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

Final report

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

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

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

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

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

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

LCI-Arbeitsgruppe erteilt. Die im Rahmen dieses Forschungsvorhabens ausgearbeiteten Stoffdossiers unterstützen und beschleunigen diesen Prozess.

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AgBB	Ausschuss zur gesundheitlichen Bewertung von Bauprodukten (Committee for Health-related Evaluation of Building Products)
AGÖF	Arbeitsgemeinschaft ökologischer Forschungsinstitute (Association of Ecological Research Institutes)
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AUC	Area under curve
CAS	Chemical abstract service
CHO	Chinese hamster ovary
CLP	Classification, labelling and packaging
DEGBE	Diethylene glycol mono butyl ether
DEGHE	Diethylene glycol mono hexyl ether
DEGMEA	Diethylene glycol mono ethyl ether acetate
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation)
DNEL	Derived no effect level
DPGMEA	Dipropylene glycol mono methyl ether acetate
DPGME	Dipropylene glycol mono methyl ether
DPGnBE	Dipropylene glycol mono n-butyl ether
DPGtBE	Dipropylene glycol mono t-butyl ether
DPM	see DPGME
ECHA	European Chemicals Agency
EGHE	Ethylene glycol monohexyl ether
EU	European Union
F	Female(s)
FOB	Functional observational battery
GD	Gestation day
GLP	Good laboratory practice
IFA	Institut für Arbeitsschutz der Deutschen Gesetzlichen Unfallversicherung (Institute for Occupational Safety and Health of the German Social Accident Insurance)
IUPAC	International union of pure and applied chemistry
LCI	Lowest concentration of interest
LOAEC/L	Lowest observed adverse effect concentration/level
LoD	Limit of detection
Log Pow	Logarithm of octanol/water partition coefficient
M	Male(s)
MAK	Maximale Arbeitsplatzkonzentration (Maximum workplace concentration)
MW	Molecular weight/mass
NIK	Niedrigste Interessierende Konzentration (Lowest concentration of interest)

NOAEC/L	No observed adverse effect concentration/level
OECD	Organization for economic cooperation and development
OEL	Occupational exposure limit
PGnBE	Propylene glycol mono n-butyl ether
PGME	Propylene glycol monomethyl ether (monopropylene glycol methyl ether)
PGtBE	Propylene glycol t-butyl ether
PND	Postnatal day
REACH	Registration, evaluation, authorisation and restriction of chemicals
SCOEL	Scientific Committee on Occupational Exposure Limits
SGOT	Serum glutamate-oxaloacetate transaminase
SGPT	Serum glutamate-pyruvate transaminase
γGT	Gamma glutamyl transferase

Zusammenfassung

Stoffprofil und EU-LCI-Wert für Dipropyleneglykol-n(t)-butylether

Dipropylenglykol-n-butylether (DPGnBE) und -t-butylether (DPGtBE) sind farblose Flüssigkeiten mit einem schwach etherischen Geruch. DPGnBE ist ein großtechnisches Produkt, das als Lösemittel in Farben und Beschichtungen eingesetzt wird, außerdem als Reinigungs- und Entfettungsmittel. Zu DPGtBE liegen kaum Angaben vor, der Stoff soll als Ersatzstoff für Tetrachlorethen in chemischen Reinigungen diskutiert worden sein.

Zum Vorkommen von DPGnBE in der Innenraumluft liegen einige Angaben vor. Bei Untersuchungen unterschiedlich genutzter Innenräume in Deutschland wurden Medianwerte unter 2 µg/m^3 gemessen, das 95. Perzentil reichte bis zu 12 µg/m^3. Zu DPGtBE liegen keine Angaben vor.

Systemische Wirkungen nach inhalativer Exposition belegen die Aufnahme des Stoffs über diese Pfade. Verlässliche quantitative Angaben liegen jedoch nicht vor. Allgemein ist bekannt, dass gesättigte aliphatische Glykole über alle Aufnahmepfade gut resorbiert werden. Nach oraler Exposition wird von Ratten der größte Anteil in Form verschiedener Metaboliten im Urin sowie als CO_2 über die Atemluft ausgeschieden. Zu toxischen Wirkungen von DPGnBE und DPGtBE beim Menschen liegen keine bewertungsrelevanten Angaben vor. Im Tierversuch wurden bei Ratten nach inhalativer Exposition gegenüber DPGnBE bei Konzentrationen von ≥ 810 mg/m^3 Veränderungen der Leber festgestellt, in erster Linie eine hepatozelluläre Hypertrophie, bei höheren Konzentrationen auch Anzeichen von Zellnekrosen. Nach subakuter Inhalation traten ab 810 mg/m^3 lokale Effekte im nasalen Epithel von Ratten auf. Die NOAEC lag in dieser Studie bei 200 mg/m^3. Studien mit längerer Exposition gegenüber DPGnBE wurden nur mit oraler sowie dermaler Verabreichung durchgeführt. Dabei bestätigte sich die geringe Toxizität dieser Verbindung. Aus einer Fütterungsstudie ergibt sich auf Basis von Wirkungen auf Körper- und Lebergewicht und geringen Veränderungen klinisch-chemischer Parameter im Serum ein NOAEL von 450 mg/(kg bw x d). Aus Untersuchungen zur Gentoxizität von DPGnBE *in vitro* und *in vivo* ergeben sich in der Gesamtbewertung keine Bedenken hinsichtlich derartiger Effekte. Zur Kanzerogenität von DPGnBE liegen keine Daten vor. Aus einem Read-Across zu Monopropylenglykolmethylether (PGME) ergeben sich keine Hinweise auf kanzerogene Effekte. In einer Kanzerogenitätsstudie mit Monopropylenglykol-t-butylether (PGtBE) wurde eine erhöhte Inzidenz von Lebertumoren bei Mäusen beobachtet. Die Befunde wurden von der IARC aber insgesamt nicht als ausreichend für eine Klassierung von PGtBE hinsichtlich der Kanzerogenität beim Menschen bewertet. DPGnBE ließ in Untersuchungen keine Wirkungen auf Reproduktionsparameter oder entwicklungstoxische Wirkungen erkennen. Auch aus einem Read-across zu Diethylenglykol-n-butylether ergeben sich keine Hinweise auf derartige Effekte. PGtBE zeigte in Ratten und Kaninchen ebenfalls keine entwicklungstoxischen Effekte.

Als kritischer Effekt zur Bewertung von DPGnBE bei inhalativer Exposition werden die lokal reizenden Effekte auf das nasale Epithel bei Ratten angesehen. Für diesen Effekt ergibt sich in einer subakuten Inhalationsstudie eine NOAEC von 200 mg/m^3 (25 ppm).

Die folgenden Standardextrapolationsfaktoren werden herangezogen:

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

Gesamtextrapolationsfaktor: 840.

Als EU-LCI-Wert (gerundet) für Dipropylenglykol-mono-n-butylether (DPGnBE) wird somit eine Konzentration von 250 µg/m³ vorgeschlagen.

Zur Geruchsschwelle von DPGnBE liegen keine Angaben vor.

Für Dipropylenglykol-mono-t-butylether liegen keine ausreichenden Angaben zur Ableitung eines EU-LCI vor. Prinzipiell kann der für DPGnBE vorgeschlagene EU-LCI auch für DPGtBE herangezogen werden. Zusätzlich wurde die Ableitung eines EU-LCI für DPGtBE auf Basis eines Read-Across zu Monopropylenglykol-t-butylether (PGtBE) geprüft. Dazu wurde eine chronische Toxizitätsstudie mit PGtBE an Ratten herangezogen, in der lokale Effekte im nasalen Epithel festgestellt wurden. Auf Basis einer Benchmarkberechnung und mittels molarer Adjustierung ließe sich daraus für DPGtBE ein Wert von 273 µg/m³ abschätzen, der nach der Rundung mit dem für DPGnBE vorgeschlagenen EU-LCI von 250 µg/m³ übereinstimmt. Es wird daher vorgeschlagen, den Wert für DPGnBE auch für DPGtBE heranzuziehen.

Stoffprofil und EU-LCI-Wert für 2-(2-Hexoxyethoxy)-ethanol

2-(2-Hexyloxyethoxy)-ethanol (DEGHE) ist eine durchscheinende Flüssigkeit von schwach etherischen Geruch. DEGHE ist ein industriell hergestellter Stoff, der als Lösemittel oder Fließhilfe in zahlreichen Anwendungen und Produkten eingesetzt wird, so etwa in Farben und Lacken, Verdünnern, Anstrichen, Fensterreinigern und Farbentfernern.

Zum Vorkommen von DEGHE in der Innenraumluft liegen kaum Angaben vor. In einer Zusammenstellung von Daten in Deutschland konnte DEGHE in der Raumluft von Büros, Wohnungen und (Vor)schulen nicht nachgewiesen werden.

Angaben zu Aufnahme, Verteilung, Metabolismus und Ausscheidung liegen nicht vor. Systemische Effekte nach oraler Exposition belegen eine Aufnahme auf diesem Weg. Die physikochemischen Eigenschaften von DEGHE (niedrige Molmasse, hohe Wasserlöslichkeit, niedriger Verteilungskoeffizient) sprechen gleichfalls für eine hohe orale und inhalative Aufnahme. Auf Basis eines Read-across zu Ethylenglykolmonohexylether (EGHE) und 2-(2-butoxyethoxy)ethanol (Diethylenglykolbutylether, DEGBE) sowie die physikochemischen Eigenschaften von DEGHE lassen eine umfassende Verteilung, keine Akkumulation und eine rasche Ausscheidung der Metaboliten mit dem Urin erwarten. In geringem Maß kann auch die Ausscheidung von Kohlenstoffdioxid als Metabolit in der Ausatemluft erfolgen.

Zur Toxizität von DEGHE beim Menschen oder nach Inhalation bei Versuchstieren liegen keine Angaben vor. In einer subakuten Toxizitätsstudie an Ratten wurden bei der höchsten geprüften Dosis von 1000 mg/(kg KG x d) Auswirkungen auf Leber- und Körpergewicht festgestellt (NOAEL 300 mg/(kg KG x d)). Nach wiederholter dermaler Exposition von Kaninchen wurden keine adversen systemischen Wirkungen beobachtet. EGHE führte in einer subchronischen Inhalationsstudie an Ratten bei der höchsten Konzentration zu erhöhtem absoluten und relative Leber- und Nierengewicht, der NOAEC lag bei 41 ppm. Inhalationsstudien mit DEGBE an Ratten ergaben nach subakuter Expositionsdauer lediglich ein leicht erhöhtes Lebergewicht mit histologischen Veränderungen bei Weibchen bei allen Konzentrationen und Veränderungen in der Lunge. Diese Veränderungen konnten nach subchronischer Expositionsdauer jedoch nicht beobachtet werden (NOEC 14 ppm = 94 mg/m³). Für DEGHE ergeben sich keine Hinweise auf gentoxische Wirkungen *in vitro* und *in vivo*. Kanzerogenitätsstudien zu DEGHE oder den Read-Across-Substanzen liegen nicht vor. Einige Untersuchungsbefunde zeigen, dass DEGHE und die Read-Across-Substanzen weder Beeinträchtigungen der Fertilität hervorrufen noch reproduktions- noch entwicklungstoxische Wirkungen aufweisen.

Wegen fehlender Inhalationsstudien mit DEGHE werden Befunde zur Read-Across-Substanz DEGBE als geeignete Basis zur Ableitung eines EU-LCI-Werts für DEGHE herangezogen. Innerhalb der Stoffklasse der Diethylenglykolether stellt DEGBE den am nächsten verwandten Stoff dar, für den geeignete Toxizitätsdaten zur Ableitung eines EU-LCI-Werts zur Verfügung stehen. Der Read-Across basiert auf der Grundlage, dass beide Substanzen denselben kritischen Endpunkt aufweisen und dieser durch die gemeinsamen funktionalen Gruppen bedingt ist (und nicht durch die zusätzlichen CH_2-Gruppen).

Für DEGBE ergab sich in einer subchronischen Inhalationsstudie eine NOAEC von 94 mg/m³ (14 ppm).

Die folgenden Standardextrapolationsfaktoren werden herangezogen:

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

Gesamtextrapolationsfaktor: 280. Daraus ergibt sich eine Konzentration von 94 mg/m³ : 280 = 335,7 µg/m³ (0,05 ppm).

Es wird vorgeschlagen, diesen Wert auf molarer Basis für DEGHE zu übernehmen (190,28 g/mol (DEGHE) : 162,23 g/mol (DEGBE) = 1,173):

335,7 µg/m³ x 1,173 = 393,7 µg/m³.

Als EU-LCI-Wert (gerundet) für DEGHE wird somit eine Konzentration von 400 µg/m³ vorgeschlagen.

Zur Geruchsschwelle von DEGHE liegen keine Angaben vor.

Stoffprofil und EU-LCI-Wert für 1-Propenylbenzol

1-Propenylbenzol (ß-Methylstyrol) ist eine blassgelbe Flüssigkeit mit unangenehmem Geruch. Die Verbindung tritt als Nebenprodukt bei der Synthese von 2-Phenylpropene (ß-Methylstyrol) auf und kann darin als Verunreinigung (bis zu 0,5 %) enthalten sein. 1-Propenylbenzol tritt in zwei isomeren Formen auf (cis und trans), zur Toxizität der reinen cis-Form wurden in der verfügbaren Literatur keine Angaben gefunden. Insgesamt sind zur Toxizität von 1-Propenylbenzol nur wenige Angaben verfügbar. Der Stoff wird unter Bildung von Zimtalkohol metabolisiert. Nach Angaben zur akuten Exposition wirkt der Stoff auf Augen, Schleimhäute und die Haut reizend. Eine vergleichende Studie zur Ototoxizität verschiedener Alkyl- und Alkenylbenzole in Ratten ergab, dass trans-1-Propenylbenzol ototoxische Effekte zeigt, jedoch ist dessen Potenz nicht höher als die des 2-Phenylpropens und niedriger als die des Styrols und Vinyltoluols. Studien zur Gentoxizität von 1-Phenylpropylen oder zu anderen toxischen Wirkungen liegen nicht vor. Zur Ableitung eines EU-LCI-Wertes für 1-Propenylbenzol erfolgte ein Read-Across zu 2-Phenylpropen (α-Methylstyrol). Dieser basiert auf der Grundlage, dass beide Stoffe aufgrund struktureller und physikochemischer Ähnlichkeiten denselben kritischen Endpunkt für eine Bewertung aufweisen. Der kritische Endpunkt bei der Inhalation von 2-Phenylpropen ist die lokale Schädigung des nasalen Epithels. Für 2-Phenylpropen wurde auf Basis dieses Effekts ein EU-LCI-Wert von 1200 µg/m³ abgeleitet. Derselbe numerische Wert von 1200 µg/m³ auf Basis des genannten Effekts ergibt sich für Vinyltoluole. Da 1-Propenylbenzol ein Strukturisomer von 2-Phenylpropen darstellt, beträgt der molare Adjustierungsfaktor eins. Für

1-Propenylbenzol wird ein EU-LCI-Wert von 1200 µg/m³ vorgeschlagen. Angaben zu Geruchsschwellenwerten für 1-Propenylbenzol liegen nicht vor.

Stoffprofil und EU-LCI-Wert für Dipropylenglykolmonomethyletheracetat

Dipropylenglykolmonomethyletheracetat (DPGMEA) ist eine farblose Flüssigkeit mit einem etherähnlichen Geruch. Die Substanz ist ein industriell hergestellter Stoff, der als Lösemittel in Mitteln zur Raumluftverbesserung, in Beschichtungen sowie in Tinten und in Druckprozessen eingesetzt wird.

Zum Vorkommen von DPGMEA in der Innenraumluft liegen kaum Angaben vor. In einer Zusammenstellung von Daten in Deutschland konnte DPGMEA in der Raumluft von Büros, Wohnungen und (Vor)schulen nur in niedriger Konzentration (< 1 µg/m³) und in weniger als 1 % aller Probe nachgewiesen werden.

Die Aufnahme, Metabolisierung und Elimination von DPGMEA wurde an Ratten untersucht. Demnach wird DPGMEA rasch aufgenommen und in Blut und Geweben hydrolysiert. Weniger als 2 % des nicht hydrolysierten Stoffs sind systemisch verfügbar. DPGMEA wird schnell metabolisiert unter Bildung von DPGME (Dipropylenglykolmonomethylether) und 2-Methylpropionsäure.

