurium* (TA 98, TA 100, TA 1535, TA 1537, TM 677) with and without metabolic activation, the tested mixture of dibasic esters did not show any mutagenic activity at the tested dose levels of up to 10000 µg/plate.

In an *in vitro* chromosome aberration test in human lymphocytes comparable to OECD test guideline 473 the mixture of dibasic esters exhibited some clastogenic activity: With S9 metabolic activation, significant increases in the proportion of chromosomally abnormal cells were seen. Additionally, the proportion of cells having more than one aberration was significantly increased.

Cytogenic effects of the dibasic ester mixture were further investigated *in vivo* in a study similar to OECD test guideline 474. During a single 6h-exposure, aerosol concentrations of 5500, 11000 and 19000 mg/m³ were administered to mice. No statistically significant differences in the proportion of erythrocytes with micronuclei were observed at any sampling time up to 72 hours.

In view of the negative results observed in the genotoxicity tests, no carcinogenicity studies with dimethyl glutarate were performed.

4.5.4 Toxicity to reproduction

Diisobutyl glutarate

No information regarding reproduction toxicity of diisobutyl glutarate could be found.

Dimethyl glutarate

4.5.4.1 Fertility

Investigation of potential effects on fertility was not carried out for dimethyl glutarate alone, but only as part of a mixture with other dibasic esters (16.5-17.8 % dimethyl succinate, 65.1-66.0 % dimethyl glutarate, 16.8-17 % dimethyl adipate). From a one-generation study according to OECD test guideline 415, a LOAEC of 160 mg/m³ for parental toxicity and a NOAEC of 1000 mg/m³ for developmental toxicity were derived. For details see chapter 3.5.4.1.

4.5.4.2 Development

Toxicity of dimethyl glutarate on prenatal development was investigated in a study according to EPA OPPTS 870.3700 (ECHA Dissemination, 2020c). During gestation days 7-28 pregnant rabbits were exposed for 6 hours per day to an aerosol of the test substance at 30, 100, 300 and 1000 mg/m³. In maternal animals of the two highest dose groups, reduced food consumption and body weight gain was observed, as well as ocular discharge. There was no evidence of developmental toxicity at any concentration tested. Examinations included viability, sex ratio, body weight, fetal variations and malformations. The NOAEC for maternal toxicity was 100 mg/m³ based on observed body weight changes, the NOAEC for developmental toxicity was >1000 mg/m³.

Developmental toxicity was also investigated for dimethyl glutarate as part of a mixture with other dibasic esters (65.1 % dimethyl glutarate, 17.8 % dimethyl succinate, 16.8 % dimethyl adipate). From that study a NOAEC of ≥1000 mg/m³ for developmental toxicity was derived. For details see chapter 3.5.4.2.

4.5.5 Odour perception

No information regarding odour perception of diisobutyl glutarate could be found.

4.6 Evaluation

4.6.1 Existing regulations and classifications

Diisobutyl glutarate

Because of lacking data, diisobutyl glutarate has not been classified according to the CLP Regulation.

The only limit value that could be found is a NIK value of 100 µg/m³ assigned by the German AgBB, which was derived by read across from the NIK value of 50 µg/m³ for dimethyl glutarate (see below) by molar adjustment.

Dimethyl glutarate

A harmonised classification of dimethyl glutarate according to the CLP Regulation is not available. Notifications submitted to ECHA by industry predominantly conclude on "not classified".

Table 13 Limit values for dimethyl glutarate in air

Organisation	AgBB	BAuA-Ausschuss für Gefahrstoffe	REACH registrants	REACH registrants
Year	2010	2006	Not reported	
Risk value name	NIK	AGW TRGS 900	DNEL (general)	DNEL (worker)
Risk value	50 µg/m³	8 mg/m³	5 mg/m³	8.3 mg/m³
Reference period	Chronic	Chronic (worker)	Chronic	Chronic (worker)
Key study	Read across from mixture of dibasic esters (see text for details)	Brebner, 2000 (cited in ECHA Dissemination, 2020c)		
Study type		Subchronic inhalation toxicity study		
Species		Rat		
Duration		90 days (exposure on 6 h/d, 5 d/wk)		
Critical effect		Degeneration of olfactory mucosa		
Critical dose value		NOAEC: 50 mg/m³		
Adjusted critical dose value		No adjustment made		
Assessment factor(s)		2 (study length) x 3 (intraspecies) = 6	2 (study length) x 5 (intraspecies) = 10	2 (study length) x 3 (intraspecies) = 6

Only few limit values for the concentration of dimethyl glutarate in air could be found (Table 13).

The NIK value of 50 µg/m³ was derived from the MAK value of 5 mg/m³ for the ester mixture. As discussed above (3.6.1), the point of departure was the LOAEC of 20 mg/m³ for degeneration of olfactory epithelium in rats observed by Keenan et al., 1990.

All other limit values (TRGS 900 AGW, DNEL worker, DNEL general public) are based on the NOAEC of 50 mg/m³, also for degeneration of olfactory mucosa in rats, that is reported in a confidential study report cited in the REACH registration dossier (ECHA Dissemination, 2020c). Correction of the critical value to account for exposure duration was not performed with the justification that a local effect is considered. With the same reasoning, the AF for remaining interspecies differences was set as 1, and the AFs for intraspecies differences were lowered from 5 to 3 for workers and from 10 to 5 for the general population. The DNEL values were derived by registrants and are not approved by ECHA or any other public institution.

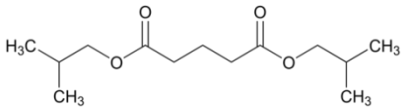
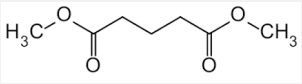
4.6.2 Derivation of an EU LCI value

Diisobutyl glutarate is an extremely data poor compound. The production volume is considered to be low. However, some uses in products of relevance for consumer exposure via indoor air have been reported and the substance was detected during investigations of indoor air quality.

No toxicity data have been published. Diisobutyl glutarate has been 'pre-registered' under REACH, but a full registration dossier is not available.

The metabolic pathway of carboxyl esters after inhalation starts with deposition in the nasal mucosa and cleavage by carboxylesterase to release the respective acid and alcohol components (Olson et al., 1993; Bogdanffy et al., 1991). The deposition rate for dibasic esters is about 98 % (Morris et al., 1991). The enzymatic release of the acid is directly linked to the induction of cytotoxicity, presumably due to the pH reduction (Trela and Bogdanffy, 1991). Thus, diisobutyl glutarate is converted to isobutanol and glutaric acid, which can be assumed to determine the main health effects of diisobutyl glutarate after inhalation by its local effects on the upper respiratory tract. Therefore, it seems appropriate to consider read across from dimethyl glutarate for the derivation of an EU-LCI value for diisobutyl glutarate. A comparison of the two compounds is shown in Table 14.

Table 14 Comparison of diisobutyl glutarate and dimethyl glutarate

Compound	CAS No.	Structural formula	Molar mass [g/mol]
Diisobutyl glutarate	71195-64-7		244.33
Dimethyl glutarate	1119-40-0		160.17

Dimethyl glutarate has an ascribed EU-LCI value of 50 µg/m³. Therefore, it is necessary to derive a new EU-LCI value for dimethyl glutarate based on toxicological evaluation before read across to diisobutyl glutarate can be performed.

Dimethyl glutarate has been registered under REACH and a full registration dossier is available (ECHA Dissemination, 2020c). Some toxicity studies were performed with the compound as

such, but some investigations were also carried out with a mixture of dibasic esters containing dimethyl succinate, dimethyl glutarate and dimethyl adipate. The toxicity of these three substances is determined by the respective acid components through pH reduction. As the acidity of the acids is very similar and the difference in chain length is not larger than two CH_2 groups, read across from toxicity data of the ester mixture to dimethyl glutarate is considered justified. A comparison of the three dibasic esters is shown in Table 10 in chapter 3.6.2.

The acute systemic toxicity of dimethyl glutarate is low. Local effects were only studied for dimethyl glutarate as part of the dibasic ester mixture. Irritation was observed on skin, but not on eyes. Single exposure to an aerosol (5900 mg/m³ over 4 h) caused nasal lesions, which were to some extent reversible, depending on their severity (Lee et al., 1992).

Two subchronic inhalation toxicity studies were carried out with the mixture of dibasic esters in rats. After exposure to concentrations of 160, 400 and 100 mg/m³ for 6 h/d on 5 days per weeks over 14 weeks, degeneration of the olfactory epithelium was found in all dose groups (ECHA Dissemination, 2020b). Slight reductions in body weight gains and liver weights observed in high dose animals were not considered biologically relevant. The LOAEC was 160 mg/m³, a NOAEC could not be derived from this study. A similar study (Keenan et al., 1990) applied lower concentrations of dibasic esters – 20, 76 and 390 mg/m³ – over 13 weeks (6 h/d, 5 d/week). In female rats, all test concentrations caused lesions of the olfactory epithelium. In male rats, this was only observed in the two higher dose groups. After a six-week recovery period, signs of tissue repair and regenerative processes were noted. Animals exposed to 390 mg/m³ showed slight reductions in body weight gain. Thus, the NOAEC for systemic toxicity was 76 mg/m³. For local effects, the LOAEC was 20 mg/m³. Dimethyl glutarate was also investigated as an individual substance in a subchronic inhalation toxicity study (ECHA Dissemination, 2020c). Exposure of rats to 10, 50 and 400 mg/m³ for 6 h/d, 5 d/week over 90 days resulted in decreased testosterone levels and increased epididymal sperm counts in males. The NOAEC for systemic toxicity was 10 mg/m³. Degeneration of nasal olfactory epithelium was only observed in female animals and only in the highest dose group. The NOAEC for local toxicity was 50 mg/m³.

Several genotoxicity studies were performed *in vitro* and *in vivo* on dimethyl glutarate alone or as part of the dibasic ester mixture, with the overall conclusion that there is no evidence for genotoxic potential.

Administration of an aerosol (160, 400 and 1000 mg/m³) of the dibasic ester mixture to rats in a one-generation reproduction toxicity study (Kelly et al., 1998) and a developmental toxicity study (Alvarez et al., 1995) did not reveal any effects on reproductive parameters or prenatal development. Dimethyl glutarate was also investigated as an individual substance in a developmental toxicity study in rabbits (ECHA Dissemination, 2020c). After exposure to test concentrations of 30, 100, 300 and 1000 mg/m³ during GD 7-28, no effects on prenatal development were observed.

The only published limit value for diisobutyl glutarate in air is the AgBB NIK value of 100 µg/m³, which was derived by read across from the NIK value of 50 µg/m³ for dimethyl glutarate. The NIK value for dimethyl glutarate was derived from the MAK value of 5 mg/m³, which is based on the LOAEC of 20 mg/m³ for the mixture of dibasic esters reported by Keenan et al., 1990.

The lowest reported NOAEC for dimethyl glutarate is the value of 10 mg/m³ for effects on male reproductive parameters. However, this value is considered questionable for two reasons: Firstly, the effects are contradictory in themselves. Decreased testosterone levels should be associated with decreases in sperm counts, not, as reported, with increases. Secondly, reproductive parameters were not affected in a dedicated reproduction study at much higher dose levels. Therefore, the local effects on the respiratory tract are still considered as decisive

for the derivation of an EU-LCI value. The study reported by Keenan et al., 1990, provides the most detailed evaluation of this effect. The study with dimethyl glutarate included in the REACH registration dossier found effects only at higher concentrations. However, the full study report is not available, and the examinations and results are not disclosed in great detail. Therefore, it is considered preferable to use the LOAEC of 20 mg/m³ from Keenan et al. 1990, as POD for the derivation an EU-LCI value for dimethyl glutarate.