Zur Toxizität von DPGMEA liegen nur wenige Untersuchungen vor. Befunde am Menschen oder tierexperimentelle Inhalationsstudien liegen nicht vor. Ergänzende Befunde können jedoch aus Untersuchungen mit strukturell ähnlichen Propylenglykolethern und -etheracetaten gewonnen werden, insbesondere mit Monopropylenglykolmethylacetat (PGMEA). In einer subakuten Inhalationsstudie mit PGMEA wurde eine Degeneration mit Metaplasie des olfaktorischen nasalen Epithels bei Ratten bei 3000 ppm (NOAEC: 1000 ppm) festgestellt, bei Mäusen bei allen untersuchten Konzentrationen (LOAEC: 300 ppm, keine NOAEC). Ähnliche Schädigungen des olfaktorischen Epithels bei Ratten und Mäusen wurden auch in einer Reihe subakuter und subchronischer Inhalationsstudien festgestellt, in denen die Tiere gegenüber anderen aliphatischen Estern von Alkansäuren exponiert worden waren. Die Epithelschäden werden auf die Bildung der entsprechenden Alkansäure durch enzymatische Hydrolyse des Esters in der Nasenschleimhaut zurückgeführt, durch die zytotoxische Schäden verursacht werden, wenn die spezifische intrazelluläre Pufferkapazität der Zellen überschritten und erschöpft wird.

Untersuchungen zur Toxizität von PGMEA und dem nicht veresterten PGME sprechen klar dafür, dass beide in toxikologischer Hinsicht als äquivalent anzusehen sind, mit Ausnahme der nasalen Reizung, die nur nach Inhalation von PGMEA beobachtet wurde, nicht aber bei PGME. Ähnliche Schlüsse lassen sich für DPGMEA und DPGME ziehen. Die Ähnlichkeit dieser beiden Substanzen hinsichtlich systemischer Effekte wird auch durch die Toxikokinetik gestützt, der zufolge DPGMEA *in vivo* schnell zu DPGME (und Acetat) hydrolysiert wird.

DPGMEA ist *in vitro* nicht gentoxisch, ebenso zeigten die strukturell verwandten Glykolether PGME und DEGMEA keine gentoxische Wirkung *in vivo*. Kanzerogenitätsstudien sind für DPGME(A) nicht verfügbar; PGME zeigte in einer Zweijahresstudie an Ratten keine kanzerogene Wirkung. Fertilitätsstudien mit DPGMEA liegen nicht vor. Der NOEL für Fertilitäts- und reproduktionstoxische Effekte für PGME lag in einer 2-Generationenstudie bei 1000 ppm (3710 mg/m³). Bei dieser Konzentration traten leichte parental toxische Effekte auf. Studien zur Entwicklungstoxizität wurden mit DPGMEA und DPGME durchgeführt. Dabei zeigten sich keine derartigen Wirkungen bis zur höchsten oral an Ratten geprüften Dosis von 1000 mg DPGMEA/(kg KG x d) und bis zur höchsten Inhalationskonzentration von 300 ppm DPGME in Ratten und Kaninchen.

Zusammengefasst weisen die Daten für DPGMEA und DPGME ebenso wie für andere Propylenglykolether auf eine geringe Toxizität hin. Zugleich ist festzuhalten, dass DPGMEA – wie strukturell ähnliche andere aliphatische Ester – lokale Wirkungen in der Riechschleimhaut von Nagern hervorrufen, die bei vergleichbaren Konzentrationen der nicht veresterten Glykole nicht zu beobachten sind. Daraus ergibt sich, dass Daten zu DPGME und anderen Propylenglykolethern keine geeignete Grundlage zur Ableitung von EU-LCI-Werten für DPGME darstellen. Stattdessen wird zur Ableitung eines EU-LCI-Werts für DPGMEA auf ein Read-Across zum strukturell ähnlichen PGMEA zurückgegriffen.

Als geeignete Basis zur Ableitung eines EU-LCI-Werts für DPGMEA wird die subakute Inhalationsstudie mit PGMEA an Ratten und Mäusen herangezogen. Der LOAEC dieser Studie von 300 ppm dient als POD für die Ableitung.

Die folgenden Standardextrapolationsfaktoren werden herangezogen:

- Adjustierung auf kontinuierliche Exposition: 5,6
- Zeitextrapolation (subakute Exposition): 6
- LOAEC zu NAEC: 3
- Interspeziesextrapolation: 2,5
- Intraspeziesextrapolation: 10

Gesamtextrapolationsfaktor: 2520. Daraus ergibt sich ein Wert von 0.119 ppm.

Es wird vorgeschlagen, diesen Wert auf molarer Basis für DPGMEA zu übernehmen:

1 ppm DPGMEA = 7,82 mg/m^3, somit ergibt sich ein Wert von 931 µg/m^3.

Als EU-LCI-Wert (gerundet) für DPGMEA wird somit eine Konzentration von 950 µg/m^3 vorgeschlagen.

Zur Geruchsschwelle von DPGMEA liegen keine Angaben vor.

Stoffprofil und EU-LCI-Wert für 1-Hydroxyaceton

Hydroxyaceton ist eine nicht flüchtige, ölige, wasserlösliche Flüssigkeit von eigenartigem Geruch. Die Verbindung kommt in der Natur vor. Im menschlichen Körper tritt Hydroxyaceton als Zwischenprodukt im Stoffwechsel der proteinogenen Aminosäuren Glycin, Serin und Threonin auf. Hydroxyaceton kann außerdem durch die Oxidation von Propylenglykol gebildet werden. Die Toxizität von Hydroxyaceton wird als gering angesehen, allerdings ist die Datenbasis äußerst begrenzt, insbesondere liegen in der zugänglichen Literatur keine Studien mit wiederholter Exposition vor. Aus diesem Grund wurde ein Read-Across zu Propylenglykol (Propan-1,2-diol) durchgeführt, um einen EU-LCI-Wert für Hydroxyaceton abzuleiten. Dieser basiert auf der Grundlage, dass beide Stoffe aufgrund struktureller und physikochemischer Ähnlichkeiten denselben kritischen Endpunkt für eine Bewertung aufweisen. Der kritische Endpunkt bei der Inhalation von Propan-1,2-diol ist die lokale Reizung. Für Propan-1,2-diol wurde ein EU-LCI-Wert von 2100 µg/m^3 abgeleitet. Es wird vorgeschlagen, diesen Wert für Hydroxyaceton auf molarer Basis zu übernehmen. Unter Berücksichtigung des molaren Adjustierungsfaktors von 0,97 wird somit in EU-LCI-Wert von 2100 µg/m^3 für Hydroxyaceton vorgeschlagen. Angaben zu Geruchsschwellenwerten für Hydroxyaceton liegen nicht vor.

Summary

Substance profile and EU-LCI value for dipropylene glckol-n(t)-butyl ether

Dipropylene glycol n-butyl ether (DPGnBE) and t-butyl ether (DPGtBE) are colourless liquids with a faint ether-like odour. DPGnBE is a large-scale industrial product used as solvent in paints and coatings and also in cleaners and degreasers. Few data are available for DPGtBE; the substance is reported to be discussed as substitute for tetrachloroethene in dry-cleaning.

Some data are available regarding the occurrence of DPGnBE in indoor air. Median values lower than 2 µg/m³ and 95th percentiles up to 12 µg/m³ were measured in indoor air samples in Germany. No data are available for DPGtBE. Systemic effects following inhalation indicate that these substances are taken up via this route of exposure. Reliable quantitative data are, however, not available. It is known that saturated aliphatic glycols in general are well resorbed via all routes of administration. After oral uptake in rats, most of the compound is excreted as various metabolites in urine and also as carbon dioxide in exhaled breath. No data are available regarding toxic effects of DPGnBE or DPGtBE in humans. Animal experiments with rats revealed changes in the liver after inhalation at concentrations ≥ 810 mg/m³. Effects were mostly hepatocellular hypertrophy but there were also signs of cell necrosis at higher concentrations. Starting at 810 mg/m³, local effects in the nasal epithelia of rats were noted following subacute inhalation exposure. A NOAEC of 200 mg/m³ was identified in that study. Studies with longer exposure duration were only conducted with oral or dermal exposure. These studies confirmed the low toxicity of the compound. A feeding study provided a NOAEL of 450 mg/(kg bw x d) based on effects on body and liver weight and on slight changes of clinical chemical parameters. Overall, studies on the genotoxicity of DPGnBE and DPGtBE *in vitro* and *in vivo* do not provide concern regarding such effects. Data on the carcinogenicity of DPGnBE are not available. Read-across to propylene glycol methyl ether (PGME) provided no evidence of carcinogenic effects. An increased incidence of liver tumors was described in a carcinogenicity study with monopropylene glycol-t-butyl ether (PGtBE). However, the data were regarded by IARC as insufficient for the classification of PGtBE with respect to its carcinogenicity to humans. Studies with DPGnBE on toxicity to reproduction and development provided no evidence for such effects. Also, read-across to diethylene glycol n-butyl ether provided no such evidence. Furthermore, PGtBE showed no developmental toxicity in rats and rabbits.

The critical endpoint in the evaluation of DPGnBE inhalation exposure is the local irritation of the nasal epithelium in rats. A NOAEC of 200 mg/m³ (25 ppm) was obtained for this effect in the subacute inhalation study.

The following standard adjustment factors are used:

- Adjustment for continuous exposure: 5.6
- Adjusted study length factor (subacute exposure): 6
- Interspecies extrapolation: 2.5
- Intraspecies extrapolation: 10

Total assessment factor: 840.

An EU-LCI value (rounded value) for DPGnBE of 250 µg/m³ is proposed.

Data on odour thresholds of DPGnBE are not available.

The data for DPGtBE are insufficient for the derivation of an EU-LCI value. Principally, the EU-LCI value derived for DPGnBE may also be used for DPGtBE. Additionally, the derivation of an EU-LCI for DPGtBE based on a read-across to PGtBE may be considered. In doing so, a chronic toxicity study in rats can be used in which local effects in the nasal epithelia were described. Performing a benchmark calculation and a molar adjustment a value of 273 µg/m^3 may be estimated for DPGtBE. After rounding, this value is identical to the EU-LCI value of 250 µg/m^3 proposed for DPGnBE. Thus, it is proposed to adopt the value for DPGnBE for DPGtBE.

Substance profile and EU-LCI value for 2-(2-hexoxyethoxy)-ethanol

2-(2-Hexyloxyethoxy)-ethanol (DEGHE) is a water-white liquid with a mild odour. DEGHE is an industrial product used as solvent or coalescing aid in a number of applications and products, e. g. paints, lacquers, thinners, varnishes, window cleaners and paint removers.

Few data are available regarding the occurrence of DEGHE in indoor air. According to a compilation of data from Germany, the substance could not be detected in samples from offices, homes and (pre)schools.

Data on absorption, distribution, excretion, and metabolism of DEGHE are not available. Systemic effects observed after oral exposure show that the substance is absorbed orally. The physicochemical properties (low molecular weight, high water solubility, and low partition coefficient) indicate a high absorption via the oral and inhalation route. Based on the read-across substances ethylene glycol mono hexyl ether (EGHE) and 2-(2-butoxyethoxy)ethanol (diethylene glycol butyl ether, DEGBE), and on DEGHE's physicochemical properties, a wide distribution, no accumulation and a rapid excretion of metabolites via urine are expected. Small amounts may appear as carbon dioxide in exhaled air.

No data are available on the toxicity of DEGHE in humans or via inhalation in animals. In a subacute oral toxicity study in rats, effects on liver and body weight were noted at the highest tested dose of 1000 mg/(kg bw x d) (NOAEL 300 mg/(kg bw x d). After repeated dermal exposure to DEGHE no adverse systemic effects were observed in rabbits. A subchronic inhalation study with EGHE in rats observed increased absolute and/or relative kidney and liver weights at the highest concentration tested (NOAEC 41 ppm). Inhalation studies with DEGBE in rats only revealed a slight increase in liver weight, histological changes in females of all concentration groups, and lung effects after subacute exposure. The observed effects could not be seen after subchronic exposure (NOEC 14 ppm = 94 mg/m^3). DEGHE provided no evidence for genotoxic effects in *in vitro* and *in vivo*. Carcinogenicity studies are not available for DEGHE or its read-across substances. A few studies showed that fertility, reproduction and development of offspring was not affected by DEGHE or its read-across substances.

Due to the lack of inhalation toxicity data for DEGHE the inhalation data of the read-across substance, DEGBE, is considered as suitable for the derivation of an EU-LCI value for DEGHE. Within the chemical class of diethylene glycol ethers, DEGBE is the closest homologue for which suitable toxicity data are available for the derivation of an EU-LCI value. The key assumption underlying the read-across is that both compounds have the same critical endpoint and this is caused by the common functional group (and not by the additional CH_2 groups).

A NOAEC of 94 mg/m^3 (14 ppm) was obtained for DEGBE in a subchronic inhalation study.

The following standard adjustment factors are used:

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

Total assessment factor: 280. This leads to a concentration of 94 mg/m^3: 280 = 335.7 µg/m^3 (0.05 ppm).

It is proposed to adopt this value for DEGBE on a molar basis (190.28 g/mol (DEGHE) : 162.23 g/mol (DEGBE) = 1.173):

335.7 µg/m^3 x 1.173 = 393.7 µg/m^3.

An EU-LCI value (rounded value) for DPGMEA of 400 µg/m^3 is proposed.

Data on odour thresholds of DEGHE are not available.

Substance profile and EU-LCI value for 1-propenylbenzene

1-Propenylbenzene (ß-methylstyrene) is a pale yellow liquid with an annoying odour. It is a by-product in the synthesis of 2-phenylpropene (α-methylstyrene) and may be present as an impurity (up to 0.5 %) in 2-phenylpropene. 1-propenylbenzene occurs in two isomeric forms (cis and trans); no data on the toxicity of the pure cis-form were identified in the available literature. Very few data are available regarding the toxicity of 1-propenylbenzene. The compound is metabolised with the formation of cinnamyl alcohol. Acute exposure is reported to be irritating to eyes, mucous membranes, and skin. A comparative study of the ototoxicity of various alkyl and alkenyl benzenes in rats revealed that trans-1-propenylbenzene does produce ototoxic effects; however, its potency is not higher than that of 2-phenylpropene and lower than that of styrene and vinyltoluene. Studies on the genotoxicity of the compound or other toxicity studies are not available. Read-across to 2-phenylpropene (α-methylstyrene) was performed to propose an EU-LCI for 1-propenylbenzene. The key assumption is that, based on structural and physico-chemical similarities, both compounds share the same critical endpoint for evaluation. The critical endpoint for 2-phenylpropene inhalation is local damage to the nasal epithelium. For 2-phenylpropene, an EU-LCI of 1200 µg/m^3 has been derived on the basis of this effect. The key assumption is further strengthened by the observation that vinyltoluenes, structurally related isomers of 2-phenylpropene and 1-propenylbenzene with an unbranched unsaturated side-chain as in 1-propylene benzene, also lead to similar lesions of the nasal epithelia of rats. The same numerical EU LCI value of 1200 µg/m^3 is derived for vinyltoluenes based on these effects. As 1-propenylbenzene is a structural isomer with the same molar mass as 2-phenylpropene, the molar adjustment factor is one. An EU-LCI value of 1200 µg/m^3 is proposed for 1-propenylbenzene. Data on odour thresholds of 1-propenylbenzene are not available.

Substance profile and EU-LCI value for dipropylene glycol mono methyl ether acetate

Dipropylene glycol mono methyl ether acetate (DPGMEA) is a colourless liquid with an ether-like odour. The substance is an industrially produced chemical used as solvent in air refresheners, coatings, and inks and in printing processes.

Few data are available regarding the occurrence of DPGMEA in indoor air. According to a compilation of data from Germany, the substance could only be detected at low concentrations (< 1 µg/m^3) and in less than 1 % of all samples from offices, homes and (pre)schools.

The absorption, metabolism, and elimination of DPGMEA was studied in rats. The results indicate that DPGMEA is rapidly absorbed and hydrolysed in blood and tissues. Less than 2 % of non-hydrolysed is systemically bioavailable. DPGMEA is rapidly metabolised to DPGME (dipropylene glycol mono methyl ether) and further to 2-methylpropionic acid.

The data basis regarding the toxicity of DPGMEA is limited. No data are available for humans. Also, no inhalation studies with repeated exposure of animals to DPGMEA are available. Additional data are available from studies with structurally related propylene glycol ethers and ether acetates, especially monopropylene glycol methyl ether acetate (PGMEA). In a subacute inhalation study with PGMEA, a degeneration with metaplasia of the olfactory nasal epithelium was observed in rats at 3000 ppm (NOAEC 1000 ppm) and in mice at all exposure concentrations (LOAEC: 300 ppm, no NOAEC). Similar lesions of the olfactory nasal epithelium of rats or mice have been described in a number of subacute or subchronic inhalation studies in which the animals had been exposed to other aliphatic esters of alkanoic acids. The epithelial lesions are attributed to the formation of the corresponding alkanoic acid by enzymatic hydrolysis of the ester in the nasal epithelium, leading to cytotoxicity when the specific intracellular buffer capacity of the cells is exceeded and exhausted. Studies on the toxic effects and the toxicokinetic of PGMEA and the non-esterified PGME clearly indicate that both are essentially toxicologically equivalent, with the exception of nasal irritation, which were only observed in inhalation studies with PGMEA but not with PGME. Similar conclusions can be drawn in case of DPGMEA and DPGME. Studies with DPGMEA indicate a low systemic toxicity, similar to that of the non-esterified DPGME. The similarity of those two compounds regarding systemic effects is corroborated by the toxicokinetic data showing that DPGMEA is rapidly hydrolysed *in vivo* with the formation of DPGME (and acetate). DPGMEA was not genotoxic *in vitro,* and no genotoxicity was observed with structurally related glycol ethers (PGME) or ether acetates (DEGMEA) *in vivo*. Carcinogenicity data are not available for DPGME(A), but PGME was not carcinogenic in a two-year carcinogenicity study with rats. No fertility study is available for DPGMEA. The no-observed-effect-level (NOEL) for fertility and reproductive effects of PGME in a two-generation inhalation reproduction study was 1000 ppm (3710 mg/m^3) PGME. Mild parental toxicity was noted at this concentration. Developmental toxicity studies have been carried with both DPGMEA and DPGME. No developmental toxicity was observed with DPGMEA up to the highest oral dose of 1000 mg/(kg bw x d) in rats and up to the highest inhalation concentration of 300 ppm DPGME in rats and rabbits.

Overall, the data for DPGMEA and DPGME as well as for other propylene glycol ethers indicate a low systemic toxicity. At the same time, data for PGMEA show that this acetate ester – as structurally similar other aliphatic esters – produces local irritation effects in the olfactory nasal epithelium of rodents which are not observed at similar concentrations with the non-esterified glycol ether. It is concluded that data for DPGME and other propylene glycol ethers do not provide a suitable basis for the derivation of an EU-LCI value for DPGMEA. Instead, read-across with data for the structurally-related PGMEA will be used for the derivation of an EU-LCI value for DPGMEA.

The subacute inhalation toxicity study with PGMEA in rats and mice is considered a suitable key study for the derivation of an EU-LCI value for DPGMEA. The LOAEC of 300 ppm observed for mice in that study is used as POD for the calculation.

The following standard adjustment factors are used:

- Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6
- Adjusted study length factor: 6
- LOAEC to NAEC extrapolation: 3
- Interspecies extrapolation: 2.5
- Intraspecies extrapolation: 10

Total assessment factor: 2520. This leads to a concentration of 300 ppm : 2520 = 0.119 ppm.

It is proposed to adopt this value for DPGMEA on a molar basis:

1 ppm DPGMEA = 7.82 mg/m^3, leading to a value of 931 µg/m^3.

An EU-LCI value (rounded value) for DPGMEA of 950 µg/m^3 is proposed.

Data on odour thresholds of DPGMEA are not available.

Substance profile and EU-LCI value for 1-hydroxyacetone

Hydroxyacetone is a non-volatile oily, water-soluble liquid with a distinct odour. It occurs naturally in food. In the human body, hydroxyacetone occurs as an intermediate in the metabolism of the protein amino acids glycine, serine and threonine metabolism. Hydroxyacetone may also be formed by the oxidation of propylene glycol. Hydroxyacetone is assumed to be of low toxicity. However, the data base is extremely limited. Especially, no studies with repeated exposure were identified in the available literature. Therefore, read-across to propylene glycol (propane-1,2-diol) was performed to propose an EU-LCI for hydroxyacetone. The key assumption is that, based on structural and physicochemical similarities, both compounds share the same critical endpoint for evaluation. The critical endpoint for propane-1,2-diol inhalation is local irritation. For propane-1,2-diol, an EU-LCI of 2100 µg/m^3 has been derived. It is proposed to adopt the value for hydroxyacetone on a molar basis. Taking into account the molar adjustment factor of 0.97, an EU-LCI value of 2100 µg/m^3 is proposed for hydroxyacetone. Data on odour thresholds for hydroxyacetone are not available.

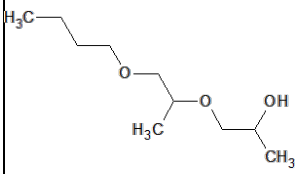
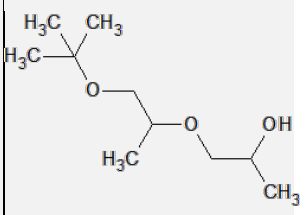
1 Toxicological evaluation of dipropylene glycol mono n-(t-)butyl ether as basis for the derivation of an EU-LCI value

1.1 Substance identification

Substance identification data and physicochemical properties of dipropylene glycol mono n-butyl ether (DPGnBE, 1-(2-butoxy-1-methylethoxy)propane-2-ol) and of the corresponding t-butyl ether (DPGtBE) are shown in Table 1, Table 2 and Table 3.

Propylene glycol ethers may appear in two isomeric forms. The predominant form, which is thermodynamically favoured during synthesis, consists of a secondary alcohol (also referred to as the α-isomer) and a minor form (the ß-isomer), consisting of a primary alcohol. Generally, only the α-isomer and isomeric mixtures consisting predominantly of α-isomer are produced commercially. Thus, the commercial product is a mixture consisting of predominantly (>95%) secondary alcohol (α-isomer) with less than 5% primary alcohol (ß-isomer) (OECD SIDS, 2003b). Unless otherwise stated, results in this evaluation pertain to commercial mixtures[1].

Table 1: Substance identification of dipropylene glycol mono n- and t-butyl ether (DPGBE) (ECHA Dissemination, 2019a)

CAS-No. EU-No. CLP-Index-No.	Systematic Name, common names	Summary formula	Structural formula
29911-28-2 (α-isomer, main component) 35884-42-5 (mixture of isomers) 24083-03-2 (α-/ß-conjugate with free secondary alcohol)	Dipropylene glycol mono n-butyl ether, 1-(2-butoxy-1-methylethoxy)-propan-2-ol, 1-[(1-butoxypropan-2-yl)oxy]-propan-2-ol, 5-Methyl-4,7-dioxaundecane-2-ol	$C_{10}H_{22}O_3$	
132739-31-2	Dipropylene glycol mono t-butyl ether, 1-(1-tert-Butoxypropan-2-yloxy)-propan-2-ol, propanol, [2-(1,1-dimethylethoxy)-methyl-ethoxy]-, 1-[1-[(2-methylpropan-2-yl)oxy]propan-2-yloxy]propan-2-ol	$C_{10}H_{22}O_3$	

1.2 Substance properties and uses

Both DPGnBE and DPGtBE are clear colourless liquids with mild ether like odour (ECHA Dissemination, 2019a; NICNAS, 1997; OECD SIDS, 2003b). No natural sources of these substances are known. About 10 000 - 100 000 tonnes of DPGnBE are manufactured and/or imported into the European Economic Area annually (ECHA Dissemination, 2019a). No such data are available for DPGtBE.

[1] Each propylene glycol moiety contains one chiral center. The commercial product is a racemic mixture of the optic isomers. No studies are available with defined enantiomers.

DPGnBE may be used as solvent in paints and coatings, in cleaning agents and degreasers for home and industrial uses, paint removers and metal cleaning agents (OECD SIDS, 2003b; Schulz et al., 2010). According to NICNAS, DPGtBE may be used in concrete or mortar mixes (NICNAS, 1997). The substance has also been considered as a substitute for tetrachloroethene (BAuA, 2013).

Table 2: Physicochemical properties of DPGnBE (OECD SIDS, 2003b)

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa) (at 25°C)	Density (g/cm³)	log Pow	Solubility in water (g/L) (at 20°C)
190.3	< -75	230	0.091	0.91	1.523	45

Table 3: Physicochemical properties of DPGtBE (ECETOC, 2005b; NICNAS, 1997)

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa) (at 25°C)	Density (g/cm³)	log Pow	Solubility in water (g/L) (at 20°C)
190.3	< -25	213 - 219	0.424	0.91	1.68	165.3

1.3 Exposure

1.3.1 Indoor air

Some data are available regarding the occurrence of DPGnBE in indoor air (Table 4). DPGnBE could be detected in 25 % of all samples from offices, homes and (pre)schools in Germany (Hofmann and Plieninger, 2008), in 18 % of all samples from rooms of flats where children (aged 3 – 14) spent most of their time (Umweltbundesamt, 2008), and in 7 % of samples from schools and kindergartens (Ostendorp et al., 2009). Concentrations were mostly low with medians around 1.0 µg/m^3. According to another evaluation based on 3526 measurements, concentrations exceeding 3 µg/m^3 may be considered as "conspicuous value" (corresponding to the 95th percentile of measured concentrations) (AGÖF, 2013).

Table 4: Data on the occurrence of DPGnBE in indoor air from homes, schools, children day care centres and offices

Rooms	N	LoD (µg/m³)	N > LoD (% > LoD)	Median (µg/m³)	P95 (µg/m³)	Maximum (µg/m³)	Source
Offices, homes, (pre)-schools, Germany	1932	0.7 – 5.0 (mean: 2.2)	434 (25)	1.0	12.0	570	(Hofmann and Plieninger, 2008)
Children's rooms in flats, Germany	555	1.0	98 (18)	< 1.0	3.2	35.0	(Umweltbundesamt, 2008)
Schools and kindergartens, Germany	285	2.0	20 (7)	< 2	4.0	48	(Ostendorp et al., 2009)
Indoor air (not further specified), Germany	3526	not reported		< 1	3.0		(AGÖF, 2013)

1.3.2 Other sources

There are no data available.

1.4 Toxicokinetics

Systemic effects after inhalation exposure indicate that DPGnBE is absorbed via this route. However, quantitative data are not available. Propylene glycol ethers as a class are known to be rapidly absorbed and distributed throughout the body when introduced by inhalation or exposure (OECD SIDS, 2003b). Glycol ethers may also be well absorbed via the skin, even in the vapour state. Once absorbed, glycol ethers are readily distributed through the body (ECETOC, 2005a).

The metabolism of glycol ethers follows two main oxidative pathways. One pathway involves oxidation by microsomal cytochrome P450 monooxygenases at the ether bond via O-dealkylation. This leads to the production of the corresponding glycol (dipropylene glycol in case of DPGnBE) and is the main pathway for dipropylene glycols. Dipropylene glycol may undergo further metabolism with oxidative cleavage of ether bonds and final oxidation of the carbon chain to carbon dioxide. Alternatively, propylene glycol ethers or their partially metabolized products may be conjugated with glucuronide or sulfate and excreted via the kidneys into the urine (OECD SIDS, 2003b). The other pathway involves oxidation by alcohol dehydrogenase and further oxidation by aldehyde dehydrogenase with the formation of alkoxyalkanoic acids. This pathway requires a primary hydroxyl (OH) group and thus is observed with the alpha isomers. Beta-isomers, which do not contain a primary but a secondary free hydroxyl group, cannot be oxidized via this pathway to alkoxyalkanoic acids but only to the corresponding ketones which are further oxidised by other pathways (ECETOC, 2005a; OECD SIDS, 2003b).

A metabolism and disposition study (equivalent to OECD guideline 417) with rats is available for **DPGnBE** (CAS No. 29911-28-2 or 35884-42-5) (ECHA Dissemination, 2019a; OECD SIDS, 2003b). Male F344 rats (4/group) received a single gavage dose of 0.4 or 4.4 mmol ^{14}C-labelled

DPnB/kg b.w. in water. Two carbon atoms of DPGnBE were radiolabeled, one each (a terminal carbon) on either of the two propylene glycol moieties. Urine, faeces, exhaled air, blood and tissues were collected and analysed for total ^{14}C-activity and urinary metabolites were identified structurally. Tissues, carcass and skin retained 11 % of the lower dose and 7% of the higher dose after 48 h. The distribution of ^{14}C-activity in tissues was similar between dose groups with liver, bone marrow and kidneys retaining the highest percentage. Peak blood levels of ^{14}C-activity occurred at 0.5 h after dosing at the lower dose and 4.0 h with the higher dose.

Faecal excretion within 48 h accounted for 4% of the dose at the low dose and 11% at the high dose, indicating high oral bioavailability of DPGnBE. Less than 1 % of the dose was eliminated as exhaled volatile organics at both dose levels. At the lower dose, 42 % of the dose was excreted in urine and 42 % as $^{14}CO_2$ within 48 h. At the higher dose, 51 % were excreted in urine and 35 % as $^{14}CO_2$ in 48 h. Profiles of urinary ^{14}C-activity were qualitatively similar between dose levels. Besides the parent material, the following metabolites were identified in urine: the sulfate conjugate of DPGnBE, propylene glycol n-butyl ether (PGnBE), dipropylene glycol, and propylene glycol. It was concluded that metabolism of DPGnBE has many similarities to that of propylene glycol methyl ether (PGME) and dipropylene glycol methyl ether (DPGME) suggestive of a common route of metabolism giving rise to the same general types of metabolites (ECHA Dissemination, 2019a).

Read-across:

Data are available for **PGtBE** (propylene glycol t-butyl ether) from two studies conducted within the scope of an NTP study of this compound. F344 rats (3 M/group) received a single gavage dose of 3.8, 37.7 and 377.1 mg/(kg bw x d) of ^{14}C-labeled PGtBE. Examination of the distribution in tissues after administration of the low dose showed that the five highest levels of radioactivity were in muscle, skin, fat, liver and blood (in sum < 5 %). Most activity was excreted within the first 24 h. Faecal elimination only accounted for 4 – 11 %, indicating a high bioavailability after oral administration. The predominant route of excretion (48 – 67 % of dose) was via urine, preferably as glucuronide (23 – 52 %) of 1-*tert*-butoxypropanol-2-ol (PGtBE glucuronide, the lowest percentage at the highest dose). A considerable amount was also excreted as sulphate conjugate (6.7 – 13 %, the highest percentage at the highest dose). Unchanged parent compound accounted for < 2 %. 22 – 26 % of the administered radioactivity was recovered as $^{14}CO_2$ in exhaled breath, whereas elimination of volatile ^{14}C-labelled organic compounds was negligible (Dill et al., 2004; IARC, 2006; NTP, 2004).

Additional data obtained in rats after intravenous administration of ^{14}C-PGtBE indicated that enterohepatic circulation may occur, since 40 % of the dose could initially be recovered as glucuronide in bile. However, faecal elimination accounted for only 11 % of the total dose (IARC, 2006).

After dermal (topical) application of PGtBE, about 5 % of the dose was absorbed in rats and about 8 % in mice (as judged from the 14C-excretion in urine and breath). The pattern of metabolites was similar to that observed after oral exposure (IARC, 2006).

After a single 6 h inhalation of rats and mice to 75, 300 or 1200 ppm PGtBE, saturation of metabolic clearance was observed with increasing concentration. Compared with rats, mice eliminated PGtBE from blood more rapidly and had a higher efficiency (Dill et al., 2004; IARC, 2006). After repeated inhalation of 75, 300 or 1200 ppm PGtBE (6 h/d, 5 d/week, 14 weeks (rats) and 16 weeks (mice)), 16 h sampling of urine showed the presence of PGtBE conjugates, predominantly the glucuronide and to a lesser amount of the sulphate. Both these conjugates were also observed in urine of mice similarly exposed. The conjugation appeared to become saturated at the highest dose. However, oxidative metabolites were not studied so that it was not

possible to assess the potential for induction of such pathways (Dill et al., 2004; IARC, 2006; NTP, 2004).

1.5 Health effects

1.5.1 Acute toxicity, sensory irritation and local effects

No human data are available for both, DPGnBE and DPGtBE.