Assessment factors are chosen as follows:

- Exposure duration: 5.6 (from 6 h/d on 5 d/week)
- Study length: 2 (standard value for subchronic to chronic extrapolation)
- Uncertainty of the dose-response: 3 (standard value for using a LOAEC instead of a NOAEC)
- Interspecies differences: 2.5 (standard value for remaining kinetic and dynamic differences)
- Intraspecies difference: 10 (standard value for the general population)

The total assessment factor of 840 and the POD of 20 mg/m³ gave an initial value of 23.8 µg/m³ (3.61 ppb) for the mixture of dibasic esters.

A molar adjustment factor for read across from the mixture to dimethyl glutarate was calculated by dividing the molar mass of dimethyl glutarate (160.17 g/mol) by the molar mass determined for the tested mixture based on the reported quantitative composition [(0.169 x 146.14 g/mol) + (0.655 x 160.17 g/mol) + (0.165 x 174.20 g/mol) = 158.35 g/mol]. Application of the resulting molar adjustment factor of 1.011 to the unrounded value of 23.8 µg/m³ resulted in an initial value of 24.1 µg/m³, which is rounded to the proposed new EU-LCI value of 25 µg/m³ for dimethyl glutarate. This value is lower than the current ascribed value of 50 µg/m³. It may be considered conservative as it is based on local effects that have been characterised as predominantly mild and may be presumed to be reversible.

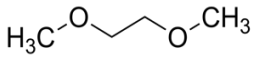
For read across to diisobutyl glutarate, the unrounded value of 24.1 µg/m³ calculated for dimethyl glutarate is used. Application of the molar adjustment factor of 1.525 (from 244.33 g/mol divided by 160.17 g/mol) leads to an initial value of 36.8 µg/m³, which is rounded to the proposed EU-LCI value of 35 µg/m³ for diisobutyl glutarate.

5 Toxicological evaluation of 1,2-dimethoxyethane as basis for the derivation of an EU-LCI value

5.1 Substance identification

Substance identification data and physicochemical properties of 1,2-dimethoxyethane are shown in Table 15 and Table 16.

Table 15 Substance identification of 1,2-dimethoxyethane

CAS No. EC No.	Systematic name; common names	Summary formula	Structural formula
110-71-4 203-794-9	1,2-Dimethoxyethane; ethylene glycol dimethyl ether (EGDME); (mono)glyme	$C_4H_{10}O_2$	

5.2 Substance properties and uses

1,2-Dimethoxyethane is at room temperature a colourless liquid that is miscible with water and organic solvents.

Table 16 Physicochemical properties of 1,2-dimethoxyethane

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa)	Conversion 1 ppm = x mg/m³	Log P_{OW}	Solubility in water (g/L)
90.12	-58.2	82-84.8	66 (20 °C)	3.71 (23 °C)	-0.21 (25 °C)	1000 (25 °C)

Source: ECHA Dissemination, 2020d.

1,2-Dimethoxyethane is currently manufactured and/or imported in the European Economic Area in quantities of 100 - 1 000 tons per year (ECHA Dissemination, 2020d). It is employed for industrial and professional uses as a solvent, for the surface treatment of metals and as laboratory reagent.

Due to its classification as Repr. 1B; H360FD, the use of 1,2-dimethoxyethane in consumer products is prohibited by a number of legal provisions:

- According to REACH, it may not be supplied to the general public in a concentration equal to or greater than 0.3 %.
- According to the Cosmetics Regulation, it may not be used in cosmetic products.
- According to the Toy Safety Directive, it may not be used in toys.

Before the first restrictions regarding consumer uses of 1,2-dimethoxyethane were adopted in the 1990s it was used as solvent in paints and varnishes and in cleaning products. Investigations in France confirmed that these uses have been discontinued and the substance can no longer be detected in marketed products (ECHA, 2012b).

5.3 Exposure

5.3.1 Indoor air

During an investigation of the living environments of 53 patients with potentially environment-related complaints, 1,2-dimethoxyethane was detected in 8 of 23 analysed indoor air samples (Eis et al., 2005). The maximum concentration found was 5 µg/m³, the median and the arithmetic mean were <1 µg/m³.

1,2-Dimethoxyethane was detected in 12 of 500 samples of indoor air from offices, homes, schools and pre-schools analysed between 2000 and 2006 (Hofmann and Plieninger, 2008). The maximum concentration found was 13 µg/m³, the arithmetic mean was 0.6 µg/m³.

5.3.2 Other sources

As an integrated measure of overall exposure to different methoxyethyl derivatives, their common metabolite, methoxy acetic acid (MAA), was analysed in urine samples obtained from German volunteers (Fromme et al., 2013). The reported value of 0.3 mg/L for the 95th percentile (maximum: 0.55 mg/L, median: 0.11 mg/L) served as the basis for a provisional reference value for the general population published by the Human Biomonitoring Commission of the German Environment Agency (UBA, 2014). If inhalation of 1,2-dimethoxyethane was the only source of MAA, this reference value of 0.3 mg/L would correspond to a chronic daily exposure to 46 µg/m³. However, there are also other sources for this metabolite, such as 2-methoxyethyl acetate, 2-methoxyethanol, 2-(2-methoxyethoxy)ethanol, or diethylene glycol dimethyl ether.

5.4 Toxicokinetics

No substance-specific data are available. However, the metabolic pathways are assumed to correspond to those established for other glycol ethers (ECETOC, 2005; ECHA Dissemination, 2020d). Glycol ethers in general are readily absorbed and distributed throughout the body. Unchanged parent substance is eliminated through the urine. After oxidative ether cleavage of 1,2-dimethoxyethane, the resulting intermediate 2-methoxyethanol is oxidised via alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) to methoxyacetic acid (MAA). The excretion of MAA is relatively slow. With an elimination half-life of 77 h it has the potential to accumulate in the organism under repeated exposure. As will be discussed below, MAA is assumed to be responsible for the observed toxicity of 1,2-dimethoxyethane, in particular its effects on male fertility and prenatal development.

5.5 Health effects

5.5.1 Acute toxicity, sensory irritation and local effects

Acute inhalation toxicity of 1,2-dimethoxyethane was studied in rats according to OECD test guideline 403 (ECHA Dissemination, 2020d). After 1 h exposure at a concentration of 240 g/m³, all animals survived. Clinical signs included ataxia, salivation, irregular respiration and reduced body weight, all of which were reversible. Prolonged exposure for 6 h resulted in the death of all animals at concentrations of 63 and 200 g/m³ and in the survival of all animals at 20 g/m³.

A dermal irritation/corrosion study similar to OECD test guideline 404 in Himalayan rabbits resulted in erythema (up to grade 4) and edema (up to grade 2) that were not reversible within the 72 h observation period (ECHA Dissemination, 2020d). This fulfills the criteria for classification as Skin Irrit. 2 (H315).

In a study on eye irritation similar to OECD test guideline 405 in New Zealand White rabbits, 1 h exposure to 1,2-dimethoxyethane resulted in redness and swelling, which subsided in the recovery phase (ECHA Dissemination, 2020d). The substance is concluded not be irritant to the eyes.

No adverse effects were observed in a local lymph node assay according to OECD test guideline 429 in mice (ECHA Dissemination, 2020d). 1,2-Dimethoxyethane does not show any potential for skin sensitisation.

5.5.2 Repeated dose toxicity

Effects of 1,2-dimethoxyethane after repeated exposure were investigated in a number of sub-acute inhalation toxicity studies according to OECD test guideline 412 (ECHA Dissemination, 2020d):

Exposure of male and female rats to 37, 187 and 935 mg/m³ for 6 h/d, 5 d/week over two weeks resulted in the reduction of cell layers of seminiferous epithelium in male rats of the highest dose group, which was reversible. No other adverse effects were observed. Examinations included clinical signs, neurological or ophthalmological effects, body weight gain, food and water consumption, haematological changes, clinical parameters, organ weights and histopathology. The NOAEC from this study is 187 mg/m³.

Exposure of male and female rabbits to 37, 187 and 935 mg/m³ for 6 h/d, 5 d/week over two weeks resulted in reduced body weight gains during the recovery phase and reduced reticulocyte counts after the last exposure in animals of the highest dose group, reduced reticulocyte counts in females of the mid dose group, and changes of the seminiferous epithelium, which caused aspermia, in males of the highest dose group. This effect was irreversible within the recovery period of 36 days. At the same dose, decreased testis weight was observed after the recovery period. The authors concluded on a NOEC of 37 mg/m³ and a NOAEC of 187 mg/m³.

Rats (males and pregnant females) were exposed to 374 and 1870 mg/m³ for 6 h/d, 5 d/week for up to 14 days. At the higher dose the leucocyte count was decreased in all animals. In females, food consumption and body weight gain were reduced at the higher dose and an increase of resorptions occurred. At 374 mg/m³ retardation of foetal development was observed. In males, microscopic examination of the testes and epididymis showed oligospermia at 374 mg/m³ and severe lesions of the seminiferous epithelium at 1870 mg/m³. The LOAEC was 374 mg/m³.

Pregnant rabbits were exposed to 374 and 1870 mg/m³ for 6 hours per day on 5 days per week for up to 14 days. All animals of the higher dose group died, their body weight, leucocyte count, lymphocyte count and reticulocyte count were decreased, and the livers were enlarged. In the lower dose group slightly reduced body weight was observed, and all embryos were resorbed. The LOAEC was 374 mg/m³.

5.5.3 Genotoxicity and carcinogenicity

Several studies were performed *in vitro* and *in vivo* to investigate the mutagenic potential of 1,2-dimethoxyethane (ECHA Dissemination, 2020d):

In a bacterial reverse mutation assay according to OECD test guideline 471 (Ames test) 1,2-dimethoxyethane was applied to *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, TA 1538 and *Escherichia coli* WP2 uvrA, with and without metabolic activation. There was no increase in reverse mutation at the tested concentrations of up to 10 µL/plate.

A gene mutation test in Chinese hamster ovary cells according to OECD test guideline 476 with and without metabolic activation was negative for the tested concentrations of 3.5-6.5 %.

Cytogenicity was investigated in Chinese hamster ovary cells according to OECD test guideline 479 (Sister Chromatid Exchange Assay), in the permanent human cell line A549 and in primary rat hepatocytes according to OECD test guideline 482 (Unscheduled DNA Synthesis). Both tests for unscheduled DNA synthesis were negative, but significant effects were observed on the frequency of sister chromatid exchange in Chinese hamster ovary cells at a concentration of 5 %, both with and without metabolic activation.

For a further investigation of cytogenicity according to OECD test guideline 475 (Mammalian Bone Marrow Chromosomal Aberration Test), Chinese hamsters received 1,2-dimethoxyethane as a single dose of 2000 mg/kg_{BW} by gavage. Animals were sacrificed 6, 26, and 50 hours post exposure for bone marrow examinations. No effects were detected.

A mammalian erythrocyte micronucleus test according to OECD test guideline 474 was performed in NMRI mice. Dose levels of 20, 200 and 2000 mg/kg_{BW} were administered by gavage as single applications on two consecutive days. No statistically significant differences in the proportion of erythrocytes with micronuclei were observed.

In view of the negative results observed in the genotoxicity tests, no carcinogenicity studies with 1,2-dimethoxyethane were performed.