DPGnBE

The acute toxicity of dipropylene glycol mono-n-butyl ether (DPGnBE) is low. A vapour- and an aerosol-inhalation study (equivalent to OECD guideline 403) are available. No mortality was observed up to the highest attainable vapour concentration tested (42.1 ppm = 330 mg/m^3) and at an aerosol concentration of 2040 mg/m^3. Also, no mortality was observed in a further study up to 5400 mg/m^3, the highest concentration tested. In this study, the head-only exposed rats showed breathing alterations, aqueous nasal discharge, and later on reddish, aqueous salivation and diminished pain reflex during exposure and staggering gait, reduced general state and partially abdominal position afterwards. All signs receded within six days. In two studies following OECD guideline 401 and two further non-guideline studies with rats oral LD50 values of 1820-3700 mg/kg b.w. have been determined. In a dermal toxicity study (OECD guideline 402), the LD50 was determined to be > 2000 mg/kg b.w. (ECHA Dissemination, 2019a).

DPGnBE was slightly irritating to the skin of rabbits (n=6) in a study following OECD guideline 404 after semi-occlusive treatment for 4 hours. The observed slight erythema and oedema were fully reversible within 14 or 7 d, respectively. The undiluted test substance would not require labelling as a skin irritant (ECHA Dissemination, 2019a).

In an eye irritation test according to OECD guideline 405, DPGnBE did not cause visible cornea or iris damage. However, fluorescence dye revealed some slight corneal damage. The conjunctivae showed slight to moderate erythema and chemosis. The effects resolved within 14 d. In summary, the results indicate a slight irritation that would not require labelling as an eye irritant (ECHA Dissemination, 2019a).

A Buehler test in guinea pigs (according to OECD 406) did not reveal a dermal sensitising potential of DPGnBE (ECHA Dissemination, 2019a).

It is also reported that DPGnBE showed no evidence of skin sensitisation to human volunteers in a patch test (ECHA Dissemination, 2019a; OECD SIDS, 2003b).

DPGtBE

The combined oral LD50 for both sexes for the notified chemical was found to be 2600 mg/kg b.w. in rats. The dermal LD50 in rabbits was found to be greater than 2000 mg/kg b.w. in a limit test. Inhalational toxicity tests were not performed (NICNAS, 1997).

Signs of irritation (very slight erythema, flaking skin) were observed after occlusive treatment with DPGtBE for 4 h in rabbits (n=6). The test substance was regarded a slight skin irritant (NICNAS, 1997).

The substance was a mild to moderate eye irritant in rabbits (n=9) in a Draize test leading to conjunctivitis with redness, chemosis, and discharge and also to corneal opacity. All effects were fully reversible within 7 d (NICNAS, 1997).

DPGtBE was regarded a mild skin sensitiser based on the results of a modified maximisation test in guinea pigs. Positive reactions were observed in 1/9 and 2/9 animals at 100 % challenge

concentration after 48 and 72 h, but not after 24 h. No effect was observed at 50 % DPGtBE (NICNAS, 1997).

1.5.2 Repeated dose toxicity

There are no data available for effects following repeated exposure of humans against DPGnBE or DPGtBE.

DPGnBE

Inhalation exposure

In a short-term repeated inhalation toxicity study (similar to OECD guideline 412), F344 rats (5 M + 5 F/group) were exposed "nose only" to 0, 200, 810 or 2010 mg/m^3 DPGnBE (0, 25, 100, or 250 ppm, concentrations analytically confirmed) for 6 h/d, 5 d/week, 2 weeks (a total of 9 exposures) (ECHA Dissemination, 2019a). No lethality was observed. At the highest exposure, most animals initially exhibited lethargic behaviour, but this disappeared for all but one male after the 2nd exposure. Body weights of high-dose animals, especially of males, were lower and weight gain was reduced compared to control. Absolute and relative liver weight was increased at high and mid concentrations. This was largely attributed to the reduced body weight on one hand and to a hepatocellular hypertrophy. At the highest concentration slight vacuolation or multifocal hepatocyte necrosis was additionally observed in some animals. Rats from the mid and high-exposure groups exhibited multifocal epithelial hyperplasia and squamous metaplasia in the anterior nasal cavity (the incidence and severity of the lesions were not reported). Nasal effects were considered a direct response to irritation from DPGnBE typical for mucosal tissue and were sometimes accompanied by suppurative inflammation or degeneration of the olfactory epithelium. No adverse effects were noted in the deeper respiratory tract. Thus, repeated inhalation exposure to DPGBE led to nasal epithelial lesions. The NOAEC in the described study was 200 mg/m^3 (ECETOC, 2005b; ECHA Dissemination, 2019a).

In a second, similarly conducted short-term inhalation toxicity study F344 rats (5 M + 5 F/ group) were exposed to nominal concentrations of 0, 20, or 40 ppm (0, 160, or 320 mg/m^3) (ECHA Dissemination, 2019a). No nasal effects were observed up to the highest tested. However, the actual concentration was lower (but not reported) due to condensation of the test material. Therefore, no quantitative data can be obtained from this study.

Inhalation studies with subchronic or chronic exposure to DPGnBE are not available.

Oral exposure

In a subchronic study, Sprague-Dawley rats (6 M + 6 F/group) received 0, 100, 200, or 400 mg/(kg bw x d) DPGnBE by gavage for 14 consecutive days. The test substance was diluted in 1,2-propylene glycol to achieve the desired dosing volume. The controls received propylene glycol only. No mortality or clinically observable signs of toxicity were observed. Body and organ weights, food consumption, and clinical chemistry were unaffected by treatment. No effects on haematology and no gross or microscopic organ pathology were observed. The NOAEL for this study is 400 mg/(kg bw x d)(no LOAEL established) (ECHA Dissemination, 2019a).

Similarly, in a further subacute study with oral exposure of Sprague-Dawley rats (5 M + 5 F/group) to DPGnBE in feed (approximately 0, 250, 500, or 750 mg/(kg bw x d)) for 14 d no treatment-related toxicologically relevant effects were observed on any parameter up to the highest dose tested (NOAEL ≥ 750 mg/(kg bw x d)) (ECHA Dissemination, 2019a).

A subchronic study with oral exposure (following OECD guideline 408) was performed with Sprague-Dawley rats (20 M + 20 F/dose). 5 M + 5 F/group were added to each dose group which

were only treated for 4 weeks and then were sacrificed in order to assess the toxicity of DPGnBE at this interim period. The animals were fed diets containing DPGnBE at concentrations equivalent to target doses of 0, 200, 450, or 1000 mg/(kg bw x d) for 13 weeks. Concentrations of DPGnBE in feed were adjusted on a weekly basis, based on food consumption patterns, to achieve the desired dose (ECHA Dissemination, 2019a).

In high dose males, body weights were decreased slightly but statistically significant, and livers were enlarged without accompanying histopathology. Slight alterations in clinical chemistries, electrolytes, and hematology also were noted in either or both sexes at the high dose level (urea, also elevated in mid-dose subjects but no dose-response; cholesterol, γGT, glucose, potassium). In females at the high dose level, absolute and relative kidney weights were increased with no accompanying histopathology. No changes in any other monitored parameters were noted at any dose level. Some urinary parameters in high dose rats were altered. Most of these findings occurred after 4 as well as after 13 weeks of exposure. The NOAEL is 450 mg/(kg bw x d) and the LOAEL, based on decreased body weights, increased liver weights (without histopathology) and slight alterations in clinical chemistry parameters, is 1000 mg/(kg bw x d) (ECHA Dissemination, 2019a).

Dermal exposure

A subchronic toxicity study was conducted with Wistar rats. The animals (10 M + 10 F/group) received 0, 91, 273, or 910 mg DPGnBE /(kg b.w. x d) as solution in propylene glycol. The solution was applied unoccluded to the clipped dorsal trunk. Rats wore collars to prevent grooming and ingestion of test material. The animals were treated 5 d/week for 13 weeks (ECHA Dissemination, 2019a).

The skin at the site of application showed irritation (erythema, edema, scaliness, incrustations, and superficial scar tissue, microscopically by focal necrosis of the epidermis, crust formation, mild inflammatory changes and acanthosis) in all treatment groups including controls. Grossly, irritation appeared as erythema, edema, scaliness, incrustations, and superficial scar tissue. These changes were more severe in the high-dose group. Untreated skin was unaffected. Body weights in mid and high-dose males were lower than controls. White cell counts (neutrophils) were increased in mid and high-dose males with a similar but lesser trend in females. SGOT (ALT) and SGPT (AST) were increased in high-dose males. Triglycerides were increased and glucose was decreased in high-dose females. Urinalyses revealed no treatment-related effects. Relative liver weights of both sexes were elevated in the high-dose group. Histopathology revealed the changes described above in the area of treated skin but no other microscopic lesions in other organs. A NOAEL for systemic toxicity of 91 mg/(kg bw x d) is derived from this study (LOAEL, based on body weight changes and increased neutrophil counts: 273 mg/(kg bw x d)) (ECHA Dissemination, 2019a).

DPGtBE

No studies with inhalation exposure of animals are available.

In a subacute oral toxicity study following OECD guideline, Sprague-Dawley rats (5 M + 5 F/group) received 0, 100, 300 or 1000 mg/(kg bw x d) DPGtBE in water by gavage. Transient post-dose salivation was noted in most animals at 300 and 1000 mg/(kg bw x d), but there were obvious treatment-related effects on body weight gain or food consumption. A slight reduction in serum alkaline phosphatase (AP) was noted for females in the high dose group. Starting at the mid dose, a marked increase in liver and kidney weight was noted in some animals; however, this did not attain statistical significance. In the liver, microscopic examination revealed a minor centrilobular hepatocellular hypertrophy in males in the high-dose group. Also in

high dose males, an accumulation of eosinophilic droplets (considered to be α2u-microglobulin) was noted in the renal cortical tubular epithelia of most animals. No other effects were described in the available summary of this study (NICNAS, 1997).

In a subchronic toxicity study following US EPA guideline, Sprague-Dawley rats (control and high dose: 25 M + 25 F/group, other: 15 M + 15 F/group) received DPGtBE in water by gavage at doses of 0, 62.5, 250 and 1000 mg/(kg bw x d) for 90 d. Post-dose salivation, closed eyelids and impairment of body coordination (unsteady gait, collapsed posture, spasms, paddling of forelimbs) were noted at the highest dose. Body weight gain and food consumption were not affected. Clinical chemistry revealed statistically significant slight reductions in white blood cell and lymphocyte counts at the mid and high dose which reversed within the 4 weeks post-exposure period. Haematology findings of increased globulin and albumin levels at the highest dose may be associated with observed changes of the liver. Minimal centrilobular hepatocellular hypertrophy and increased liver weight were observed in both sexes at the highest dose; these changes were also reversible within the post-exposure period. Increased kidney and adrenal weights were noted in both sexes in the high dose group and males in the mid dose group; this was associated with increased degree and incidence of cortical tubules with eosinophilic inclusions in males at all dose levels and a dose-related incidence of minimal basophilic cortical tubules in males only. These changes had partially reversed by the end of the post-exposure period. There were no equivalent treatment-related effects in females. An increased incidence of minimally increased width of the zona fasciculata was seen in female rats in the high dose group; this may have been related to the increased relative adrenal weight seen in this group; no microscopic changes were noted (NICNAS, 1997). No treatment-related neurobehavioural effects (FOB, motor activity test) were present in rats after treatment with 1000 mg DPGtBE/(kg b.w. x d) for 13 weeks (other doses not studied). Morphometric and micro-structural examination of the brain proved unremarkable (ECETOC, 2005b). Based on macroscopic and/or microscopic changes in liver and adrenal gland, the subchronic NOAEL was 250 mg/(kg bw x d).

Read-across:

A chronic inhalation toxicity/carcinogenicity study with exposure of rats and mice to propylene glycol t-butyl ether **(PGtBE)** is available. F344 rats or B6C3F1 mice (50 M + 50 F/group) were exposed to 0, 75, 300, or 1200 ppm PGtBE vapour (0, 590, 2350, 9400 mg/m^3) on 6 h/d, 5 d/week, for 104 weeks (Doi et al., 2004; NTP, 2004).

In rats, survival of 300 ppm males was less than that of the chamber controls. Mean body weights of 1200 ppm males and females were less than those of the chamber controls during the second year of the study. Kidney and liver were targets of systemic PGtBE toxicity. The incidences of renal tubule hyperplasia, renal tubule hyaline droplet accumulation, papilla mineralisation, and transitional epithelial hyperplasia were increased in male rats. There was also a marginally increased incidence of renal tubule adenoma and adenoma or carcinoma (combined) in 300 and 1200 ppm F344 males. These effects were attributed to the well-known α2u-nephropathy in male F344 rats. No such nephropathy occurred in a parallel study conducted with male NBR rats (which do not produce α2u globulin and are resistant against such effects) and is not considered relevant for risk assessment in humans (NTP, 2004).

The severities of chronic nephropathy increased with increasing exposure concentration in males and females and were significantly increased in all exposed groups of males and in 1200 ppm females. In the liver of males, a positive trend was noted for the incidences of hepatocellular adenoma. Furthermore, the incidences of basophilic foci of the liver were

significantly increased in all exposed groups of males; in females, the incidence of hepatic clear foci was significantly increased at 1.200 ppm (NTP, 2004).

Table 5: Incidence of olfactory epithelium hyaline degeneration in rats after chronic inhalation of PGtBE (NTP, 2004)

Concentration (ppm)	Incidence in males	Incidence in females
0	0/50	10/49
75	25/49	22/49
300	45/49	48/50
1200	50/50	50/50

Regarding local effects, hyaline degeneration of the olfactory epithelium were observed in all groups of treated male and female rats (Table 5). Additionally, the incidence of cornea mineralisation was increased in high dose females (10/50, control: 0/49). According to NTP, hyaline degeneration (and goblet cell hyperplasia) of the olfactory epithelium are commonly observed in aging rats. In chronic inhalation studies, the incidence and severity may be exacerbated often in an exposure dependent manner. These changes are considered nonspecific adaptive or protective responses to prolonged inhalation of irritants (NTP, 2004).

In mice, survival was not affected by treatment. The mean body weight 1200 ppm females was slightly less than those of the chamber control group at the end of the study. Clinical findings included ataxia, shallow breathing, and lethargy in 1200 ppm mice during the first 6 months of the study. At 1200 ppm females, pale foci of the eyes were also noted in the last month of the study, and the incidence of mild corneal mineralisation was significantly increased at termination. The incidences of hepatocellular adenoma, hepatocellular adenoma or carcinoma (combined), and hepatoblastoma occurred with positive trends in males and females, and the incidences in the 1200 ppm groups were increased. The incidences of eosinophilic foci and multinucleated hepatocytes in 1200 ppm males and eosinophilic foci in 1200 ppm females were also significantly increased. No local effects in any part of the respiratory tract were observed in mice (NTP, 2004).

1.5.3 Genotoxicity and carcinogenicity

Genotoxicity

DPGnBE

In vitro, DPGnBE was not mutagenic in a bacterial mutation assay (Ames test) with and without exogenous metabolic activation system (S9 mix from rat liver) in all tested strains of Salmonella typhimurium (TA98, TA100, TA1535, TA1537, TA1538). DPGnBE was also not mutagenic in a HGPRT assay with mammalian cells (Chinese hamster ovary cell: CHO cells) in the absence or presence of exogenous metabolic activation system (S9 mix from rat liver). Inconsistent results were obtained in altogether five chromosome aberration tests in CHO cells performed in two different laboratories. The reasons for the discrepant interlaboratory results could not be fully resolved but may have been related to the use of DMSO (ECHA Dissemination, 2019a).

In vivo, DPGnBE was not clastogenic in a micronucleus test in male and female CD-1 mice at doses up to 2500 mg/kg bw, the highest dose causing lethality in both sexes (ECHA Dissemination, 2019a).

DPGtBE

In vitro, DPGtBE showed no mutagenic activity in a bacterial mutation assay (Ames test) with and without exogenous metabolic activation system (S9 mix from rat liver) in all tested strains of Salmonella typhimurium (TA98, TA100, TA1535, TA1537) (NICNAS, 1997).

In vivo, DPGnBE was not clastogenic in a micronucleus test in male and female CD-1 mice at doses up to 800 mg/kg bw (ECETOC, 2005b; ECHA Dissemination, 2019a).

Carcinogenicity

No data are available for this endpoint for both compounds, DPGnBE and DPGtBE.

Read-across:

No evidence of carcinogenicity was observed in a two-year carcinogenicity study (according to OECD guideline 453) with inhalation exposure of F344 rats (50 M + 50 F/group) to **PGME** (propylene glycol monomethyl ether, CAS No. 107-98-2) up to the highest concentration tested (3000 ppm). Non-neoplastic effects observed in this study included decreased activity, incoordination, and transient sedation during and immediately after exposure to 3000 ppm. Body weights were also decreased at the 3000 ppm exposure level. Liver and kidney weights were increased at 3000 ppm in both sexes. Dark foci in the liver were observable in male rats exposed to 1000 and 3000 ppm PGME after 24 months. These animals also exhibited eosinophilic hepatocellular foci and cystic degeneration microscopically that was not reported in female rats. In the kidney, histopathology revealed that male rats had α2u-globulin nephropathy. The incidence and severity of this condition was increased in males exposed to 1000 and 3000 ppm PGME compared to controls. A NOAEC of 300 ppm based on altered hepatocellular foci in males can be derived from this study (OECD SIDS, 2003b).

A carcinogenicity study was conducted with propylene glycol t-butyl ether **(PGtBE)** inhalation exposure of rats and mice (Doi et al., 2004; NTP, 2004). Based on the results of this study (see chapter 1.5.2.), NTP concluded that there was *equivocal evidence* of carcinogenic activity of PGtBE in male rats based on marginally increased incidences of renal tubule and liver neoplasms and *no evidence* of carcinogenic activity in female rats. NTP further concluded that there was *clear evidence* of carcinogenic activity of PGtBE in male and female mice based on increased incidences of liver neoplasms (NTP, 2004).

1.5.4 Toxicity to reproduction

There are no studies available with exposure to DPGtBE.

Fertility

DPGnBE

A reproduction/developmental toxicity screening test according to OECD Guideline 421 was conducted with Sprague-Dawley rats (12 M + 12 F/group) (ECHA Dissemination, 2019a). 0, 100, 300 or 1000 mg/(kg bw x d) DPGnBE was given by gavage (as aqueous solution) to females and males for two weeks prior to breeding and through breeding (two weeks). Males were necropsied on test day 29. Females were further treated during gestation (three weeks) and lactation up to postpartum day 4 and necropsied on postpartum day 5. The first day of treatment, three females of the high-dose group showed a transiently incoordinated gait which resolved within 1-2 hours after dosing and was not seen again during the further course of the study. Transient, post-dosing salivation was noted sporadically in several high-dose males and

females during the study. Treatment-related increases in the incidence of hepatocellular hypertrophy occurred in males of all dose groups, and in females at the mid and high dose. The hypertrophy was associated with increased absolute and relative liver weights in males at the mid dose and in both sexes at the high dose. Treatment-related increases in absolute and relative kidney weights also were found in males and females given the high dose. Hyaline droplet formation in the proximal renal tubules of male rats was observed at the mid and high dose. In females, no histopathologic effects could be observed in the kidney. There were no treatment-related effects on any reproductive parameters. The NOAEL for systemic toxicity was considered to be 100 mg/kg/day, based on very slight to slight hepatocellular hypertrophy with no corresponding increases in liver weights in low-dose males. The NOEL for reproductive effects was 1000 mg/(kg bw x d), the highest dose tested (ECHA Dissemination, 2019a).

In subacute or subchronic toxicity studies with DPGnBE (see chapter 1.5.2), no effects on reproductive organs were observed (ECHA Dissemination, 2019a).

Read-across:

A one-generation study was performed with **DEGBE** (diethylene glycol mono butyl ether) in CD rats (see chapter 2.5.4). No adverse effects or signs of reproduction toxicity were observed in (gavage) treated males or females. A reduction in pup weight gain was statistically significant in the highest tested dose group of exposed dams on GD 14. The finding was not considered toxicologically relevant, due to its occurrence at a single time point and not in pups of males exposed to the highest dose. In the registration dossier the NOAELs for parental, reproduction, and F1 toxicity were 1000 mg/(kg bw x d), respectively (ECHA Dissemination, 2019b). A NOEL of 1000 mg/(kg bw x d) for parental animals is given in the SCOEL recommendation (SCOEL, 2002).

A further one-generation study was performed with **DEGBE** in Wistar rats (see chapter 2.5.4). Animals were exposed to DEGBE in drinking water for 10 weeks (males) or 9 weeks (females). Reproductive parameters up to the maximum tested dose of 1000 mg/(kg bw x d) were not adversely affected. The derived NOAELs for parental toxicity and reproduction in the registration dossier were 250 and 1000 mg/(kg bw x d), respectively (ECHA Dissemination, 2019b).

In a fertility study female Wistar rats were exposed to **DEGBE** by gavage, 5 d/w for 8 weeks. Up to the maximum tested dose of 1000 mg/(kg bw x d) no effects on reproductive parameters (e.g., oestrous cycle) were observed. Five mortalities occurred in the high exposure group, thereby all animals had dark livers at necropsy and hyperkeratosis in forestomach. Furthermore, high dose animals revealed reduced body weight gain and adverse clinical observations. In the registration dossier a NOAEL for reproductive toxicity of 1000 mg/(kg bw x d) was derived, based on no effects on oestrous cycle. No NOAEL was derived for maternal toxicity (ECHA Dissemination, 2019b).

DPGtBE

No data are available for this endpoint for DPGtBE.

Read-across:

In a one-generation study, Sprague-Dawley rats (8 M + 8 F/group) received 0, 100, 300 or 1000 mg/(kg bw x d) of **PGtBE** by gavage. For males, treatment began 71 d prior to mating until termination (total: 18 weeks). Females were treated from 15 d prior to pairing, throughout mating, gestation and lactation until study termination (total: 8 weeks). No deaths occurred. Clinical signs were limited to salivation after dosing the mid and high dose. No systemic effects

were apparent in either sex during treatment or at necropsy. Sperm parameters in high dose males were normal. Mean litter sizes were comparable, but offspring from dams exposed to 1000 mg/(kg bw x d) had slightly lowered birth body weights, reduced weight gains from birth to weaning and a slight decrease in postnatal survival. All other litter- and individual off-spring parameters were normal. The parental NOAEL was 1000 mg/(kg bw x d), the NOAEL for growth and development in the offspring was 300 mg/(kg bw x d). Similarly, no evidence of toxicity (except post-dose salivation) were noted in a pilot study to this one-generation conducted study with the same dose levels and size groups (but treatment of males starting at day 15 prior to mating) (ECETOC, 2005b).

Development

DPGnBE

A study was conducted with dermal exposure of rats to DPGnBE. The test substance was applied to the clipped skin of pregnant Wistar rats on GD 6 – 15. DPGnBE was applied to the clipped skin of two groups of Wistar rats (21 – 25 F/dose level) at various dilutions in propylene glycol (PG) equivalent to doses of 0, 273, or 910 mg/(kg bw x d). Rats wore neck collars to prevent grooming and ingestion of test material. Solutions were applied unoccluded since the low vapour pressure precluded evaporative losses. Animals were sacrificed on GD21. Slight skin reactions were found in the dams from all treatment groups and thus were not considered to be related to treatment with DPGnBE. No maternal toxicity was found, clinical signs and organ or body weights did not differ between treatment and controls groups. Fecundity was comparable among groups. No embryo- or fetotoxicity was observed. DPGnBE did not cause frank developmental toxicity in skeletal or soft tissue. The high dose group exhibited a slight non-significant increase in the incidence of supernumerary rudimentary thoracic ribs when compared to controls. This finding was not considered biologically significant by the authors of the study since the incidence was within normal limits for these species. It was concluded that DPGnBE is not maternally toxic, embryo- or fetotoxic, or teratogenic in Wistar rats receiving dermal doses up to 910 mg/(kg bw x d) (NOAEL). A LOAEL was not established (ECHA Dissemination, 2019a).

Read-across:

The developmental toxicity of **DPGME** (dipropylene glycol monomethyl ether)was studied in rats and rabbits via the inhalation route of exposure at concentrations of 0, 50, 150, or 300 ppm (0, 303, 909, or 2728 mg/m^3) (Breslin, 1990; OECD SIDS, 2003b):

Mated F344 rats (32-37/group) were exposed for 6 h/d on GD 6-15. On day 21 of gestation, all animals were euthanised prior to cesarean section and examined. No treatment-related effects were observed on any of the maternal, embryonal and fetal parameters evaluated.

In a similar study, New Zealand rabbits (16 mated F/group) were exposed for 6 h/d on GD 7-19. On day 28 of gestation, all animals were euthanised and examined. No treatment related effects were observed on any of the maternal and embryonal/fetal parameters evaluated at any exposure level.

Thus, the highest vapour concentration of 300 ppm (2728 mg/m^3) which was practically attainable at normal room temperature represents a NOAEC for DPGME for the studies in both species.

In a prenatal developmental toxicity study (see chapter 2.5.4) mated female Wistar rats received **DEGBE** in diet from GD 0 – GD 20. Neither significant signs of maternal nor developmental toxicity were observed up to the maximum tested dose of 633 mg DEGBE/(kg bw x d) (ECHA Dissemination, 2019b; SCOEL, 2002).

DPGtBE

No data are available for this endpoint for DPGtBE.

Read-across:

In a developmental toxicity study with inhalation exposure to **PGtBE**, pregnant Sprague-Dawley rats (25 F/group) were exposed whole-body to 0, 230, 725 or 990 ppm for 6 h/d on GD 6 – GD 15. Maternal toxicity was observed in high-dose female, with about half of the dams appearing pale through most of the exposure period and displaying significant increases in absolute and relative liver weights at the mid and high dose. Fetal development was unaffected by treatment. A NOAEC for foetal development of 990 ppm was obtained from this study (no LOAEC). The NOAEC for maternal toxicity was 230 ppm (LOAEC: 725 ppm) (ECETOC, 2005b).

In a similar study with pregnant New Zealand rabbits (16 F/group), the animals were exposed (whole body) 6 h/d to 0, 230, 720 or 980 ppm **PGtBE** on GD7 – GD 19. There was no evidence of maternal toxicity. Foetal parameters (including litter size, body weights and morphology) were unaffected by treatment. A NOAEC of 980 ppm for developmental toxicity was obtained (ECETOC, 2005b).

1.5.5 Odour perception

No data on odour or odour threshold are available for DPGnBE and DPGtBE.

1.6 Evaluation

1.6.1 Existing regulations and classifications

There is no harmonised classification for DPGnBE or DPGtBE (ECHA C&L Inventory, 2019).

Existing guide values for DPGnBE in air are summarised in Table 6.

A NIK (Lowest Concentration of Interest) value of 810 µg/m³ is reported for DPGnBE. This value was adopted from the EU-LCI value for DEGBE of 670 µg/m³. This EU-LCI value is an "ascribed EU-LCI value" based on the German NIK value. The NIK value was set by adopting the EU OEL value of 67.5 mg/m³ (10 ppm), which was derived by SCOEL from a subchronic inhalation study in rats (NOEL = 94 mg/m³ (15 ppm)) (SCOEL, 2002) and applying a default factor of 100. A molar adjustment from DEGBE to DPGnBE was performed in order to derive the NIK value of DPGnBE (AGBB, 2018; 2008).

Table 6: Guide values for DPGnBE in air (for explanation, see text)

Guidance value Parameter/ Organisation	AgBB (2018)	ECHA Dissemination (2019)	ECHA Dissemination (2019)
Name (reference period)	NIK Value (2008)	DNEL (chronic, general population)	DNEL (chronic, workers)
Value (mg/m³)	0.81 (read-across from DEGBE)	56	189
Organ/critical effect	No critical effect	Increased liver and kidney weight	Increased liver and kidney weight
Species	rat	rat	rat
Basis	NOAEC (DEGBE): 100 mg/m³ (14 ppm)	NOAEL: 450 mg/(kg bw x d)	NOAEL: 450 mg/(kg bw x d)
Adjusted for cont. exposure	Value derived using "preferred value approach"	450 mg/(kg bw x d) : 1.15 m³/(kg b.w. x d) = 391 mg/m³	450 : 0.38 x 6.7/10 = 793 mg/m³
Extrapolation factors Time LOAEC to NOAEC Interspecies Intraspecies Total	 - - - - 100 (was used as default factor)	 1.4 - 1 5 7	 1.4 - 1 3 4.2
Remarks	Read-across was performed: The EU-LCI value of 670 µg/m³ for DEGBE (diethylene glycol mono butyl ether) was adopted for the NIK value for DEGBE. The EU-LCI value for DPGBE (2013) is an "ascribed EU-LCI-value". The derived NIK value for DEGBE was transformed into a NIK value for DPGBE by molar adjustment.	A route-to-route extra-polation was performed, using the NOAEL from a subchronic study with oral exposure of rats as the starting point	A route-to-route extrapolation was performed, using the NOAEL from a subchronic study with oral exposure of rats as the starting point

General population

In the registration dossier for DPGnBE, a DNEL of 56 mg/m³ for the protection of the general population via inhalation route has been derived on the basis of a route-to-route extrapolation, using the data from a subchronic oral toxicity study with DPGnBE in rats. The NOAEL for oral exposure was converted into a NAEC for inhalation exposure using the standard factor recommended by ECHA (ECHA, 2012). A time extrapolation factor of 1.4 and an intraspecies factor of 5 were applied by the registrant (no details presented) (ECHA Dissemination, 2019a).

The German Ad-hoc Working Group on Indoor Guidelines has evaluated the toxicity of glycol ethers and glycol esters and derived substance-specific guide values for substances with sufficient data. No substance-specific value was derived by the working group for DPGnBE or DPGtBE. A default guide value I of 0.005 ppm was recommended for glycol ethers and glycol esters with insufficient data basis (Ad-hoc AG, 2013). This recommendation was based on a statistical analysis of the available data of all glycol ethers, not taking into account substance-

specific structural criteria for individual compounds. In case of DPGnBE, the recommended guide value I of 0.005 ppm corresponds to a mass-based concentration of 39 µg/m³.

Workplace

An inhalation DNEL of 189 mg/m³ for workers is also reported in the REACH registration dossier for DPGnBE (ECHA Dissemination, 2019a). This DNEL is based on the same subchronic oral toxicity study as noted above. A time factor of 1.4, an intraspecies factor of 3 and an interspecies factor of 1 were taken into account, referring to a study of Bätke et al. (2011).

There are no other OELs available for DPGnBE (IFA, 2019).

1.6.2 Derivation of an EU-LCI value

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

No data are available on the toxicity of DPGnBE or DPGtBE in humans.

DPGnBE

Limited data from subacute inhalation studies with rats indicate that DPGnBE has a low systemic toxicity. Hepatocellular hypertrophy was observed at concentrations ≥ 810 mg/m³. This is probably an adaptive reaction and not a toxic effect. However, some evidence of hepatotoxicity with liver cell necrosis was noted at 2010 mg/m³. After subacute inhalation with ≥ 810 mg DPGnBE/m³, local effects in the nasal epithelium of rats with multifocal epithelial hyperplasia and squamous metaplasia in the anterior nasal cavity were observed. These effects were sometimes accompanied by inflammation or degeneration of the olfactory epithelium. The NOAEC in the study was 200 mg/m³. The study is not published but described in sufficient detail in the REACH registration dossier (ECHA Dissemination, 2019a) and the OECD SIDS (OECD SIDS, 2003b). However, the incidences and the severity scores of the nasal lesions are not reported in these reports.

No inhalation studies are available with a second animal species. However, such local irritation effects of otherwise non-reactive chemicals as PGnBE and other glycol ethers can be expected not to show pronounced differences between various species.

Studies with longer (subchronic) exposure duration are only available with oral or dermal exposure of rats. These studies confirm the low toxicity of DPGnBE observed in subacute studies. A NOAEL of 450 mg/(kg bw x d) can be derived from a feeding study, based on decreased body weight, increased liver weight (without histopathological changes) and slight clinical chemical alterations in serum (ECHA Dissemination, 2019a). Effects on the liver (increased weight and slight increases of liver enzymes in serum) were also observed after subchronic dermal exposure of rats at 910 mg/(kg bw x d). Other systemic effects (decreased weight gain and increased neutrophil counts in blood) were already observed at 91 mg/(kg bw x d) in this study (ECHA Dissemination, 2019a) but are probably secondary to the marked local irritation at the exposure site.

In vitro data provide no evidence for genotoxic effects of DPGnBE in prokaryotes. Also, no mutagenicity was observed in mammalian cells. *In vitro* data on chromosomal aberrations were somewhat inconclusive, probably because of differences in the assay conditions. However, an *in vivo* micronucleus assay with mice was clearly negative, indicating that DPGnBE is not clastogenic. Overall, the data do not provide concern for genotoxic effects of DPGnBE.