5.5.4 Toxicity to reproduction

5.5.4.1 Fertility

Effects on male fertility were observed during sub-acute inhalation toxicity studies in male rats and rabbits (see above). The NOAEC was 187 mg/m^3 based on changes of seminiferous epithelium (rabbits and rats) and aspermia (rabbits only). No further studies regarding fertility were performed.

5.5.4.2 Development

In a teratogenicity study according to OECD test guideline 414, pregnant rats were exposed to 37, 120 and 374 mg/m^3 1,2-dimethoxyethane for 6 hours per day, daily, on gestation days 7-16 (ECHA Dissemination, 2020d). At the two highest exposure levels, retarded development and increased incidences of foetal malformations were observed. No adverse effects were observed in the maternal animals at any dose level. The NOAEC for developmental toxicity was 37 mg/m^3.

In a similar teratogenicity study, pregnant rabbits were exposed to 19, 60 and 187 mg/m^3 1,2-dimethoxyethane for 6 hours per day, daily, on gestation days 6-18 (ECHA Dissemination, 2020d). At the highest exposure level, the vitality of the litters was considerably decreased, and skull malformations as well as irregularities in skull ossification were observed in several foetuses. No adverse effects were observed in the maternal animals, except for a slightly decreased food consumption. The NOAEC for developmental toxicity was 60 mg/m^3.

5.5.5 Odour perception

1,2-Dimethoxyethane is reported to have an ethereal odour. No information regarding the odour perception threshold could be found.

5.6 Evaluation

5.6.1 Existing regulations and classifications

As listed in the CLP regulation (1272/2006), 1,2-dimethoxyethane is assigned an official harmonised classification of Flam. Liquid 2 (H225); Acute Tox. 4 (H332); Repr. 1B (H360).

Based on its reproductive toxicity, 1,2-dimethoxyethane has been identified as a substance of very high concern (ECHA, 2012b; 2012c) and included in the candidate list for authorisation.

Relevant limit values for the concentration of 1,2-dimethoxyethane are summarised in Table 17.

Table 17 Limit values for 1,2-dimethoxyethane in air

Organisation	AgBB	ANSES	REACH registrants	REACH registrants
Year	2010	2009	Not reported	Not reported
Risk value name	NIK	CLI	DNEL (general)	DNEL (worker)
Risk value	4 µg/m³	20 µg/m³	1.5 mg/m³	3.1 mg/m³
Reference period	Chronic	Chronic	Chronic	Chronic (worker)
Key study	Read across from 2-methoxyethanol	Read across from 2-methoxyethanol	Confidential study report, 1988 (cited in ECHA Dissemination, 2020d)	Confidential study report, 1986 (cited in ECHA Dissemination, 2020d)
Study type			Teratogenicity	Sub-acute inhalation tox.
Species			Rabbit	Rat
Duration			14 d	14 d
Critical effect			Decreased pup vitality	Changes in the seminiferous epithelium
Critical dose value			NOAEC: 60 mg/m³	NOAEC: 187 mg/m³
Adjusted critical dose value			15 mg/m³	94 mg/m³
Assessment factor(s)			10 (intraspecies)	6 (study length) x 5 (intraspecies) = 30

Both the German AgBB and the French ANSES have issued values for the lowest concentration of interest for 1,2-dimethoxyethane based on read across from 2-methoxyethanol. The reasoning is that the common metabolite methoxyacetic acid is responsible for the observed toxicity of both substances, in particular their reproductive toxicity. As the two organisations list different limit values for 2-methoxyethanol, the values for 1,2-dimethoxyethane are also different: The NIK value from AgBB is 4 µg/m³, the CLI value from ANSES is 20 µg/m³.

The REACH registration dossier for 1,2-dimethoxyethane (ECHA Dissemination, 2020d) includes DNEL values of 1.5 and 3.1 mg/m³ for the general public and workers, respectively. The value for

the general public is derived from the NOAEC of 60 mg/m³ observed for teratogenicity in rabbits. Adjustment for exposure duration gives the POD of 15 mg/m³. The only assessment factor applied is the default value of 10 for intraspecies differences. Interspecies differences were disregarded without explanation. The value for workers is based on the NOAEC of 187 mg/m³ observed for effects on male fertility in rats during a sub-acute inhalation toxicity study. Adjustment for exposure duration and taking into account the default factor for light work gives the POD of 94 mg/m³. The total assessment factor of 30 includes the default values of 6 for study length and 5 for intraspecies differences. Again, interspecies differences were disregarded without explanation. The DNEL values were derived by registrants and are not approved by ECHA or any other public institution.

5.6.2 Derivation of an EU LCI value

1,2-Dimethoxyethane is used by professional users as a solvent and process chemical for the surface treatment of metals. It is legally banned from the use in cosmetic products and toys and from supply to the general public in concentrations ≥0.3 %. Prior to these restrictions, 1,2-dimethoxyethane was used in paints, varnishes and cleaning products, and it was still detected in indoor air during investigations conducted between 2000 and 2006. Its major metabolite, methoxyacetic acid, was found in the urine of German volunteers in a concentration of 0.3 mg/L (95th percentile), which would correspond to a chronic daily exposure to 46 µg/m³, if 1,2-dimethoxyethane was the only source (Fromme et al., 2013).

The European Chemicals Agency has published an Annex XV dossier for 1,2-dimethoxyethane with a proposal for its identification as a substance of very high concern based on its classification as Repr. 1B, H360FD and a summary of the underlying toxicological data (ECHA, 2012b; ECHA, 2012c). A registration dossier under REACH is available (ECHA Dissemination, 2020d).

Metabolism of 1,2-dimethoxyethane proceeds via the intermediate 2-methoxyethanol to the main metabolite methoxyacetic acid (MAA), which is assumed to be responsible for the observed toxicity. The excretion of MAA is relatively slow ($t_{1/2}$ = 77 h).

After acute inhalation exposure to 1,2-dimethoxyethane, clinical signs are only observed at very high concentrations (ECHA Dissemination, 2020d). The substance is irritant to skin (Cat. 2), but not to eyes (ECHA Dissemination, 2020d).

Sub-acute inhalation toxicity studies were performed in rabbits and rats with dose levels of 37, 187, and 935 mg/m³ administered for 6 h/d, 5 d/week for two weeks (ECHA Dissemination, 2020d). Effects on male fertility were observed in animals of both species in the highest dose groups, namely changes of seminiferous epithelium (rabbits and rats) and aspermia (rabbits only). The NOAEC was 187 mg/m³. At higher concentrations, effects on body weight gain and haematological parameters were noted.

Experimental data from *in vitro* and *in vivo* genotoxicity studies indicate that 1,2-dimethoxyethane does not have any mutagenic potential (ECHA Dissemination, 2020d).

Teratogenicity studies were performed with rabbits and rats (ECHA Dissemination, 2020d). After exposure of pregnant rats to 1,2-dimethoxyethane at concentrations of 37, 120 and 374 mg/m³ for 6 h/d, daily, on GD 7-16, retarded development and increased incidences of foetal malformations were observed at the two highest exposure levels. The NOAEC for developmental toxicity from this study was 37 mg/m³. Exposure of pregnant rabbits to 19, 60 and 187 mg/m³ for 6 h/d, daily, on GD 6-18 resulted in decreased vitality of the litters and increased incidences of skull malformations in foetuses at the highest dose level. The NOAEC for developmental toxicity from this study was 60 mg/m³.

Toxicological data indicate that teratogenicity is the leading adverse health effect of 1,2-dimethoxyethane. From the available teratogenicity studies, the NOAEC of 37 mg/m³ obtained from the rat study is chosen as POD because it is the lowest NOAEC reported for the critical effect.

Assessment factors are chosen as follows:

- Exposure duration: 4 (from 6 h/d)
- Study length: 1 (exposure throughout the relevant time frame for the critical effect))
- Severity of the effect: 3 (standard value for developmental toxicity)
- Interspecies differences: 2.5 (standard value for kinetic and dynamic differences)
- Intraspecies difference: 10 (standard value for the general population)

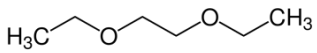
The total assessment factor of 300 and the POD of 37 mg/m³ gave an initial value of 123 µg/m³ (33.2 ppb), which was rounded to 100 µg/m³ as the proposed EU-LCI value for 1,2-dimethoxyethane.

6 Toxicological evaluation of 1,2-diethoxyethane as basis for the derivation of an EU-LCI value

6.1 Substance identification

Substance identification data and physicochemical properties of 1,2-diethoxyethane are shown in Table 18 and Table 19.

Table 18 Substance identification of 1,2-diethoxyethane

CAS No. EC No.	Systematic name; common names	Summary formula	Structural formula
629-14-1 211-076-1	1,2-Diethoxyethane; ethylene glycol diethyl ether (EGDEE); ethyl glyme	$C_6H_{14}O_2$	

6.2 Substance properties and uses

1,2-Diethoxyethane is at room temperature a colourless liquid that is miscible with water and organic solvents.

Table 19 Physicochemical properties of 1,2-diethoxyethane

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa)	Conversion 1 ppm = x mg/m³	Log P_{OW}	Solubility in water (g/L)
118.18	-74	121.4	4.5 (25 °C)	4.86 (23 °C)	0.66	83.7 (25 °C)

Source: ECHA, 2012c.

No registration dossier for this substance has been submitted to ECHA, but it has been pre-registered under REACH by 59 companies. Production volume in the EU is estimated to be low (1-10 t/a). The available information on uses of the substance is limited. It belongs to the chemical substance class of glycol ethers (glymes), which are generally used as solvents in a variety of processes and products.

Due to its classification as Repr. 1B; H360f, the use of 1,2-diethoxyethane in consumer products is prohibited by a number of legal provisions:

- According to REACH, it may not be supplied to the general public in a concentration ≥0.3 %.
- According to the Cosmetics Regulation, it may not be used in cosmetic products.
- According to the Toy Safety Directive, it may not be used in toys.

According to the SPIN database, the substance was present in consumer preparations in Sweden during the years 1999-2001 before the above-listed restrictions were adopted.

6.3 Exposure

6.3.1 Indoor air

1,2-Diethoxyethane was detected in 11 of 500 samples of indoor air from offices, homes, schools and pre-schools analysed between 2000 and 2006 (Hofmann and Plieninger, 2008). The maximum concentration found was 5 µg/m³, the arithmetic mean was 0.7 µg/m³.

6.3.2 Other sources

No relevant information could be found.

6.4 Toxicokinetics

No substance-specific data are available. However, the metabolic pathway is assumed to correspond to those established for other glycol ethers (ECETOC, 2005). Glycol ethers in general are readily absorbed and distributed throughout the body. Unchanged parent substance is eliminated through the urine. After oxidative ether cleavage of 1,2-diethoxyethane, the resulting 2-ethoxyethanol is oxidised via alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) to ethoxyacetic acid. The excretion of the acid is relatively slow. With an elimination half-life of 24 h it has the potential to accumulate in the organism under repeated exposure. As will be discussed below, 2-ethoxyacetic acid is assumed to be responsible for the observed toxicity of 1,2-diethoxyethane, in particular its effects on male fertility and prenatal development.

6.5 Health effects

6.5.1 Acute toxicity, sensory irritation and local effects

The acute systemic toxicity of 1,2-diethoxyethane is low (Bingham et al., 2001). LD_{50} values after oral exposure were determined in rabbits (2.5 g/kg bw), guinea pigs (2.4 g/kg bw), and rats (4.4 g/kg bw). Inhalation of 10000 ppm (49 g/m³) for 1 h caused irritation in the mucous membranes and central nervous system depression in cats, guinea pigs and rabbits. All animals survived.