Carcinogenicity studies are not available for DPGnBE. A read-across with an inhalation study in rats with propylene glycol methyl ether (PGME) provided no evidence for a carcinogenic activity of this compound. Generally, glycol ethers are not regarded as to reveal a carcinogenic potential for humans (Ad-hoc AG, 2013; ECETOC, 2005a; OECD SIDS, 2003a; OECD SIDS, 2003b) (For effects of PGtBE, see discussion below for DPGtBE).

DPGnBE had no effects on reproductive parameters or reproductive organs in male and female rats in a reproduction/developmental toxicity screening assay (ECHA Dissemination, 2019a). Read-across using data from one-generation and fertility studies in rats with DEGBE also provided no evidence for reproduction toxicity (ECHA Dissemination, 2019b).

No maternal, embryo- or fetotoxicity or teratogenicity was observed in a dermal exposure study in rats up to the highest concentration tested (ECHA Dissemination, 2019a). Read-across data support the lack of developmental toxic effects since no such effects were observed in an inhalation developmental toxicity with DPGME in rats and rabbits (Breslin, 1990; OECD SIDS, 2003b) and in such a study with DEGBE in rats (ECHA Dissemination, 2019b; SCOEL, 2002).

The subacute inhalation toxicity study with rats summarised above is considered a suitable key study for the derivation of an EU-LCI value for DPGnBE. The study is not published but described in sufficient detail in the REACH registration dossier (ECHA Dissemination, 2019a) and the OECD SIDS (OECD SIDS, 2003b). The NOAEC of 200 mg/m³ (25 ppm) from that study is used as POD for the calculation (see Table 7).

The following adjustment factors are used:

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

Total assessment factor: 840. This leads to a concentration of 200 mg/m³: 840 = 0.238 mg/m³ (rounded to 250 µg/m³).

Table 7: Derivation of EU-LCI-value for DPGnBE and DPGtBE (for explanation, see text)

Organ/endpoint	POD	Exposure duration	Time	Inter-species	Intra-species	Value	Reference
DPGnBE: nose/ lesions of nasal epithelium	NOAEC 200 mg/m³	5.6	6	2.5	10	0.238 mg/m³	(ECHA Dissemination, 2019a)
DPGtBE: read-across data from PGtBE, nose/ lesions of olfactory epithelium	$BMDL_{10}$ 4.89 ppm	5.6	1	2.5	10	0.035 ppm = 0.273 µg/m³	

Studies with oral exposure of rats indicate a subchronic NOAEL of 450 mg/(kg bw x d) for systemic effects. Toxicokinetic data indicate a rapid and nearly complete absorption of

DPGnBE after oral administration (see chapter 1.4). No substance-specific data are available regarding absorption after inhalation. However, glycol ethers in general are known to be well absorbed by inhalation (ECETOC, 2005a; OECD SIDS, 2003b). Therefore, similar absorption may be assumed when performing a route-to-route extrapolation.

Using standard extrapolation factors (EC, 2013; ECHA, 2012):

- Route-to-route extrapolation (rats): 1.15 m^3(kg b.w. x d)
- Adjusted study length factor (subchronic exposure study): 2
- Allometric scaling: already included in route-to-route extrapolation
- Interspecies extrapolation: 2.5
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 57.5 m^3/(kg b.w. x d). This leads to a concentration of 450 mg/(kg bw x d): 57.5 m^3/(kg b.w. x d) = 7.83 mg/m^3 (1 ppm). This value is more than a factor of 30 higher than that derived on the basis of local effects in the respiratory tract observed after inhalation exposure to DPGnBE. It is concluded that the latter value will also offer protection against systemic effects of DPGnBE.

An EU-LCI value (rounded) for DPGnBE of 250 µg/m^3 is proposed.

DPGnBE is reported to have a mild odour. However, data on odour thresholds are not available.

DPGtBE

DPGtBE is slightly irritating to skin and eyes. A weakly positive sensitisation reaction was described in a modified maximisation test in guinea pigs for undiluted but not for diluted DPGtBE (NICNAS, 1997).

There are no data for DPGtBE with repeated inhalation of animals. Data with oral administration are available indicating a subchronic NOAEL of 250 mg/(kg bw x d), based on slight changes in the liver and adrenal gland (ECETOC, 2005).

DPGtBE showed no mutagenic activity in a bacterial mutation assay and was not clastogenic in a micronucleus test in mice at doses up to 800 mg/kg bw (ECETOC, 2005).

No studies are available regarding the carcinogenicity, the reproductive or the developmental toxicity of DPGtBE.

Altogether, the data basis for DPGtBE is considered insufficient for the derivation of an EU LCI value. Principally, the value for the n-butyl ether of dipropylene glycol could be adopted for the tert-butyl ether. However, taking in to account known differences in the metabolism and in the toxicity of primary and tertiary butyl alcohol, an additional read-across is performed with propylene glycol mono-tert-butyl ether (PGtBE).

A chronic toxicity/carcinogenicity study with rats and mice performed within the NTP is available for PGtBE (Doi et al., 2004; NTP, 2004). PGtBE led to effects in the kidneys of male F344 (but not in male NBR rats). The effects can be attributed to the well-known α2u-nephropathy of male rats which are not considered relevant for risk assessment in humans. In the NTP study, there were also some slight changes in the kidney and of urinary parameters in female rats from the lowest concentration tested (75 ppm) indicating that other effects with a

different mode of action could play a role (progression of spontaneously occurring chronic nephropathy). Exposure to PGtBE also led to non-neoplastic effects in the liver of male rats, and positive trends or increased incidences of liver neoplasias were observed in male but not in female rats. A positive trend for hepatocellular adenoma was also noted in males but not females. In male and female mice, an increased incidence of liver neoplasms was noted (NTP, 2004).

These findings were discussed by IARC (2006). Regarding genotoxicity of PGtBE, there are some marginally positive results in bacteria and in mammals in vivo, though most data do not indicate a genotoxic potential. IARC concluded that there is limited evidence in experimental animals and that overall PGtBE is not classifiable as to its carcinogenicity to humans (IARC, 2006).

In the NTP study (2004), PGtBE also caused concentration-dependent local effects, i.e. degeneration of the olfactory nasal epithelium of rats (see Table 5). The incidence was already increased at the lowest concentrations tested (LOAEC: 75 ppm). A benchmark calculation was performed using PROAST software (see Annex in chapter 1.8) which led to a weighted $BMCL_{10}$ from all suitable models of 4.89 ppm. This value may be used as the starting point for the derivation of an EU LCI value.

The following adjustment factors are used:

- Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6
- Adjusted study length factor (chronic exposure study): 1
- Interspecies extrapolation: 2.5 (factor for systemic effects at inhalation exposure)
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 140. This leads to a concentration of 4.89 : 140 = 0.0349 ppm. With the conversion factor for DPGtBE, this value is equivalent to a mass concentration of 0.273 mg DPGtBE/m^3.

A value for DPGtBE based on this read-across using data from PGtBE would be very close to the value derived for DPGnBE and would be rounded to the same EU LCI value as proposed for DPGnBE. Thus, it is proposed to adopt the EU LCI value of 250 µg/m^3 for DPGtBE.

A route-to-route extrapolation, based on the oral NOAEL of 250 mg/(kg bw x d) from the subchronic oral toxicity study with DPGtBE mentioned above (ECETOC, 2005), would lead to a value of 250 mg/(kg bw x d) : 1.15 m^3/mg/(kg bw x d) : (2 x 2.5 x 10) = 4350 µg/m^3, a value more than 15fold higher than the proposed EU LCI which is based on local effects. It is concluded that the EU-LCI value derived on the basis of local irritation effects in the upper respiratory tract will also offer protection against systemic effects of DPGtBE.

An EU-LCI value (rounded) for DPGtBE of 250 µg/m^3 is proposed.

DPGtBE is reported to have a mild odour. However, data on odour thresholds are not available.

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1.8 Fact and data sheet for dipropylene glycol mono n- and t-butyl ether (DPGBE)

Table 8: Data collection sheet for dipropylene glycol mono n-butyl ether

Compound	Dipropylene glycol mono n-butyl ether	*Data collection sheet*
N° CAS 29911-28-2 1 ppm = 7.83 mg/m³ at 23 °C	**EU-Classification: -** **CLP,** harmonised classification: -	
Organisation name	AgBB	Reach registrants
Risk value name	NIK ('Lowest Concentration of Interest')	DNEL
Risk value (mg/m³)	0.81 mg/m³ (read-across from DEGBE)	56 mg/m³
Reference period	Chronic (general population)	Chronic (general population)
Risk value (mg/m³) Short term (15 min)	-	-
Year	2008	2018
Key study		Unpublished study from 1989 reported as „key" study for repeated dose
Study type		Subchronic study with oral exposure (OECD 408) via food (doses: 0, 200, 450, or 1000 mg/(kg bw x d))
Species		Sprague-Dawley rats (n=20/sex/group)
Duration of exposure in key study		daily for 13 weeks
Critical effect		increase in kidney and liver weights without accompanying histopathology
Critical dose value		NOAEL: 450 mg/(kg bw x d)
Adjusted critical dose		450 mg/(kg bw x d) : 1.15 m³/kg b.w. x d = 391 mg/m³
Single assessment factors		UF_H 5 x UF_A 1 x UF_S 1.5 = 7
Other effects		
Remarks	Read-across was performed using data for diethylene glycol mono-butyl ether (DEGBE) for NIK values for dipropylene glycol mono n- and t-butyl ether. The EU-LCI value for DEGBE was adopted for the NIK value for DEGBE. The EU-LCI of 670 µg/m³ for DEGBE is an "ascribed EU-LCI" (2013).	The NOAEL from a subchronic oral toxicity study in rats served as the starting point, using the standard factor for rats to calculate a NAEC for inhalation (ECHA Dissemination, 2019a)
AgBB = Ausschuss zur gesundheitlichen Bewertung von Bauprodukten UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study UF_D data deficiencies.		

Table 9: Fact sheet dipropylene glycol mono n-butyl ether (DPGnBE)

Compound	**Dipropylene glycol mono n-butyl ether (DPGnBE)**		***Factsheet***
Parameter	**Note**	Comments	Value / descriptor
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2019
General information			
CLP-Index No.	4	INDEX	-
EC-No.	5	EINECS	249-951-5
CAS-No.	6	Chemical Abstract Service number	29911-28-2 (α-isomer, main component) 35884-42-5 (mixture of isomers)
Harmonised CLP classification	7	Human health risk related classification	-
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	190.28 1 ppm = 7.83 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	ECHA Dissemination (2019a) short-term repeated dose toxicity: inhalation, OECD guideline 412
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	Rat, F344 (5/sex/dose)
Route / type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic, etc.	2 weeks
Exposure duration	14	h/d, d/w	6 h/d, 5 d/week, 9 d
Critical endpoint	15	Effect (s), site of	Lesions of nasal epithelia: multifocal epithelial hyperplasia and squamous metaplasia
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEC
POD value	17	[mg/m³] or ppm or [mg/kg_{BW}×d]	200 mg/m³
Assessment factors (AF)	18		
Adjustment for exposure duration	19	Study exposure h/d, d/w	5.6
Study length	20	sa→sc→c	6 (subacute to chronic)
Route-to-route extrapolation factor	21	-	1
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	1
	22b	Severity of effect (R8 6d)	1
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	1
	23b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		1
Other adjustment factors Quality of database	26		1
Result			
Summary of assessment factors	27	Total Assessment Factor	840
POD/TAF	28	Calculated value [µg/m³ and ppb]	238 µg/m³ (30.4 ppb)

Molar adjustment factor	29		
Rounded value	30	[µg/m³]	250
Additional comments	31		
Rationale section	32		

- **Rationale for critical effects**

Dipropylene glycol mono n-butyl ether (DPGnBE)

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

The acute toxicity of dipropylene glycol mono-n-butyl ether **(DPGnBE)** in animal experiments is low. A vapour- and an aerosol-inhalation study are available for DPGBE. No mortality was observed up to the highest attainable vapour concentration tested (42.1 ppm = 330 mg/m³) and at an aerosol concentration of 2040 mg/m³. Also, no mortality was observed in a further study up to 5400 mg/m³, the highest concentration tested. In this study, the head-only exposed rats showed breathing alterations, aqueous nasal discharge, and later on reddish, aqueous salivation and diminished pain reflex during exposure and staggering gait, reduced general state and partially abdominal position afterwards. All signs receded within six days. In two studies following OECD guideline and two further non-guideline studies with rats oral LD50 values of 1820-3700 mg/kg b.w. have been determined. In a dermal toxicity study, the LD50 was determined to be > 2000 mg/kg b.w. No sensitisation was observed in a Buehler test with rabbits (ECHA Dissemination, 2019a).

In a short-term repeated inhalation toxicity study following OECD guideline 412, F344 rats (5 M + 5 F/group) were exposed "nose only" to 0, 200, 810 or 2010 mg/m³ DPGnBE (0, 25, 100, or 250 ppm, concentrations analytically confirmed) for 6 h/d, 5 d/week, 2 weeks (a total of 9 exposures). No lethality was observed. At the highest exposure, most animals initially exhibited lethargic behaviour, but this disappeared for all but one animal after the 2nd exposure. Body weights of high-dose animals, especially of males, were lower and weight gain reduced compared to control. Absolute and relative liver weight was increased at high and mid concentrations. This was largely attributed to the reduced body weight and to a hepatocellular hypertrophy, at the highest concentration slight vacuolation or multifocal hepatocyte necrosis was additionally observed in some animals. Rats from the mid and high-exposure groups exhibited multifocal epithelial hyperplasia and squamous metaplasia in the anterior nasal cavity (the incidence and severity of the lesions were not reported). Nasal effects were considered a direct response to irritation from DPGnBE typical for mucosal tissue and were sometimes accompanied by suppurative inflammation or degeneration of the olfactory epithelium. No adverse effects were noted in the deeper respiratory tract. Thus, repeated inhalation exposure to DPGnBE led to nasal epithelial lesions. The NOAEC in the described study was 200 mg/m³ (ECHA Dissemination, 2019a).

In a second, similarly conducted short-term inhalation toxicity study with rats no nasal effects were observed at the highest tested nominal concentration of 320 mg/m³. However, the actual concentration was lower (but not reported) due to condensation of the test material (ECHA Dissemination, 2019a). Therefore, no quantitative data can be obtained from this study.

Inhalation studies with subchronic or chronic exposure to DPGnBE are not available. In a subchronic oral (feeding) toxicity study with rats following OECD guideline 408, an increase in kidney and liver weight without accompanying histopathological effects (but with a slight increase of gamma-glutamyl transferase in serum) were observed at the highest delivered dose (1000 mg/(kg bw x d)). No effects were observed at 450 mg/(kg bw x d) (NOAEL) (ECHA Dissemination, 2019a).

In vitro genotoxicity studies in bacteria and mammalian cells do not provide evidence of mutagenic or clastogenic effects of DPGnBE. Inconsistent results were obtained in altogether five chromosome aberration tests in CHO cells at two different laboratories. The discrepancies could not be fully resolved but positive results may be related to the use of DMSO in the positive experiments. DPGnBE did not induce micronuclei in the bone marrow of mice *in vivo* (ECHA Dissemination, 2019). Taking into account the overall evidence and considering (negative) findings with other propylene glycols, DPGnBE cannot be regarded as mutagenic.

Carcinogenicity studies are not available for DPGnBE. A read-across with an inhalation study in rats with propylene glycol methyl ether (PGME) provided no evidence for a carcinogenic activity of this compound. Generally, glycol ethers are not regarded as to reveal a carcinogenic potential for humans (Ad-hoc AG, 2013; ECETOC, 2005a; OECD SIDS, 2003a; OECD SIDS,

2003b) (See discussion below at DPGtBE for data on propylene glycol t-butyl ether (PGtBE)).

DPGnBE had no effects on reproductive parameters or reproductive organs in male and female rats in a reproduction/developmental toxicity screening assay (ECHA Dissemination, 2019a). Read-across using data from one-generation and fertility studies in rats with DEGBE (diethylene glycol monobutyl ether) also provided no evidence for reproduction toxicity (ECHA Dissemination, 2019b).

No maternal, embryo- or fetotoxicity or teratogenicity was observed in a dermal exposure study in rats up to the highest concentration tested (ECHA Dissemination, 2019a). Read-across data support the lack of developmental toxic effects since no such effects were observed in an inhalation developmental toxicity with DPGME (dipropylene glycol monomethyl ether) in rats and rabbits (Breslin, 1990; OECD SIDS, 2003b) and in a study with DEGBE in rats (ECHA Dissemination, 2019b; SCOEL, 2002).