1,2-Diethoxyethane has an official harmonised classification as Eye Irrit. 2 (H319). Toxicological data underlying this classification could not be found. No information about effects on skin could be found.

6.5.2 Repeated dose toxicity

Sub-acute inhalation toxicity was studied in small numbers of mice, guinea pigs, rabbits and cats (Bingham et al., 2001). After exposure to 500 ppm (2.4 g/m³) for 8 h/d on 12 consecutive days, both cats and one of two rabbits died. Mice and guinea pigs survived.

In the course of oral teratogenicity studies (see below), reduced body weight gain was observed in maternal animals at the highest dose level of 1000 mg/kg bw x d administered to pregnant mice on gestation days 6-15 (NTP, 1987a; George et al. 1992). The NOAEL for maternal toxicity from this study was 500 mg/kg bw x d. In pregnant rabbits, only minimal effects on body weight gain were observed (NTP, 1987b; George et al. 1992). The highest dose level of 100 mg/kg bw x d was considered as the NOAEL for maternal toxicity from this study.

6.5.3 Genotoxicity and carcinogenicity

No substance-specific experimental data regarding the potential genotoxicity or carcinogenicity of 1,2-diethoxyethane could be found.

6.5.4 Toxicity to reproduction

6.5.4.1 Fertility

No information could be found regarding potential effects of 1,2-diethoxyethane on fertility.

6.5.4.2 Development

The United States National Toxicology Program commissioned the performance of teratogenicity studies with 1,2-diethoxyethane in rabbits and mice (George et al., 1992; NTP, 1987a; 1987b).

Pregnant CD-1 mice received 1,2-diethoxyethane by gavage at dose levels of 50, 150, 500 and 1000 mg/kg bw x d during gestation days 6-15 and were sacrificed on gestation day 17. Increases in the incidence of foetuses with malformations were observed at dose levels of 150 mg/kg bw x d and above. The NOAEL for developmental toxicity from this study was 50 mg/kg bw x d. The NOAEL for maternal toxicity was 500 mg/kg bw x d, based on reduced body weight gains.

1,2-Diethoxyethane was administered to pregnant rabbits (New Zealand White) by gavage at dose levels of 25, 50 and 100 mg/kg bw x d during gestation days 6-19, followed by euthanasia on gestation day 30. Increased numbers of litters with malformed foetuses were observed in the high and mid dose group. The NOAEL for developmental toxicity from this study was 25 mg/kg bw x d. As only minimal effects on body weight gain in maternal animals of the high dose group were noted, the authors concluded on a NOAEL of 100 mg/kg bw x d for maternal toxicity.

6.5.5 Odour perception

1,2-Diethoxyethane is reported to have an ethereal odour. No information regarding the odour perception threshold could be found.

6.6 Evaluation

6.6.1 Existing regulations and classifications

As listed in the CLP regulation (1272/2006), 1,2-diethoxyethane is assigned an official harmonised classification of Flam. Liquid 2 (H225); Eye Irrit. 2 (H319); Repr. 1B (H360).

Based on its reproductive toxicity, 1,2-diethoxyethane has been identified as a substance of very high concern (ECHA, 2012d; 2012e) and included in the candidate list for authorisation.

Limit values for 1,2-ethoxyethane in air with regard to the general public could only be found from the German AgBB and the French ANSES. Based on read across from 2-ethoxyethanol, the primary metabolite of 1,2-diethoxyethane, AgBB issued a NIK value of 10 µg/m³, and ANSES adopted a CLI value of 70 µg/m³. However, for the derivation of an EU-LCI value, *de novo* derivation seemed preferable to read across as suitable toxicological data for 1,2-diethoxyethane are available.

6.6.2 Derivation of an EU LCI value

Only very little information is available regarding the use and occurrence of 1,2-diethoxyethane. The production volume appears to be low. It is legally banned from most consumer uses based on its classification as reproductive toxicant but was still detected in some indoor air samples analysed between 2000 and 2006.

The available toxicological database for 1,2-diethoxyethane is very limited. A registration dossier under REACH is not available. Although the European Chemicals Agency published an Annex XV dossier for the identification of 1,2-diethoxyethane as substance of very high concern based on its harmonised classification as Repr. 1B (H360), the underlying toxicological data for this classification were not made available (ECHA, 2012d; 2012e). Animal studies focus almost exclusively on the investigation of developmental toxicity, which had been observed previously for other, similar glycol ethers.

It can be assumed that metabolism of 1,2-diethoxyethane follows the usual pathway established for glycol ethers and results in the main metabolite ethoxyacetic acid, which is known to cause significant toxicity to reproduction.

1,2-Dimethoxyethane is of low acute toxicity (Bingham et al., 2001). It is classified as Eye Irrit. 2 (H319), but the underlying data for this classification could not be found. There is no information regarding effects on skin.

Information on repeated dose toxicity is only available from oral teratogenicity studies. Reduced body weight gains were observed in mice at the dose level of 1000 mg/kg bw x d. The NOAEL was 500 mg/kg bw x d. No significant adverse effects were found in rabbits at the tested dose levels up to 100 mg/kg bw x d.

There is no information regarding genotoxicity or carcinogenicity of 1,2-diethoxyethane.

Well-documented teratogenicity studies were performed with CD-1 mice and New Zealand White rabbits (George et al., 1992; NTP, 1987a; NTP 1987b). Following oral exposure of pregnant mice to 50, 150, 500, and 1000 mg/kg bw x d during gestation days 6-15, increased incidences of foetal malformations were observed at dose levels of 150 mg/kg bw x d and above. The NOAEL for developmental toxicity from this study was 50 mg/kg bw x d, the NOAEL for maternal toxicity was 500 mg/kg bw x d, based on reduced body weight gain. Administration of 1,2-diethoxyethane to rabbits at dose levels of 25, 50, and 100 mg/kg bw x d during gestation days 6-19 resulted in increased incidences of foetal malformations in the mid and high dose groups. The NOAEL for developmental toxicity from this study was 25 mg/kg bw x d, the NOAEL for maternal toxicity was 100 mg/kg bw x d (no adverse effects observed).

The main adverse health effect of 1,2-diethoxyethane documented in toxicological studies is teratogenicity. This is in accordance with observations made for similar glycol ether derivatives. From the available data, the NOAEL of 50 mg/kg bw x d for developmental toxicity in mice was chosen for the derivation of an EU-LCI, because this resulted in the lowest value, as demonstrated below.

For route-to-route extrapolation, the oral NOAEL is divided by the standard human respiratory rate (20 m^3/d), multiplied with the standard human body weight (70 kg), then divided by a default factor of 2 to account for potential differences in absorption between the oral and inhalation route, respectively. The resulting POD is 87.5 mg/m^3.

Assessment factors are chosen as follows:

- Study length: 1 (exposure throughout the relevant time window for the critical effect)
- Severity of the effect: 3 (standard factor for developmental toxicity)
- Interspecies differences: 17.5 (7 for allometric scaling from mouse to human and 2.5 as standard value for remaining kinetic and dynamic differences)
- Intraspecies difference: 10 (standard value for the general population)

With a total assessment factor of 525 and a POD of 87.5 mg/m^3, an initial value of 167 µg/m^3 (34.4 ppb) is obtained and rounded to an EU-LCI value of 150 µg/m^3 as the proposed EU-LCI value for 1,2-diethoxyethane.

If the rabbit study was used for the derivation of an EU-LCI, the POD would be 44 mg/m^3. This POD is lower than the one obtained from the study in mice. However, assessment factors of 3 (severity of effect), 2.4 (allometric scaling), 2.5 (remaining interspecies differences) and 10

(intraspecies differences) result in a total assessment factor of only 180. Therefore, a calculated value of 244 µg/m³ (50.2 ppb) is obtained and rounded to an EU-LCI value of 250 µg/m³, which is higher than the value derived from the mouse study.

The proposed EU-LCI of 150 µg/m³ derived from the oral teratogenicity study in mice is preferred because it can be considered to be more protective.

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National Toxicology Program (1987a): Ethylene glycol diethyl ether (CAS No. 629-14-1) administered to CD-1 mice on gestational days 6 through 15, NTP Study No. TER87074 (abstract available only).

National Toxicology Program (1987b): Ethylene glycol diethyl ether (CAS No. 629-14-1) administered to New Zealand White rabbits on gestational days 6 through 19, NTP Study No. TER90075 (abstract available only).

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U.S. EPA, United States Environmental Protection Agency (2020b): Chemistry Dashboard, Diisobutyl glutarate. https://comptox.epa.gov/dashboard/DTXSID9072282 (11.04.2020)

A Appendix: Summary Fact Sheets

A.1 Neopentyl glycol

Compound		Neopentyl glycol	Factsheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m³]	8700
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2020
General information			
CLP-INDEX No	4	INDEX	-
EC No	5	EINECS – ELINCS - NLP	204-781-0
CAS No	6	Chemical Abstracts Service number	126-30-7
Harmonised CLP classification	7	Human health risk related classification	Not available
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	104.15 1 ppm = 4.29 mg
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	BASF, 2013 (cited in ECHA, 2020)
Read across compound	10	Where applicable	-
Species	11	Rat, human etc.	Rat
Route/type of study	12	Inhalation, oral feed etc.	Oral
Study length	13	Days, subchronic, chronic	Subchronic (90 d)
Exposure duration	14	Hrs/day, days/week	Continuous
Critical endpoint	15	Effect(s), site of	No treatment-related adverse findings
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, etc.	Adjusted NOAEL
POD value	17	[mg/m³] or [ppm] or [mg/kg$_{BW}$×d]	500 mg/kg$_{BW}$ x d
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	1
Study length	20	sa→ sc→ c *(R8-5)*	2

Route-to-route extrapolation factor	21		1.15 m^3/kg_{BW} x d
Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	1
	22 b	Severity of effect *(R 8-6d)*	1
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	1[1]
	23 b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic Worker - general population	10
AF (sensitive population)	25	Children or other sensitive groups	1
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	1
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	57.5
POD/TAF	28	Calculated value (µg/m^3 and ppb)	8696 µg/m^3 (2027 ppb)
Molar adjustment factor	29	Used in read-across	-
Rounded value	30	[µg/m^3]	8700
Additional comments	31		

Rationale section	32		

Neopentyl glycol was included in the OECD assessment programme for High Production Volume Chemicals in the 1990s. A Screening Information Data Set (SIDS) summarising available toxicity data was published (OECD, 2002), but no risk assessment was performed. A more recent assessment was performed by BASF as part of the REACH registration dossier, which is published on the ECHA dissemination site (ECHA, 2020). In order to identify additional relevant information, targeted searches were performed in HSDB, TOXLINE and PubMed.

Neopentyl glycol is a water-soluble solid that is primarily excreted in urine as glucuronic acid conjugate (Gessner et al., 1960). Its odour is described as sweetish, but no information regarding an odour threshold could be found. It is slightly irritant to skin and can cause serious eye damage. Its acute systemic toxicity is low for all exposure routes. Relevant information on repeated dose toxicity is only available for oral exposure. A combined repeated dose toxicity study with reproductive/developmental toxicity screening test (OECD test guideline 422), performed in Japan, is reported in the OECD SIDS (2002). A subchronic toxicity study (OECD test guideline 408) was performed by BASF and is included in the REACH registration dossier (ECHA, 2020).

In the OECD 408 study, Wistar rats were dosed with 50, 250 and 1000 mg/kg_{BW} x d neopentyl glycol in drinking water for a period of 90 days. The performed examinations included clinical signs, body weight, food and water consumption, ophthalmoscopic examination, haematology, clinical chemistry, urinalysis, neurobehavioural examination, oestrous cycle determination, sperm parameters, gross pathology, and histopathology of all organs. No treatment-related adverse effects were observed in any dose group. Observed changes such as increases in haematocrit and urine volume in high dose females as well as increase

[1] Allometric scaling issues are included in the route-to-route extrapolation factor (line 21).

in cholesterol and decrease in urine pH in high dose males were judged as possibly treatment-related but not adverse. Increases in relative kidney weights in males of the two highest dose groups and in relative liver weights in high dose males were regarded as adaptive rather than adverse, because there were no concurrent histopathological changes. Thus, the NOAEL derived from this study is ≥ 1000 mg/kg$_{BW}$ x d.

In the OECD 422 study, Sprague-Dawley rats received 100, 300, or 1000 mg/kg$_{BW}$ x d neopentyl glycol per gavage over 45 days (males) or from 14 d premating until day 4 of lactation (females), respectively. No treatment-related effects were observed in maternal animals and in off-spring. In male animals of the parent generation, elevated levels of total protein, albumin and bilirubin were measured in the two higher dose groups. At these doses, absolute and relative liver weights were also increased. However, as histopathological examination revealed no lesions of the liver, the observed changes are considered an adaptive reaction rather than an adverse effect. Male animals dosed with 1,000 mg/kg$_{BW}$ x d also had increased absolute and relative kidney weights and histopathological changes in the kidneys such as basophilic alteration of the renal tubular epithelium and increased incidences in hyaline droplets and protein casts. These changes are considered treatment-related adverse effects. However, the reported findings indicate that the observed nephrotoxicity is likely to be caused by α_{2u}-globin *via* a mode of action (MoA) that is specific for male rats. Typical signs of this MoA include the absence of nephrotoxicity in females, the formation of hyaline droplets and an increased number of granular casts, as they are reported here. Since humans, like female rats, do not produce a protein like α_{2u}-globulin, such effects are not considered relevant for human health risk assessment (Hard et al., 1993; Swenberg, 1993).

In conclusion, the NOAEL value of 1000 mg/kg$_{BW}$ x d (BASF, 2013, cited in ECHA, 2020) is considered most relevant for the derivation of an EU-LCI value for neopentyl glycol. This value is adjusted by a default factor of 2 to account for potential differences in absorption between the oral and inhalation route, respectively, to give a POD value of 500 mg/kg$_{BW}$ x d.

Assessment factors are chosen as follows:

- Study length: 2 for subchronic to chronic extrapolation
- Route-to-route extrapolation: 1.15
- Interspecies differences: 2.5 (default value for kinetic and dynamic differences)
- Intraspecies difference: 10 (default value for the general population)

With a total assessment factor of 57.5 and a POD of 500 mg/kg$_{BW}$ x d, the LCI value is calculated as 8696 µg/m^3 (2027 ppb) and rounded to 8700 µg/m^3.

References:

BASF (2013): Unnamed study report. Cited in ECHA, 2020: https://echa.europa.eu/registration-dossier/-/registered-dossier/15079/7/6/2. Last accessed on 6 May 2020.

European Chemicals Agency (2020): Registration dossier for 2,2-dimethylpropane-1,3-diol. https://echa.europa.eu/registration-dossier/-/registered-dossier/15079/1. Last accessed on 8 April 2020.

Gessner, P.K.; Parke, D.V.; Williams, R.T. (1960): Studies in detoxication. The metabolism of glycols, Biochem. J. 74 (1): 1-5.

Hard, G.C.; Rodgers, I.S.; Baetcke, K.C., Richards, W.L.; McGaughy, R.E.; Valcovic, L.R. (1993): Hazard evaluation of chemicals that cause accumulation of α_{2u}-globulin, hyaline droplet nephropathy, and tubule neoplasia in the kidneys of male rats, Environ. Health Perspect. 99, 313-349.

Organization for Economic Cooperation and Development (2002): SIDS for Neopentyl Glycol. https://hpvchemicals.oecd.org/ui/handler.axd?id=21fe8103-2fb5-4d44-bc41-5d4fc90a031c.

Swenberg, J.A. (1993): α_{2u}-Globulin nephropathy: review of the cellular and molecular mechanisms involved and their implications for human risk assessment, Environ. Health Perspect. Suppl. 101 (Suppl.6), 39-44.

A.2 Diisobutyl succinate and read across compound dimethyl succinate

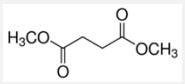
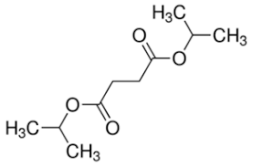
Compound		Diisobutyl succinate	Factsheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m³]	35
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2020
General information			
CLP-INDEX No	4	INDEX	-
EC No	5	EINECS – ELINCS - NLP	213-113-7
CAS No	6	Chemical Abstracts Service number	925-06-4
Harmonised CLP classification	7	Human health risk related classification	Not available
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	230.30 1 ppm = 9.48 mg/m³
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	Dimethyl succinate
Species	11	Rat, human etc.	
Route/type of study	12	Inhalation, oral feed etc.	
Study length	13	Days, subchronic, chronic	
Exposure duration	14	Hrs/day, days/week	
Critical endpoint	15	Effect(s), site of	
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, etc.	
POD value	17	[mg/m³] or [ppm] or [mg/kg$_{BW}$×d]	
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	-
Study length	20	sa→ sc→ c *(R8-5)*	-
Route-to-route extrapolation factor	21		-
Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	-

	22 b	Severity of effect *(R 8-6d)*	-
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	-
	23 b	Kinetic + dynamic	-
Intraspecies differences	24	Kinetic + dynamic Worker - general population	-
AF (sensitive population)	25	Children or other sensitive groups	-
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	-
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	
POD/TAF	28	Calculated value (µg/m³ and ppb)	
Molar adjustment factor	29	Used in read-across	1.576
Rounded value	30	[µg/m³]	35
Additional comments	31		

Rationale section	32		

There is only very little information available on the toxicity of diisobutyl succinate. Targeted data base and literature searches were conducted in eChemPortal, the ECHA chemicals registry, HSDB, TOXNET and PubMed.

In analogy to other dibasic esters (Bogdanffy et al., 1991), diisobutyl succinate can be assumed to be metabolised to isobutanol and succinic acid, which are both of very low systemic toxicity. The main health effect after inhalation of the ester is determined by the cytotoxicity of the acid after its release by carboxylesterase in the olfactory epithelium (Trela and Bogdanffy, 1991). This effect will not be covered by route-to-route extrapolation, which speaks in favour of a read-across from an available LCI value for another dialkyl succinate, such as dimethyl succinate. The rationale behind this approach is that the toxicity of these two compounds is based on their common metabolite, succinic acid, and is independent of the respective alcohol components.

Compound	Structure	Molar mass [g/mol]	EU-LCI value
Dimethyl succinate		146.14	50 µg/m³ (ascribed) 20 µg/m³ (newly derived)
Diisobutyl succinate		230.3	35 µg/m³ (read-across from dimethyl succinate)

When applying the molar adjustment factor of 1.576 (230.3 ÷ 146.14) to the unrounded LCI value for dimethyl succinate of 21.9 µg/m³ an initial value of 34.5 µg/m³ is obtained, which is rounded to 35 µg/m³ as the LCI value for diisobutyl succinate.

References:

Bogdanffy, M.S.; Kee, C.R.; Hinchman, C.A.; Trela, B.A. (1991): Metabolism of dibasic esters by rat nasal mucosal carboxylesterase, Drug Metab. Dispos. 19 (1), 124-129.

Trela, B.A.; Bogdanffy, M.S. (1991): Carboxylesterase-dependent cytotoxicity of dibasic esters in rat nasal explants, Toxicol. Appl. Pharmacol. 107 (2), 285-301.

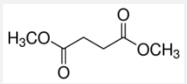
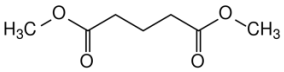
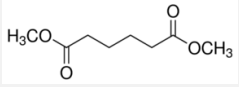
Compound	**Dimethyl succinate**		**Factsheet**
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m³]	20
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2020
General information			
CLP-INDEX No	4	INDEX	-
EC No	5	EINECS – ELINCS - NLP	203-419-9
CAS No	6	Chemical Abstracts Service number	106-65-0
Harmonised CLP classification	7	Human health risk related classification	Not available
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	146.14 1 ppm = 6.02 mg/m³
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	Keenan et al. (1990)
Read across compound	10	Where applicable	Mixture of dibasic esters: 65.5 % dimethyl glutarate, 16.9 % dimethyl succinate, 16.5 % dimethyl adipate
Species	11	Rat, human etc.	Rat
Route/type of study	12	Inhalation, oral feed etc.	Inhalation
Study length	13	Days, subchronic, chronic	Subchronic (90 d)
Exposure duration	14	Hrs/day, days/week	6 h/d, 5 d/wk
Critical endpoint	15	Effect(s), site of	Degeneration of nasal olfactory epithelium
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, etc.	LOAEC
POD value	17	[mg/m³] or [ppm] or [mg/kg$_{BW}$×d]	20 mg/m³
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	5.6
Study length	20	sa→ sc→ c *(R8-5)*	2
Route-to-route extrapolation factor	21		1

Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	3
	22 b	Severity of effect *(R 8-6d)*	1
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	1
	23 b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic Worker - general population	10
AF (sensitive population)	25	Children or other sensitive groups	1
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	1
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	840
POD/TAF	28	Calculated value (µg/m³ and ppb)	23.8 µg/m³ (3.61 ppb)
Molar adjustment factor	29	Used in read-across	0.922
Rounded value	30	[µg/m³]	20
Additional comments	31		

Rationale section	32		

For dimethyl succinate, no comprehensive risk assessment reports from international bodies could be found. Occupational limit values have been issued based on read across from a mixture of dibasic esters including dimethyl succinate. A REACH registration dossier for dimethyl succinate is available on the ECHA dissemination site (ECHA, 2020). In order to identify additional relevant information, targeted searches were performed in HSDB, TOXLINE and PubMed. No additional information on (sub)chronic inhalation studies with the substance could be found.

Dimethyl succinate is liquid at room temperature. Its odour is reported as sweetish, information regarding an odour threshold could not be found. It is metabolised to methanol and succinic acid by carboxylesterase in the nasal olfactory epithelium (Bogdanffy et al., 1991). The release of carboxylic acid causes dose-dependent cytotoxicity (Trela and Bogdanffy, 1991) that results in degenerative changes in the nasal mucosa (Keenan et al., 1990). This effect will not be covered by route-to-route extrapolation, which speaks in favour of a read-across approach based on an available inhalation study for similar short-chain dimethyl dicarboxylates, such as glutarate and adipate. Between these homologues the difference in chain length is not larger than two CH_2 units and the free acids are of similar acidity, as characterised by their pK_A values.