DPGnBE is reported to have a mild ether like odour. However, no data on odour thresholds are available.

Rationale for starting point

The derivation of the EU-LCI is based on data from a guideline study with subacute inhalation exposure. The NOAEC for effects on the nasal epithelium at 200 mg/m³ served as the POD for the derivation of the EU-LCI. The study is not published, but described in detail in the REACH registration dossier and considered as “reliable without restrictions", RL 1) (ECHA Dissemination, 2019a).

Rationale for extrapolation factors

- Factor for adjustment for exposure duration: 5.6
- Adjusted study length factor: 6 (subacute exposure)
- Interspecies differences:
  allometry 1 (inhalation exposure, local effect)
  remaining differences 2.5 (According to the ECA report No. 29, no correction has to be made for differences in systemic metabolism when the POD is related to local effects. For remaining uncertainties, a value of 1 is used for remaining specific differences for effects on skin, eye and GI tract if the mode of action implies only a simple destruction of membranes, and a default value of 2.5 is used for effects on the skin, eye and GI tract if local metabolism or receptor binding reactions are involved. However, although an important role of metabolism or receptor binding seems unlikely, no data are available. Therefore, the factor of 2.5 is retained.)
- Intraspecies differences: 10

Total extrapolation factor: 840, leading to a value of 200 000 µg/m³ : 840 = 238 µg/m³.
The following EU-LCI is proposed for DPGnBE: 250 µg/m³.

DPGnBE is reported to have a mild odour. However, data on odour thresholds are not available.

Comparison of the proposed EU-LCI with a derived value from a subchronic oral exposure study

In the registration dossier of DPGnBE a subchronic oral toxicity study with rats was used to derive a DNEL (see data collection sheet). The derivation is based on a NOAEL of 450 mg/(kg bw x d) for an increase in kidney and liver weights without accompanying histopathology, i.e. a NOAEL for systemic effects. Performing a route-to-route extrapolation assuming similar absorption at oral and inhalation exposure and using standard factors for time and inter- and intraspecific extrapolation would lead to a value of:

450 mg/(kg bw x d) : 1.15 m³/mg/(kg bw x d) : (2 x 2.5 x 10) = 7830 µg/m³, a value more than 30fold higher than the proposed EU LCI which is based on local effects. It is concluded that the EU-LCI value derived on the basis of local irritation effects in the upper respiratory tract will also offer protection against systemic effects.

Dipropylene glycol mono t-butyl ether (DPGtBE)

DPGtBE is slightly irritating to skin and eyes. A weakly positive sensitisation reaction was described in a modified maximisation test in guinea pigs for undiluted but not for diluted DPGtBE (NICNAS, 1997).

There are no data with repeated inhalation of animals. Data with oral administration are available indicating a subchronic

NOAEL of 250 mg/(kg bw x d), based on slight changes in the liver and adrenal gland (ECETOC, 2005).

DPGtBE showed no mutagenic activity in a bacterial mutation assay and was not clastogenic in a micronucleus test in mice at doses up to 800 mg/kg bw (ECETOC, 2005).

No studies are available regarding the carcinogenicity, reproductive or developmental toxicity of DPGtBE.

The data basis for **DPGtBE** is considered insufficient for the derivation of an EU LCI value. Principally, the value for the n-butyl ether could be adopted for the *tert*-butyl ether. However, taking in to account known differences in the metabolism and in the toxicity of primary and tertiary butyl alcohol, an additional read-across is performed with propylene glycol mono-tert-butyl ether.

Read-across: Propylene glycol mono-tert-butyl ether (PGtBE, CAS No. 57018-52-7)

A chronic toxicity/carcinogenicity study with rats and mice performed within the NTP is available for PGtBE (Doi et al., 2004; NTP, 2004). PGtBE led to increased kidney weight and kidney damage in male rats. This effect is attributed to the well-known α2u-nephropathy, did not occur male NBR rats (which are resistant against such effects) and is not considered relevant for risk assessment in humans. There were also some slight changes in the kidney and of urinary parameters in female rats from the lowest concentration tested (75 ppm) indicating that other effects with a different mode of action could play a role (progression of spontaneously occurring chronic nephropathy). Exposure to PGtBE led to an increased liver weight in rats and mice. In male rats, basophilic foci in the liver were seen at all exposure concentrations more often than in control, and a positive trend for hepatocellular adenoma was noted in males but not females. In male and female mice, an increased incidence of liver neoplasms was noted (NTP, 2004). The findings were discussed by IARC (2006). Regarding genotoxicity of PGtBE, there are some marginally positive results in bacteria and in mammals in vivo, though most data do not indicate a genotoxic potential. IARC concluded that there is limited evidence in experimental animals and that overall PGtBE is not classifiable as to its carcinogenicity to humans (IARC, 2006).

In the NTP study (2004), PGtBE also caused concentration-dependent local effects, i.e. degeneration of the olfactory nasal epithelium of rats. The incidence was already increased at the lowest concentrations tested (LOAEC: 75 ppm).

Table: Incidence of olfactory epithelium hyaline degeneration in rats after chronic inhalation of PGtBE (NTP, 2004)

Concentration (ppm)	Incidence in males	Incidence in females
0	0/50	10/49
75	25/49	22/49
300	45/49	48/50
1200	50/50	50/50

Rationale for starting point

An EU-LCI value for DPGtBE may be derived by a read-across using data from the chronic toxicity study with PGtBE. In that study, local effects in the olfactory nasal epithelium of rats were observed. A benchmark calculation was performed using PROAST software version 65.2 which led to a weighted BMCL10 from all suitable models of 4.89 ppm. This value may be used as starting point for the derivation of an EU LCI value.

Rationale for extrapolation factors

- Factor for adjustment for exposure duration: 5.6
- Adjusted study length factor: 1 (chronic exposure)
- Interspecies differences:
  allometry 1 (inhalation exposure, local effect)
  remaining differences 2.5 (According to the ECA report No. 29, no correction has to be made for differences in systemic metabolism when the POD is related to local effects. For remaining uncertainties, a value of 1 is used for remaining specific differences for effects on skin, eye and GI tract if the mode of action implies only a simple destruction of membranes, and a default value of 2.5 is used for effects on the skin, eye and GI tract if local metabolism or receptor binding reactions are involved. However, although an important role of metabolism or receptor binding seems unlikely, no data are available. Therefore, the factor of 2.5 is retained.)
- Intraspecies differences: 10

Total extrapolation factor: 5.6 x 25, leading to a value of 4.89 : 140 = 0.0349 ppm PGtBE.

This value may be adopted for DPGtBE on a molar basis:

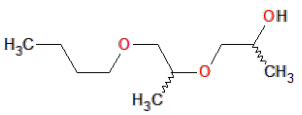
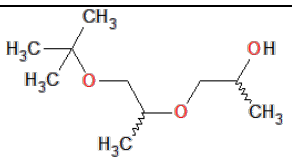
1 ppm DPGtBE = 7.83 mg/m³, thus 0.0349 ppm = 273 µg/m³, which would lead to a proposed EU LCI value of 250 µg/m³.

An EU-LCI value for DPGtBE based on read-across using data from PGtBE would be identical with the EU LCI value proposed for DPGnBE. Thus, the proposed EU LCI value of 250 µg/m³ for DPGnBE may be adopted for DPGtBE.

A route-to-route extrapolation, based on the oral NOAEL of 250 mg/(kg bw x d) from the subchronic oral toxicity study with DPGtBE mentioned above (ECETOC, 2005) would lead to a value of 250 mg/(kg bw x d) : 1.15 m³/mg/(kg bw x d) : (2 x 2.5 x 10) = 4350 µg/m³, a value more than 15fold higher than the proposed EU LCI which is based on local effects. It is concluded that the EU-LCI value derived on the basis of local irritation effects in the upper respiratory tract will also offer protection against systemic effects of DPGtBE.

An EU-LCI value (rounded) of 250 µg/m³ is proposed for DPGtBE.

Data on odour thresholds are not available.

Compound	Structure	MW [g/mol]	EU-LCI value
dipropylene glycol mono n-butyl ether (DPGnBE)		190.28	250 µg/m³ (proposed)
dipropylene glycol mono tert-butyl ether (DPGtBE)		190.28	250 µg/m³ (proposed)

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Annex: Benchmark calculation of BMC10 and BMCL10 for the incidence of olfactory epithelium hyaline degeneration in male rats after chronic inhalation of PGtBE (Data from NTP, 2004)

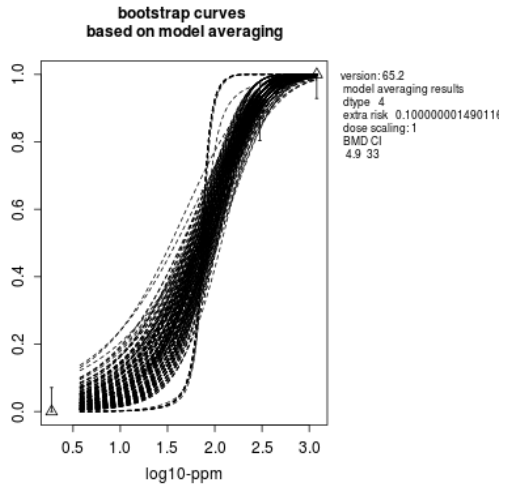
Calculation was performed using the statistical program PROAST version 65.2.

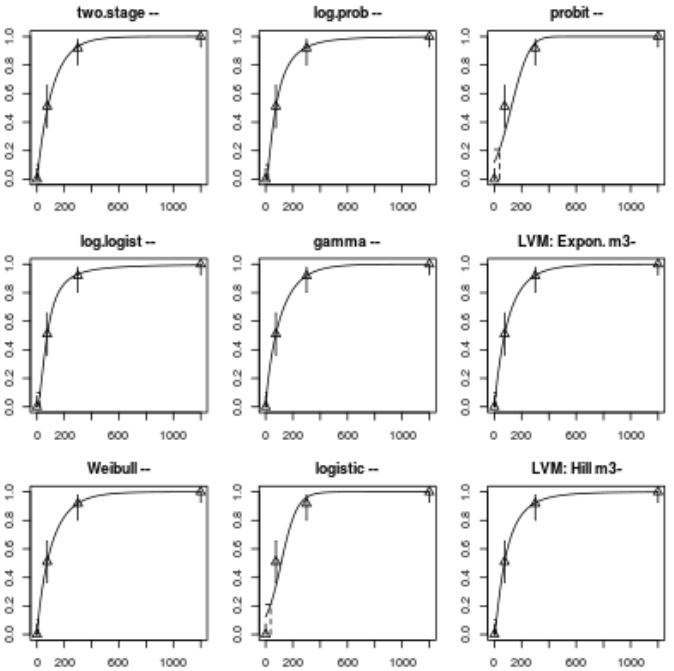
Fitted models

model	No.par	loglik	AIC	accepted	BMDL	BMDU	BMD	conv
null	1	-132.75	267.50		NA	NA	NA	NA
full	4	-47.81	103.62		NA	NA	NA	NA
two.stage	3	-47.92	101.84	yes	9.44	17.4	12.0	yes
log.logist	3	-48.15	102.30	yes	10.50	35.6	23.0	yes
Weibull	3	-47.82	101.64	yes	2.32	20.7	9.2	yes
log.prob	3	-47.93	101.86	yes	9.29	34.6	21.0	yes
gamma	3	-47.81	101.62	yes	0.76	23.0	8.3	yes
logistic	2	-58.34	120.68	no	NA	NA	37.0	yes
probit	2	-58.45	120.90	no	NA	NA	38.0	yes
LVM: Expon. m3-	3	-47.85	101.70	yes	2.48	25.7	11.0	yes
LVM: Hill m3-	3	-47.88	101.76	yes	4.04	31.4	15.0	yes

BMD confidence interval based on model averaging:

BMDL	BMDU
4.89	32.6



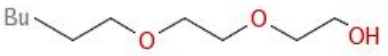


2 Toxicological evaluation of 2-(2-hexyloxyethoxy)-ethanol as basis for the derivation of an EU-LCI value

2.1 Substance identification

Substance identification data and physicochemical properties of 2-(2-hexyloxyethoxy)-ethanol (diethylene glycol monohexyl ether, DEGHE) are shown in Table 10 and Table 11.

Table 10: Substance identification of 2-(2-hexyloxyethoxy)-ethanol (DEGHE) (ECHA Dissemination, 2019a)

CAS-No. EU-No. CLP-Index-No.	Systematic name, common names	Summary formula	Structural formula
112-59-4 203-988-3 603-175-00-7	2-(2-hexoxyethoxy)-ethanol, 2-[2-(hexyloxy)ethoxy]ethan-1-ol, diethylene glycol ether monohexyl, DEGHE, 3,6-dioxa-1-dodecanol, hexyl carbitol, 3,6-dioxadodecan-1-ol	$C_{10}H_{22}O_3$	

2.2 Substance properties and uses

2-(2-Hexyloxyethoxy)-ethanol (DEGHE) is a water-white liquid with a mild odour (ECHA Dissemination, 2019a).

Each year, around 100 – 1000 t of DEGHE are manufactured and/or imported into the European Economic Area (ECHA Dissemination, 2019b). Predominantly DEGHE is used as solvent or coalescing aid in formulations for many industrial applications (e.g., surface coatings, automotive coatings, metal cleaners, printing and silk screen inks or brake fluids) and to a lesser degree (ca. 30%) in consumer product formulations, such as latex, paints, lacquers, thinners, varnishes, window cleaners, air fresheners, floor polishes and finishes, and paint and varnish removers (Cragg, 2012; OECD, 2005).

Table 11: Physicochemical properties of 2-(2-hexyloxyethoxy)-ethanol (DEGHE) (ECHA Dissemination, 2019b)

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa) (at 20°C)	Relative density (at 20°C)	log Pow	Solubility in water (g/L) (at 20°C)
190.28	< -20	262.15	0.002	0.93	1.7	17

2.3 Exposure

2.3.1 Indoor air

Regarding the occurrence of DEGHE in indoor air only very limited data is available (see Table 12). DEGHE was below the detection limit in all 66 samples from various indoor rooms in Germany (Hofmann and Plieninger, 2008). Additionally the substance was not detectable in 1591 samples from various indoor air sources (AGÖF, 2013).

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

Rooms	N	LoD (µg/m³)	N > LoD	Median (µg/m³)	P95 (µg/m³)	Maximum (µg/m³)	LoD (µg/m³)
Offices, homes, (pre)-schools, Germany	66	1	0	0.5	0.5	0.5	(Hofmann and Plieninger, 2008)
Indoor air sources	1591	1	0	<1	<1 (P90)		(AGÖF, 2013)

2.3.2 Other sources

There are no data available.

2.4 Toxicokinetic

Systemic effects observed after oral exposure show that the substance is absorbed orally. However, no reliable quantitative data are available.

Data on absorption, distribution, excretion, and metabolism of DEGHE are not available. Based on physicochemical properties (low molecular weight, high water solubility, and low partition coefficient) a high absorption (100%) via the oral route and inhalation route - less likely due to the low vapour pressure - are expected.

Read-across:

The available data on dermal absorption of other glycol ethers with similar physicochemical features, such as ethylene glycol monohexyl ether (EGHE) and 2-(2-butoxyethoxy)ethanol (diethylene glycol butyl ether, DEGBE), were used as read-across substances for DEGHE. After dermal application of 25 mg EGHE/kg to rats or rabbits, bioavailability of EGHE was greater than 75 or 65%, respectively. EGHE penetrates the skin fast and is widely distributed (ECHA Dissemination, 2019b). Due to the fact that DEGHE is more hydrophilic (higher partition coefficient and water solubility) than EGHE an efficient dermal uptake is less likely. In an *in vivo* study in rats 200 or 2000 mg DEGBE/kg were applied under occlusive conditions. After 24 hours, between 30 - 54% in the lower dose group and 3.4 - 19% in the higher dose group were absorbed, which corresponds to an absorption rate between 0.73 and 1.46 mg/cm^2/h (ECHA Dissemination, 2019b; SCOEL, 2002). In an *in vitro* study, an absorption rate of 0.51 mg/cm^2/h for rat skin and 0.29 mg/cm^2/h for human skin was obtained. Thus, it can be concluded that human skin is less permeable than rat skin for DEGBE and also for DEGHE. Taking into account the lower permeability of human skin and a calculated permeability coefficient (Kp value) of

0.00181 cm/h for DEGHE (equal to 30 µg/cm²/h), dermal absorption of DEGHE will not exceed 50% compared to oral absorption (ECHA Dissemination, 2019b).