Compound	Structure	Molar mass [g/mol]	Acidity of the free acid		EU-LCI value
			pKA1	pKA2	
Dimethyl succinate		146.14	4.16	5.61	50 µg/m³ (ascribed) 20 µg/m³ (newly derived)
Dimethyl glutarate		160.17	4.32	5.42	50 µg/m³ (ascribed) 25 µg/m³ (newly derived)
Dimethyl adipate		174.20	4.43	5.42	50 µg/m³ (ascribed)

A mixture of dimethyl succinate (16.9 %), dimethyl glutarate (65.5 %), and dimethyl adipate (16.5 %) was investigated in a subchronic inhalation toxicity study similar to OECD guideline 413 (Keenan et al., 1990). Sprague-Dawley rats were exposed to concentrations of 0, 20, 76, or 390 mg/m³ during 6 hours per day on 5 days per week over 13 weeks. Although it is reported that the test substance was administered as a vapour, it must be assumed, based on other studies with similarly high concentrations (ECHA, 2020), that most of it was actually present as an aerosol. However, as deposition of the vapour in the nasal mucosa is reported to occur instantly with efficiency rates around 98 % (Morris et al., 1991), there seems no reason to expect a difference in toxicity between aerosol and vapour in this case. All test concentrations caused degeneration or atrophy of the olfactory epithelium in female rats. In male rats, these effects were only observed in the two highest dose groups. After a six-week recovery period, regenerative processes and signs of tissue repair such as respiratory metaplasia, disorganization of the olfactory epithelium and decreased numbers of neuronal cells were noted. Animals exposed to 390 mg/m³ showed slight reductions in body weight gain. Thus, the NOAEC for systemic toxicity was 76 mg/m³. For local effects, the LOAEC was 20 mg/m³. This value is used as point of departure for the determination of an EU-LCI value for dimethyl succinate based on read across from the mixture of dimethyl dicarboxylates as specified above.

Assessment factors were chosen as follows:

- 5.6 to adjust for exposure duration (from 6 h/d on 5 d/wk to 24/7)
- 2 for the extrapolation from subchronic to chronic
- 3 to account for the uncertainty of the dose-response by using a LOAEC instead of a NOAEC
- 2.5 for interspecies differences (default value for kinetic and dynamic differences)
- 10 for intraspecies differences (default value for the general population)

The total assessment factor of 840 and the POD of 20 mg/m³ gave an initial value of 23.8 µg/m³ (3.61 ppb) for the mixture of dimethyl esters. Application of a molar adjustment factor of 0.922 for read-across – calculated by dividing 146.14 by [(0.169 x 146.14) + (0.655 x 160.17) + (0.165 x 174.20)] – resulted in an initial value of 21.9 µg/m³, which is rounded to the EU-LCI value of 20 µg/m³ for dimethyl succinate. This newly derived EU-LCI value is lower than the current ascribed value of 50 µg/m³. It may be considered conservative as it is based on local effects that have been characterised as predominantly mild and may be presumed to be reversible.

References:

Bogdanffy, M.S.; Kee, C.R.; Hinchman, C.A.; Trela, B.A. (1991): Metabolism of dibasic esters by rat nasal mucosal carboxylesterase, Drug Metab. Dispos. 19 (1), 124-129.

European Chemicals Agency (2020): Registration dossier for dimethyl succinate. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/15043. Last accessed on 14 April 2020.

Keenan, C.M.; Kelly, D.P.; Bogdanffy, M.S. (1990): Degeneration and recovery of rat olfactory epithelium following inhalation of bibasic esters, Fundam. Appl. Toxicol. 15 (2), 381-393.

Morris, J.B.; Clay, R.J.; Trela, B.A.; Bogdanffy, M.S. (1991): Deposition of dibasic esters in the upper respiratory tract of the male and female Sprague-Dawley rat, Toxicol. Appl. Pharmacol. 108 (3), 538-546.

Trela, B.A.; Bogdanffy, M.S. (1991): Carboxylesterase-dependent cytotoxicity of dibasic esters in rat nasal explants, Toxicol. Appl. Pharmacol. 107 (2), 285-301.

A.3 Diisobutyl glutarate and read across compound dimethyl glutarate

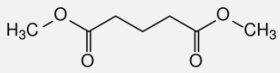
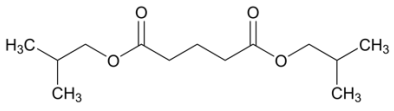
Compound	Diisobutyl glutarate		Factsheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m³]	35
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2020
General information			
CLP-INDEX No	4	INDEX	-
EC No	5	EINECS – ELINCS - NLP	275-257-7
CAS No	6	Chemical Abstracts Service number	71195-64-7
Harmonised CLP classification	7	Human health risk related classification	Not available
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	244.33 1 ppm = 10.05 mg/m³
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	Dimethyl glutarate
Species	11	Rat, human etc.	
Route/type of study	12	Inhalation, oral feed etc.	
Study length	13	Days, subchronic, chronic	
Exposure duration	14	Hrs/day, days/week	
Critical endpoint	15	Effect(s), site of	
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, etc.	
POD value	17	[mg/m³] or [ppm] or [mg/kg$_{BW}$×d]	
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	-
Study length	20	sa→ sc→ c *(R8-5)*	-
Route-to-route extrapolation factor	21		-
Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	-

	22 b	Severity of effect *(R 8-6d)*	-
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	-
	23 b	Kinetic + dynamic	-
Intraspecies differences	24	Kinetic + dynamic Worker - general population	-
AF (sensitive population)	25	Children or other sensitive groups	-
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	-
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	
POD/TAF	28	Calculated value (µg/m³ and ppb)	
Molar adjustment factor	29	Used in read-across	1.525
Rounded value	30	[µg/m³]	35
Additional comments	31		

Rationale section	32		

There is only very little information available on the toxicity of diisobutyl glutarate. Targeted data base and literature searches were conducted in eChemPortal, the ECHA chemicals registry, HSDB, TOXNET and PubMed.

In analogy to other dibasic esters (Bogdanffy et al., 1991), diisobutyl glutarate can be assumed to be metabolised to isobutanol and glutaric acid, which are both of very low systemic toxicity. The main health effect after inhalation of the ester is determined by the cytotoxicity of the acid after its release by carboxylesterase in the olfactory epithelium (Trela and Bogdanffy, 1991). This effect will not be covered by route-to-route extrapolation, which speaks in favour of a read-across from an available LCI value for another dialkyl glutarate, such as dimethyl glutarate. The rationale behind this approach is that the toxicity of these two compounds is based on their common metabolite, glutaric acid, and is independent of the respective alcohol components.

Compound	Structure	Molar mass [g/mol]	EU-LCI value
Dimethyl glutarate		160.17	50 µg/m³ (ascribed) 25 µg/m³ (newly derived)
Diisobutyl glutarate		244.33	35 µg/m³ (read-across from dimethyl glutarate)

When applying the molar adjustment factor of 1.525 (244.33 / 160.17) to the unrounded LCI value for dimethyl glutarate of 24.1 µg/m3 an initial value of 36.8 µg/m³ is obtained, which is rounded to 35 µg/m³ as the LCI value for diisobutyl glutarate.

References:

Bogdanffy, M.S.; Kee, C.R.; Hinchman, C.A.; Trela, B.A. (1991): Metabolism of dibasic esters by rat nasal mucosal carboxylesterase, Drug Metab. Dispos. 19 (1), 124-129.

Trela, B.A.; Bogdanffy, M.S. (1991): Carboxylesterase-dependent cytotoxicity of dibasic esters in rat nasal explants, Toxicol. Appl. Pharmacol. 107 (2), 285-301.

Compound	Dimethyl glutarate		Factsheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m³]	25[2]
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2020
General information			
CLP-INDEX No	4	INDEX	-
EC No	5	EINECS – ELINCS - NLP	214-277-2
CAS No	6	Chemical Abstracts Service number	1119-40-0
Harmonised CLP classification	7	Human health risk related classification	Not available
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	160.17 1 ppm = 6.59 mg/m³
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	Keenan et al. (1990)
Read across compound	10	Where applicable	Mixture of dibasic esters: 65.5 % dimethyl glutarate, 16.9 % dimethyl succinate, 16.5 % dimethyl adipate
Species	11	Rat, human etc.	Rat
Route/type of study	12	Inhalation, oral feed etc.	Inhalation
Study length	13	Days, subchronic, chronic	Subchronic (90 d)
Exposure duration	14	Hrs/day, days/week	6 h/d, 5 d/wk
Critical endpoint	15	Effect(s), site of	Degeneration of nasal olfactory epithelium
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, etc.	LOAEC
POD value	17	[mg/m³] or [ppm] or [mg/kg$_{BW}$×d]	20 mg/m³
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	5.6
Study length	20	sa→ sc→ c *(R8-5)*	2

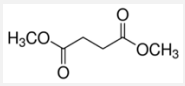
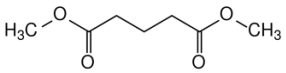
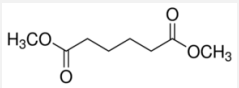
[2] Newly derived EU-LCI value. The current EU-LCI value of 50 µg/m³ is an ascribed value.

Route-to-route extrapolation factor	21		1
Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	3
	22 b	Severity of effect *(R 8-6d)*	1
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	1
	23 b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic Worker - general population	10
AF (sensitive population)	25	Children or other sensitive groups	1
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	1
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	840
POD/TAF	28	Calculated value (µg/m³ and ppb)	23.8 µg/m³ (3.61 ppb)
Molar adjustment factor	29	Used in read-across	1.011
Rounded value	30	[µg/m³]	25
Additional comments	31		

Rationale section	32		

For dimethyl glutarate, no comprehensive risk assessment reports from international bodies could be found. Occupational limit values have been issued based on read across from a mixture of dibasic esters including dimethyl glutarate. A REACH registration dossier for dimethyl glutarate is available on the ECHA dissemination site (ECHA, 2020). In order to identify additional relevant information, targeted searches were performed in HSDB, TOXLINE and PubMed. No additional information on (sub)chronic inhalation studies with the substance could be found.

Dimethyl glutarate is liquid at room temperature. Its odour is reported as sweetish, information regarding an odour threshold could not be found. It is metabolised to methanol and glutaric acid by carboxylesterase in the nasal olfactory epithelium (Bogdanffy et al., 1991). The release of carboxylic acid causes dose-dependent cytotoxicity (Trela and Bogdanffy, 1991) that results in degenerative changes in the nasal mucosa (Keenan et al., 1990). This effect will not be covered by route-to-route extrapolation, which speaks in favour of a read-across approach based on an available inhalation study for similar short-chain dimethyl dicarboxylates, such as succinate and adipate. Between these homologues the difference in chain length is not larger than two CH_2 units and the free acids are of similar acidity, as characterised by their pK_A values.

Compound	Structure	Molar mass [g/mol]	Acidity of the free acid		EU-LCI value
			pK_{A1}	pK_{A2}	
Dimethyl succinate		146.14	4.16	5.61	50 µg/m³ (ascribed) 20 µg/m³ (newly derived)
Dimethyl glutarate		160.17	4.32	5.42	50 µg/m³ (ascribed) 25 µg/m³ (newly derived)
Dimethyl adipate		174.20	4.43	5.42	50 µg/m³ (ascribed)

A mixture of dimethyl succinate (16.9 %), dimethyl glutarate (65.5 %), and dimethyl adipate (16.5 %) was investigated in a subchronic inhalation toxicity study similar to OECD guideline 413 (Keenan et al., 1990). Sprague-Dawley rats were exposed to concentrations of 0, 20, 76, or 390 mg/m³ during 6 hours per day on 5 days per week over 13 weeks. Although it is reported that the test substance was administered as a vapour, it must be assumed, based on other studies with similarly high concentrations (ECHA, 2020), that most of it was actually present as an aerosol. However, as deposition of the vapour in the nasal mucosa is reported to occur instantly with efficiency rates around 98 % (Morris et al., 1991), there seems no reason to expect a difference in toxicity between aerosol and vapour in this case. All test concentrations caused degeneration or atrophy of the olfactory epithelium in female rats. In male rats, these effects were only observed in the two highest dose groups. After a six-week recovery period, regenerative processes and signs of tissue repair such as respiratory metaplasia, disorganization of the olfactory epithelium and decreased numbers of neuronal cells were noted. Animals exposed to 390 mg/m³ showed slight reductions in body weight gain. Thus, the NOAEC for systemic toxicity was 76 mg/m³. For local effects, the LOAEC was 20 mg/m³. This value is used as point of departure for the determination of an EU-LCI value for dimethyl glutarate based on read across from the mixture of dimethyl dicarboxylates as specified above.

Assessment factors were chosen as follows:

- 5.6 to adjust for exposure duration (from 6 h/d on 5 d/wk to 24/7)
- 2 for the extrapolation from subchronic to chronic
- 3 to account for the uncertainty of the dose-response by using a LOAEC instead of a NOAEC
- 2.5 for interspecies differences (default value for kinetic and dynamic differences)
- 10 for intraspecies differences (default value for the general population)

The total assessment factor of 840 and the POD of 20 mg/m³ gave an initial value of 23.8 µg/m³ (3.61 ppb) for the mixture of dimethyl esters. Application of a molar adjustment factor of 1.011 for read-across – calculated by dividing 160.17 by [(0.169 x 146.14) + (0.655 x 160.17) + (0.165 x 174.20)] – resulted in an initial value of 24.1 µg/m³, which is rounded to the EU-LCI value of 25 µg/m³ for dimethyl glutarate. This newly derived EU-LCI value is lower than the current ascribed value of 50 µg/m³. It may be considered conservative as it is based on local effects that have been characterised as predominantly mild and may be presumed to be reversible.

References:

Bogdanffy, M.S.; Kee, C.R.; Hinchman, C.A.; Trela, B.A. (1991): Metabolism of dibasic esters by rat nasal mucosal carboxylesterase, Drug Metab. Dispos. 19 (1), 124-129.

European Chemicals Agency (2020): Registration dossier for dimethyl glutarate. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/5377. Last accessed on 14 April 2020.

Keenan, C.M.; Kelly, D.P.; Bogdanffy, M.S. (1990): Degeneration and recovery of rat olfactory epithelium following inhalation of bibasic esters, Fundam. Appl. Toxicol. 15 (2), 381-393.

Morris, J.B.; Clay, R.J.; Trela, B.A.; Bogdanffy, M.S. (1991): Deposition of dibasic esters in the upper respiratory tract of the male and female Sprague-Dawley rat, Toxicol. Appl. Pharmacol. 108 (3), 538-546.

Trela, B.A.; Bogdanffy, M.S. (1991): Carboxylesterase-dependent cytotoxicity of dibasic esters in rat nasal explants, Toxicol. Appl. Pharmacol. 107 (2), 285-301.

A.4 1,2-Dimethoxyethane

Compound		**1,2-Dimethoxyethane Monoglyme, EGDME**	**Factsheet**
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m³]	100
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2020
General information			
CLP-INDEX No	4	INDEX	603-031-00-3
EC No	5	EINECS – ELINCS - NLP	203-794-9
CAS No	6	Chemical Abstracts Service number	110-71-4
Harmonised CLP classification	7	Human health risk related classification	Repr. 1B (H360FD); Acute Tox. 4* (H332)
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	90.12 1 ppm = 3.71 mg/m³
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	Confidential study report, 1988 (cited in ECHA, 2020)
Read across compound	10	Where applicable	
Species	11	Rat, human etc.	Rat
Route/type of study	12	Inhalation, oral feed etc.	Teratogenicity study (OECD 414)
Study length	13	Days, subchronic, chronic	10 d
Exposure duration	14	Hrs/day, days/week	6 h/d,daily (GD 7-16)
Critical endpoint	15	Effect(s), site of	Decreased pup vitality
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, etc.	NOAEC
POD value	17	[mg/m³] or [ppm] or [mg/kg$_{BW}$×d]	37 mg/m³
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	4
Study length	20	sa→ sc→ c *(R8-5)*	1
Route-to-route extrapolation factor	21		1

Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	1
	22 b	Severity of effect *(R 8-6d)*	3
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	1
	23 b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic Worker - general population	10
AF (sensitive population)	25	Children or other sensitive groups	1
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	1
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	300
POD/TAF	28	Calculated value (µg/m³ and ppb)	123 µg/m³ (33.2 ppb)
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	100
Additional comments	31		

Rationale section	32		

The European Chemicals Agency has published an Annex XV dossier for identification of 1,2-dimethoxyethane (EGDME) as a substance of very high concern based on its classification as Repr. 1B, H360FD (ECHA, 2012a). The substance has been included in the candidate list in 2012. The underlying toxicological data are summarised in a support document (ECHA, 2012b). No other comprehensive risk assessment reports from international bodies could be found. A registration dossier for 1,2-dimethoxyethane is published on the ECHA dissemination site (ECHA, 2020). In order to identify additional relevant information, targeted searches were conducted in eChemPortal, HSDB, TOXLINE and PubMed.

1,2-Dimethoxyethane is at room temperature a colourless liquid with an ethereal odour. No information regarding an odour threshold could be found. Its metabolism proceeds via oxidation of the intermediate 2-methoxyethanol (EGME) to the main metabolite 2-methoxyacetic acid, which is assumed to be responsible for causing the observed reproductive toxicity. Inhalation leads to moderate acute toxicity (the substance is classified as Acute Tox. 4, H332).

Sub-acute inhalation toxicity studies were performed in rabbits and rats with dose levels of 37, 187, and 935 mg/m³, administered during 6 hours per day on 5 days per week for two weeks (ECHA, 2020). Effects on male fertility were observed in animals of both species in the highest dose groups, namely changes of seminiferous epithelium (rabbits and rats) and aspermia (rabbits only). The NOAEC was 187 mg/m³.

In a teratogenicity study (OECD guideline 414), pregnant rats were exposed to 37, 120 and 374 mg/m³ EGDME for 6 hours per day, daily, on gestation days 7-16 (confidential study report, 1988a, as cited in ECHA, 2020). At the two highest exposure levels, retarded development and increased incidences of foetal malformations were observed. No adverse effects were observed in the maternal animals at any dose level. The NOAEC for developmental toxicity was 37 mg/m³.

In a similar teratogenicity study, pregnant rabbits were exposed to 19, 60 and 187 mg/m³ EGDME for 6 hours per day, daily, on gestation days 6-18 (confidential study report, 1988b, as cited in ECHA, 2020). At the highest exposure level, the vitality of the litters was considerably decreased, and skull malformations as well as irregularities in skull ossification were observed in several foetuses. No adverse effects were observed in the maternal animals, except for a slightly decreased food consumption. The NOAEC for developmental toxicity was 60 mg/m³.

The toxicity studies indicate that teratogenicity is the leading adverse health effect of EGDME. From the available teratogenicity studies, the NOAEC of 37 mg/m³ obtained from the study in rats is chosen as POD because it is the lowest NOAEC reported for this endpoint.

Assessment factors were chosen as follows:

- 4 to account for the exposure duration of 6 h/d
- No adjustment for study length because exposure occurred throughout the critical time window for the studied endpoint
- 3 to account for the severity of the effect
- 2.5 for interspecies differences (default value for kinetic and dynamic differences)
- 10 for intraspecies variation (default value for the general population)

With a total assessment factor of 300 and a POD of 37 mg/m³ an initial value of 123 µg/m³ (33.2 ppb) is calculated and rounded to an EU-LCI value of 100 µg/m³.

References:

European Chemicals Agency (2012a): Annex XV dossier for 1,2-dimethoxyethane (EGDME). https://echa.europa.eu/documents/10162/5acc50db-aba1-46f9-87ec-d2cbad906b4b. Last accessed on 15 April 2020.

European Chemicals Agency (2012b): Support document for identification of 1,2-dimethoxyethane (EGDME) as a substance of very high concern because of its CMR properties, https://echa.europa.eu/documents/10162/466dce51-6adf-4936-874b-2c1fe8c9de5e. Last accessed on 15 April 2020.

European Chemicals Agency (2020): Registration dossier for 1,2-dimethoxyethane. https://echa.europa.eu/registration-dossier/-/registered-dossier/14829. Last accessed on 15 April 2020.

A.5 1,2-Diethoxyethane

Compound	**1,2-Diethoxyethane EGDEE**		**Factsheet**
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m³]	150
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2020
General information			
CLP-INDEX No	4	INDEX	603-208-00-5
EC No	5	EINECS – ELINCS - NLP	211-076-1
CAS No	6	Chemical Abstracts Service number	629-14-1
Harmonised CLP classification	7	Human health risk related classification	Flam. Liq. 2 (H225); Eye Irrit. 2 (H319); Repr. 1B (H360Df)
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	118.18 1 ppm = 4.86 mg/m³
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	George et al., 1992
Read across compound	10	Where applicable	
Species	11	Rat, human etc.	Mouse
Route/type of study	12	Inhalation, oral feed etc.	Oral
Study length	13	Days, subchronic, chronic	30 d (exposure on GD 6-15)
Exposure duration	14	Hrs/day, days/week	Daily gavage in water
Critical endpoint	15	Effect(s), site of	Foetal malformations
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, etc.	Adjusted NOAEL
POD value	17	[mg/m³] or [ppm] or [mg/kg$_{BW}$×d]	87.5 mg/m³
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	1
Study length	20	sa→ sc→ c *(R8-5)*	1

Route-to-route extrapolation factor	21		1[3]
Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	1
	22 b	Severity of effect *(R 8-6d)*	3
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	7
	23 b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic Worker - general population	10
AF (sensitive population)	25	Children or other sensitive groups	1
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	1
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	525
POD/TAF	28	Calculated value (µg/m³ and ppb)	167 µg/m³ (34.4 ppb)
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	150
Additional comments	31		

Rationale section	32		

The European Chemicals Agency has published an Annex XV dossier for identification of 1,2-diethoxyethane (EGDEE) as a substance of very high concern based on its classification as Repr. 1B, H360Df (ECHA, 2012a). The substance is on the candidate list since 2012. The underlying toxicological data are summarised in a support document (ECHA, 2012b). No other comprehensive risk assessment reports from international bodies could be found, and no registration dossier for 1,2-diethoxyethane is published on the ECHA dissemination site. In order to identify relevant information, targeted searches were conducted in eChemPortal, HSDB, TOXLINE and PubMed.

1,2-Diethoxyethane is at room temperature a colourless liquid with an ethereal odour. No information regarding an odour threshold could be found. Its metabolism proceeds via oxidation of the intermediate 2-ethoxyethanol to the main metabolite 2-ethoxyacetic acid, which is assumed to be responsible for causing the observed reproductive toxicity. Acute toxicity after inhalation was not investigated. Acute systemic toxicity after oral exposure is low. 1,2-Diethoxyethane acts irritating on the eyes and is classified as Eye Irrit. 2, H319.

Well-documented teratogenicity studies were performed under contract by the National Toxicology Program on CD-1 mice and New Zealand White rabbits (George et al., 1992; NTP, 1987a; NTP 1987b). Following oral exposure to 50, 150, 500, or 1000 mg/kg$_{BW}$ x d during gestation days 6-15 (mice) and to 25, 50, or 100 mg/kg$_{BW}$ x d during gestation days 6-19 (rabbits), adverse effects on foetal development (foetal malformations) were observed in both species well below dose levels that caused maternal toxicity. Compared to the mouse with

[3] For mice, no standard route-to-route extrapolation factor is available. Route-to-route extrapolation is included in the POD (line 17), for details see line 32.

a NOAEL of 50 mg/kg_{BW} x d, lower effect levels were observed in the rabbit, with a LOAEL of 50 mg/kg_{BW} x d and a NOAEL of 25 mg/kg_{BW} x d. However, taken into account the differences in allometric scaling for the two species (AF 2.4 for rabbits as compared to AF 7 for mice), the mouse can in fact be considered the more sensitive species for the observed effect. Therefore, the NOAEL in mice is chosen to determine the point of departure.

No adjustment for exposure duration or study length is needed, since the animals were exposed continuously during the time window that is considered critical for the studied endpoint. The POD is adjusted for route-to-route extrapolation by dividing the oral NOAEL in mice (50 mg/kg_{BW} x d) by a default factor of 2 to account for potential absorption differences between the oral and inhalation route, then multiplying with the standard human body weight (70 kg) divided by the standard human respiratory rate (20 m^3/d). The resulting POD is 87.5 mg/m^3.

Assessment factors were chosen as follows:

- Route-to-route extrapolation: 1 (as there is no standard extrapolation factor available for rabbits, route-to-route extrapolation was integrated into the POD, see above)
- Severity of effect: 3 (foetal malformations)
- Interspecies differences:
  7 for allometric scaling
  2.5 for remaining kinetic and dynamic differences
- Intraspecies difference: 10 (default value for the general population)

With a total assessment factor of 525 and a POD of 87.5 mg/m^3, an initial value of 167 µg/m^3 (34.4 ppb) is obtained and rounded to an EU-LCI value of 150 µg/m^3.

Comparison of proposed EU-LCI with a derived EU-LCI from the teratogenicity study in rabbits

As mentioned above, an oral teratogenicity study in rabbits resulted in a NOAEL of 25 mg/kg_{BW} x d. If this study was used for the derivation of an EU-LCI, the POD would be 44 mg/m^3, calculated from the oral NOAEL, the default factor of 2 to account for potential absorption differences between the oral and inhalation route, and the standard human respiratory rate of 0.286 m^3/kg x d. This POD is lower than the one obtained from the study in mice. However, assessment factors of 3 (severity of effect), 2.4 (allometric scaling), 2.5 (remaining interspecies differences) and 10 (intraspecies differences) result in a total assessment factor of only 180. Therefore a calculated value of 244 µg/m^3 (50.2 ppb) is obtained and rounded to an EU-LCI value of 250 µg/m^3, which is higher than the value derived from the mouse study. The proposed EU-LCI of 150 µg/m^3 derived from the oral teratogenicity study in mice is preferred because it can be considered to be more protective.

References:

European Chemicals Agency (2012a): Annex XV dossier for 1,2-diethoxyethane. https://echa.europa.eu/documents/10162/c52546c1-89ad-4b0e-a141-b33bc279d853. Last accessed on 16 April 2020.

European Chemicals Agency (2012b): Support document for identification of 1,2-diethoxyethane as a substance of very high concern because of its CMR properties. https://echa.europa.eu/documents/10162/8c04401d-d0bb-409c-9250-c6e574f47305. Last accessed on 16 April 2020.

George, J.D.; Price, C.J; Marr, M.C.; Kimmel, C.A.; Schwetz, B.A.; Morissey, R.E. (1992): The developmental toxicity of ethylene glycol diethyl ether in mice and rabbits, Fundam. Appl. Toxicol. 19 (1): 15-25.

B Appendix: Data Collection Sheets

B.1 Neopentyl glycol

Compound	**2,2-Dimethylpropane-1,3-diol (Neopentyl glycol)**		**Data collection sheet (1/1)**
N°CAS 126-30-7	**EU- Classification:** **CLP:** Self-classification by industry: Eye dam. 1 (H318); Skin irrit. 2 (H315); STOT SE 3 (H335)		
Organisation name	**REACH registrants**	**REACH registrants**	**AgBB NIK-AG**
Risk value name	DNEL (General population)	DNEL (worker)	NIK
Risk value	8.7 mg/m^3	35 mg/m^3	1 mg/m^3
Reference period	Chronic	Chronic (worker)	Chronic
Year	not reported (2013 or later)	not reported (2013 or later)	2012
Key study	BASF SE (2013)	BASF SE (2013)	Biosafety Research Center, Japan (1993)
Study type	Repeated dose toxicity study (OECD 408)	Repeated dose toxicity study (OECD 408)	Combined repeated dose tox. study with reproductive/developmental tox. screening test (OECD 422)
Species	rat	rat	rat
Duration of exposure in key study	90 d	90 d	45 d (males); ca. 60 d (females)
Critical effect	No treatment-related adverse findings	No treatment-related adverse findings	Males: increased liver and kidney weights; moderate tubular nephropathy
Critical dose value	NOAEL (oral): 1000 mg/kg bw	NOAEL (oral): 1000 mg/kg bw	NOAEL (oral): 300 mg/kg bw
Adjusted critical dose	434.8 mg/m^3	881.6 mg/m^3	130.4 mg/m^3
Single assessment factors	2 (study length) x 2.5 (interspecies) x 10 (intraspecies) = 50	2 (study length) x 2.5 (interspecies) x 5 (intraspecies) = 25	6 (study length) x 2 (interspecies) x 10 (intraspecies) = 120

B.2 Diisobutyl succinate

Compound	**Bis(2-methylpropyl) butanedioate (Diisobutyl succinate)**	**Data collection sheet (1/1)**
N°CAS 925-06-4	**EU- Classification:** not available **CLP:** not available (data lacking)	
Organisation name	**AgBB NIK-AG**	
Risk value name	NIK	
Risk value	100 µg/m³ (read-across from a mixture of dimethyl dicarboxylates, see below ('Remarks')	
Reference period	Chronic	
Year	2010	
Key study	Keenan, C.M.; Kelly, D.P.; Bogdanffy, M.S. (1990): Degeneration and recovery of rat olfactory epithelium following inhalation of dibasic esters. Fund. Appl. Toxicol. 15 (2) 381-393.	
Study type	Subchronic inhalation study (OECD 413)	
Species	rat	
Duration of exposure in key study	90 days (6 h/d, 5 d/wk)	
Critical effect	Degeneration of nasal olfactory epithelium	
Critical dose value	LOAEC: 20 mg/m³	
Adjusted critical dose	3.6 mg/m³	
Single assessment factors	Not specified	
Remarks	Read-across: The study was performed with a mixture of 66.5 % dimethyl glutarate, 16.9 % dimethyl succinate, and 16.5 % dimethyl adipate. The occupational exposure limit (MAK) value of 0.75 ppm (5 mg/m³) derived for this mixture was transformed into a worker DNEL value of 0.75 ppm (10 mg/m³) for diisobutyl succinate by molar adjustment. This was then divided by 100 to obtain the NIK value, according to the former standard procedure of the AgBB.	

B.3 Diisobutyl glutarate

Compound	Bis(2-methylpropyl) pentanedioate (Diisobutyl glutarate)	Data collection sheet (1/1)
N°CAS 71195-64-7	**EU- Classification:** not available **CLP:** not available (data lacking)	
Organisation name	**AgBB NIK-AG**	
Risk value name	NIK	
Risk value	100 µg/m³ (read-across from a mixture of dimethyl dicarboxylates, see below ('Remarks')	
Reference period	Chronic	
Year	2010	
Key study	Keenan, C.M.; Kelly, D.P.; Bogdanffy, M.S. (1990): Degeneration and recovery of rat olfactory epithelium following inhalation of dibasic esters. Fund. Appl. Toxicol. 15 (2) 381-393.	
Study type	Subchronic inhalation study (OECD 413)	
Species	rat	
Duration of exposure in key study	90 days (6 h/d, 5 d/wk)	
Critical effect	Degeneration of nasal olfactory epithelium	
Critical dose value	LOAEC: 20 mg/m³	
Adjusted critical dose	3.6 mg/m³	
Single assessment factors	Not specified	
Remarks	Read-across: The study was performed with a mixture of 66.5 % dimethyl glutarate, 16.9 % dimethyl succinate, and 16.5 % dimethyl adipate. The occupational exposure limit (MAK) value of 0.75 ppm (5 mg/m³) derived for this mixture was transformed into a worker DNEL value of 0.75 ppm (10 mg/m³) for diisobutyl glutarate by molar adjustment. This was then divided by 100 to obtain the NIK value, according to the former standard procedure of the AgBB.	

B.4 1,2-Dimethoxyethane

Compound	**1,2-Dimethoxyethane**		**Data collection sheet (1/1)**	
N°CAS 110-71-4	**EU- Classification:** F (R11); R19; Repr. Cat.2 (R60; R61); Xn (R20) **CLP:** Flam. Liq. 2 (H225); Repr. 1B (H360FD); Acute Tox. 4* (H332)			
Organisation name	**REACH registrants**	**REACH registrants**	**AgBB NIK-AG**	**ANSES**
Risk value name	DNEL worker	DNEL general population	NIK	CLI
Risk value	3.1 mg/m³	1.5 mg/m³	4 µg/m³	20 µg/m³
Reference period	chronic (worker)	chronic	chronic	chronic
Year			2010	2009
Key study	Confidential study report (1986)	Confidential study report (1988)	Read-across from 2-methoxyethanol	Read-across from 2-methoxyethanol
Study type	Subacute inhalation study (OECD 412)	Teratogenicity study (OECD 414)		
Species	rat	rabbit		
Duration of exposure in key study	14 d	14 d		
Critical effect	males: reversible reduction of cell layers of the seminiferous epithelium	dams: reduced food consumption; pups: decreased vitality within the first 24h		
Critical dose value	NOAEC: 187 mg/m³	NOAEC: 60 mg/m³		
Adjusted critical dose	94 mg/m³	15 mg/m³		
Single assessment factors	5 (intraspecies) x 6 (study length)	10 (intraspecies)		

B.5 1,2-Diethoxyethane

Compound	**1,2-Diethoxyethane**		**Data collection sheet (1/1)**	
N°CAS 629-14-1	**EU- Classification:** F (R11); R19; Repr. Cat.2 (R61); Repr. Cat.3 (R62); Xi (R36) **CLP:** Flam. Liq. 2 (H225); Eye Irrit. 2 (H319); Repr. 1A (H360Df)			
Organisation name	**National Toxicology Program**	**National Toxicology Program**	**AgBB NIK-AG**	**ANSES**
Risk value name	No risk value derived	No risk value derived	NIK	CLI
Risk value			10 µg/m³	70 µg/m³
Reference period			chronic	chronic
Year				
Key study	NTP (1987)/George et al. (1992)	NTP (1987)/George et al. (1992)		
Study type	Teratogenicity	Teratogenicity		
Species	CD-1 Mice	New Zealand White Rabbits		
Duration of exposure in key study	Gestation days 6-15	Gestation days 6-19		
Critical effect	Increased incidence of litters with malformed fetuses	Increased incidence of litters with malformed fetuses		
Critical dose value	NOAEL = 50 mg/kg bw/d	NOAEL = 25 mg/kg bw/d		
Adjusted critical dose				
Single assessment factors	No assessment made	No assessment made		