Based on the read-across substances and DEGHE's physicochemical properties, a wide distribution, no accumulation and rapid excretion via urine are expected (ECHA Dissemination, 2019b).

From a dermal exposure study with DEGBE in rats the following metabolites and approximate proportions were derived for DEGHE: 2-(2-(hexyloxy)ethoxy)acetic acid (60 – 80%), diethylene glycol (5 - 15%), EGHE (negligible), 2-(2-,3- or 4- hydroxyhexyloxyethoxy)ethanol (approx. 12%), and DEGHE conjugates, principally glucuronide (5 - 15%). Detoxification and elimination are achieved by alcohol dehydrogenase and conjugation to glutathione (ECHA Dissemination, 2019b; OECD, 2005).

DEGBE or EGHE and their metabolites are mainly excreted in urine and only small amounts were found in exhaled breath or faeces (ECHA Dissemination, 2019b; OECD, 2005). In case of DEGBE 97% of dermally absorbed substance was excreted during 24 hours in rats. After dermal uptake the half-lives of EGHE were 29 hours in rats and 39 hours in rabbits. For DEGHE similar half-lives are expected (ECHA Dissemination, 2019a).

2.5 Health effects

2.5.1 Sensory irritation and local effects

No human data are available.

Signs of irritation (oedema) were observed after occlusive treatment with DEGHE for 4 hours in six rabbits (Ballantyne and Myers, 1987; ECHA Dissemination, 2019b). However, skin contact for a longer time period may cause severe irritation (Cragg, 2012).

In eye irritation tests with rabbits (n=6) DEGHE was severely irritating and caused corneal injuries (Ballantyne and Myers, 1987; ECHA Dissemination, 2019b).

A local lymph node assay in mice (according to OECD 429, reliability 1) did not reveal a dermal sensitising potential of DEGHE (ECHA Dissemination, 2019a).

2.5.2 Repeated dose toxicity

There is no data available for effects after repeated exposure of humans against DEGHE. Animal studies only report data for repeated oral and dermal exposure to DEGHE.

In a combined repeated dose toxicity study with a reproduction/developmental toxicity screening test (according to OECD 422 and GLP, reliability 1) CD rats (12 M + 12 F/ group) were orally exposed to 0, 100, 300, and 1000 mg DEGHE/(kg bw x d) in diet for 33 days (males) or 39 – 52 days (females) including 14 days prior to breeding (ECHA Dissemination, 2019b). No overt signs of toxicity or mortalities were observed. In the highest dose group body weights were slightly decreased for males (not statistically significant) and statistically significantly decreased in females on test day 14, throughout gestation and lactation. Bodyweight gains of dams in the highest test dose were significantly decreased during gestation. In the highest dose group the feed consumption was statistically reduced in males and females during the pre-breeding period and in females during gestation. Males and females of the highest test dose had treatment-related increases in relative liver weight and histopathological findings (males: slight periportal hepatocyte hypertrophy, females: slight panlobular hepatocyte hypertrophy). Treatment-related increases in serum alanine transaminase (ALT) and alkaline phosphatase (ALP) activities were observed in females of the highest test dose. Further findings in females

observed in the highest test dose were slightly increased blood urea nitrogen and decreased absolute thymus weights and in males decreased urine pH and increased relative kidney weights. Based on liver and body weight effects observed in the highest tested dose, a NOAEL of 300 mg/(kg bw x d) was derived in the registration dossier (ECHA Dissemination, 2019b).

The repeated dermal exposure to 0, 100, 300 or 1000 mg DEGHE/(kg bw x d) for 6 hours/day and nine days (daily for 5 days and after a 2-day rest period for 4 more consecutive days) caused no toxicity in rabbits, but led to skin irritation and dermatitis (ECHA Dissemination, 2019b). The documentation was considered as insufficient for assessment (no guideline followed, reliability 4) (ECHA Dissemination, 2019a).

Read-across:

Fischer 344 rats (20 M + 20 F/group) were exposed to a vapour of 0, 20, 41, or 71 ppm **EGHE** (whole body) for 6 h/d, 5 d/week for 14 weeks (similar to OECD 413 and GLP, reliability 1). No mortalities were observed. Urogenital wetness in males of the highest test concentration was observed and a concentration-dependency for this effect in females of all exposed groups, as well as lying on the side during exposure in animals of the highest test concentration from week 9 onwards until end of exposure. Body weight gains were statistically decreased in males (highest test concentration) and females (mid and highest test concentration). Food consumption was statistically increased in males at the end of treatment period and in females of the highest test concentration at the end of treatment and during the recovery period. At the end of the exposure period, decreases in transaminases (aspartate transaminase and ALT) and sorbitol dehydrogenase were observed, and an increase in ALP and at the end of the recovery period a statistically significant increase in gamma-glutamyl-transferase in females of the highest test concentration. In both sexes the absolute and/or relative kidney and liver weights were statistically significantly increased in the highest test concentration and to a lesser degree (not statistically significant) in the mid test concentration. Gross pathology and histopathology observed no effects. A NOAEC of 41 ppm was derived in the registration dossier (ECHA Dissemination, 2019a).

A subchronic inhalation toxicity study (similar to OECD 413 and GLP, reliability 1) was conducted with Wistar rats (10 M + 10 F/group), which were exposed to **DEGBE** vapour at 0, 2, 6, or 14 ppm (13, 40, 94 mg/m^3, whole body) for 6 h/d, 5 d/w for 90 days (ECHA Dissemination, 2019b; SCOEL, 2002). Satellite recovery groups were included for all concentration groups. The highest test concentration was the maximum concentration that could be tested (effective saturated vapour pressure for a dynamic atmosphere). No mortalities were observed. Single findings in clinical signs, body weight (gain) changes, haematology, clinical chemistry, and urinalysis were considered as spontaneous findings unrelated to exposure. No adverse effects were observed in any of the concentration groups. The highest concentration group of the recovery group had a significant increase in absolute and relative liver weights (15 and 8% respectively, males only) and relative testes and female lung weight (both ca. 10%). These findings were not considered as treatment-related. Therefore a NOAEC of 14 ppm (94 mg/m^3) was derived in the registration dossier (ECHA Dissemination, 2019b). Prior to the subchronic study a subacute inhalation toxicity study with **DEGBE** (0, 2, 6, or 18 ppm, similar to OECD 412 and GLP, reliability 1) was conducted, in which liver effects in females (statistically significant increase in relative liver weight (6%, highest concentration group females), paleness of liver (highest concentration group females) and hepatocyte vacuolisation consistent with fatty change (all concentration groups females)) were observed. These liver effects were considered as an adaptive response and were not confirmed in the subchronic study.

In two additional subacute studies, a 2-week long exposure to **DEGBE** led in rats to lung effects (perivascular and peribronchial infiltrates) from 100 mg/m^3 (vapour) onwards. The observed lung effects in subacute studies at 100 mg/m^3 were not seen in the subchronic study at 94 mg/m^3 (SCOEL, 2002).

SCOEL and the MAK commission based their derivation of an OEL or MAK value for DEGBE on the above mentioned subchronic study (Greim, 2008; SCOEL, 2002). SCOEL derived a NOEL of 94 mg/m^3 for the subchronic study, which also protects from lung effects seen in subacute studies (SCOEL, 2002).

2.5.3 Genotoxicity and carcinogenicity

Genotoxicity

In vitro, DEGHE was not mutagenic in bacterial mutation assays tested with and without exogenous metabolic activation system (S9 mix from rat liver) in all tested strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, TA1538). The negative and positive controls were valid and the study was considered reliable without any restrictions (Ballantyne and Vergnes, 2001; ECHA Dissemination, 2019b).

In mammalian cells, DEGHE did not lead to a significant increase in gene mutations in CHO cells or increased DNA damage in a sister chromatid exchange assay with and without exogenous metabolic activation system compared to controls (Ballantyne and Vergnes, 2001; ECHA Dissemination, 2019b).

In vivo, DEGHE did not induce chromosome aberrations in bone marrow of rats. Furthermore, DEGHE was also not clastogenic in a micronucleus test in mice up to a dose of 600 mg/kg bw (Ballantyne and Vergnes, 2001; ECHA Dissemination, 2019b).

Carcinogenicity

No data are available for this endpoint, including the registration dossiers for the read-across substances EGHE and DEGBE according to ECHA dissemination database or the SCOEL recommendation for DEGBE (ECHA Dissemination, 2019b; SCOEL, 2002).

2.5.4 Toxicity to reproduction

There are no studies available with inhalation exposure to DEGHE.

Fertility

In a subchronic oral toxicity study (OECD 422, reliability 1) with CD rats (see chapter 2.5.2), no effects on fertility, reproduction or offspring were observed up to 1000 mg/(kg bw x d), the highest dose tested (ECHA Dissemination, 2019b).

Read-across:

In a one-generation study (similar OECD 415, reliability 2) CD rats (25 M + 25 F/group) received 0, 250, 500 or 1000 mg DEGBE/(kg bw x d) by gavage for 60 days (males) or for 2 week premating until GD13 in case of scheduled sacrifice or until weaning of offsprings (females). The mating was conducted with an untreated animal (cross-over design). No adverse effects or signs of reproduction toxicity were observed in treated males or females. A reduction in pup weight gain was statistically significant in the highest tested dose group of exposed dams on GD 14. The finding was not considered toxicologically relevant, due to its occurrence at a single time point (only on GD14, not GD4 or 21) and not in pups of males exposed to the highest dose. In the registration dossier the NOAELs for parental, reproduction, and F1 toxicity were 1000 mg/(kg

bw x d), respectively (ECHA Dissemination, 2019b). A NOEL of 1000 mg/(kg bw x d) for parental animals is given in the SCOEL recommendation (SCOEL, 2002).

A one-generation study (similar OECD 415, reliability 2) was performed with DEGBE in Wistar rats (25 M + 25 F/group). Animals were exposed to 0 or 1000 mg DEGBE/(kg bw x d) in drinking water for 10 weeks (males) or 9 weeks (females). Additionally, satellite groups for the analysis of clinical chemistry, haematology, and oxidative stress markers were exposed to 250 or 500 mg DEGBE/(kg bw x d). Reproductive parameters up to the maximum tested dose of 1000 mg/(kg bw x d) were not adversely affected. Organ weights were treatment-relatedly affected in males (relative spleen weight, absolute kidney weight) at 500 mg/(kg bw x d) and in females (absolute spleen, kidney, thyroid and pituitary gland) at 250 mg/(kg bw x d) (no further information available). As histopathological findings (cell proliferation in the spleen red pulp and partial disappearance of the lymph nodules) were observed in females at 1000 mg/(kg bw x d). Statistically significant differences in haematological parameters, clinical chemistry parameters and some markers of oxidative stress between exposed and control groups, but without a manifesting adverse health effect were observed. The derived NOAELs for parental toxicity and reproduction in the registration dossier were 250 and 1000 mg/(kg bw x d), respectively (ECHA Dissemination, 2019a).

In a fertility study (not according to OECD guideline, reliability 2) 15 female Wistar rats were exposed to 0, 250, 500 or 1000 mg DEGBE/(kg bw x d) by gavage, 5 d/w for 8 weeks. Up to the maximum tested dose of 1000 mg/(kg bw x d) no effects on reproductive parameters (e.g., oestrous cycle) were observed. Five mortalities occurred in the high exposure group, thereby all animals had dark livers at necropsy and hyperkeratosis in forestomach. Furthermore, high dose animals revealed reduced body weight gain and adverse clinical observations (e.g., inactivity, dyspnoea, blood on nose and mouth). In the registration dossier a NOAEL for reproductive toxicity of 1000 mg/(kg bw x d), based on no effects on oestrous cycle, was derived. No NOAEL was derived for maternal toxicity (ECHA Dissemination, 2019a).

Development

No data on DEGHE is available.

Read-across:

Female mated Fischer 344 rats (25 animals/group) were exposed to aerosol atmospheres of 0, 20, 40, or 85 ppm EGHE on 6 h/d during GD 6-15 and evaluated for maternal and developmental toxicity after delivery on GD20 or natural delivery (similar OECD 414, reliability 1). No treatment-related effects were observed on any of the embryonal and fetal parameters evaluated up to the maximum tested dose. Toxicity in dams was observed (treatment-related clinical signs, increased water consumption, decreased food intake at 85 ppm and significant decreased body weight gain at 40 and 85 ppm, NOEC = 20 ppm) (ECHA Dissemination, 2019a).

In a prenatal developmental toxicity study (similar OECD 414, reliability 1) mated female Wistar rats received 0.04, 0.2, or 1% DEGBE in diet (equivalent to 25, 115 or 633 mg DEGBE/(kg bw x d)) from gestation day 0 to 20. Neither significant signs of maternal nor developmental toxicity were observed up to the maximum tested dose of 633 mg DEGBE/(kg bw x d) (ECHA Dissemination, 2019b; SCOEL, 2002).

2.5.5 Odour perception

The odour of DEGHE has been described as mild at ambient temperature (ECHA Dissemination, 2019b; IFA, 2019a). No data on an odour threshold is available.

2.6 Evaluation

2.6.1 Existing regulations and classifications

DEGHE is classified for acute toxicity category 4 * (H312, * = minimum classification) and eye damage category 1 (H318) (harmonised classification according to ECHA C&L Inventory, 2019).

In 2013, an EU-LCI value of 670 µg/m³ was ascribed for the read-across substance DEGBE. This EU-LCI values is based on the German NIK value. The NIK value was set by adopting the EU OEL value of 67.5 mg/m³ (10 ppm), which was derived by SCOEL from a subchronic inhalation study in rats (NOEL = 94 mg/m³ (15 ppm)) (SCOEL, 2002) and applying a default factor of 100. The most critical effect for DEGBE is local irritation in lungs, which is not time- but concentration-dependent. Therefore, SCOEL set the OEL to 10 ppm, which corresponds to 67 mg/m³ (SCOEL, 2002). In Germany, an OEL value of 67 mg/m³ is also in force and the MAK commission has also derived a value of 67 mg/m³ (10 ppm) (AGS, 2018; Greim, 2008).

A NIK (Lowest Concentration of Interest) value of 740 µg/m³ is reported for DEGHE (AgBB, 2018). This value is based on the EU OEL/MAK value for DEGBE (read-across substance). The toxicologically critical endpoint for DEGBE, as well as for DEGHE, is local irritation (of eyes, mucous membranes, and lung). Molar adjustment from DEGBE to DEGHE was performed in order to derive the NIK value of DEGHE.

The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) stated a CLI value (Concentration Limite d'Intérêt) of 650 µg/m³ for DEGHE, based on the EU OEL for DEGBE, which was rounded to 650 µg/m³. The molar adjustment has not been applied(EC, 2013).

In the registration dossier of DEGHE, a DNEL of 4.1 mg/m³ for the protection of the general population via inhalation route has been derived on the basis of a subchronic inhalation toxicity study with EGHE (read-across) in rats. The NOAEC of 41 ppm (245 mg/m³) for EGHE was transformed into a NOAC for DEGHE (325 mg/m³) by considering a molar adjustment. No interspecies factor was applied by the registrant, because an increase in liver weight was regarded as an unspecific effect not significantly differing between species. Thus, only a time extrapolation factor of 2 and an interspecies factor of 10 were considered in the calculation of DNEL (ECHA Dissemination, 2019a).

An inhalation DNEL of 16.3 mg/m³ for workers is reported in the REACH registration dossier for DEGHE (ECHA Dissemination, 2019b). The DNEL is based on a subchronic inhalation toxicity study with EGHE (read-across) in rats (ECHA Dissemination, 2019b). A time factor of 2 and an intraspecies factor of 5 were considered. For interspecies differences, the registrant applied no extrapolation factor, because the increase in liver weight was regarded as an unspecific effect not significantly differing between species. For further details, see Table 13.

There are no further OELs available for DEGHE (IFA, 2019b).

Table 13: Guide values for DEGHE in air (for explanation, see text)

Guidance value Parameter/ Organisation	AgBB (2018)	ECHA Dissemination (2018)	ECHA Dissemination (2018)
Name (reference period)	NIK Value	DNEL (chronic, general population)	DNEL (chronic, workers)
Value (mg/m³)	0.74	4.1	16.3
Organ/critical effect	No critical effect	Increased liver weight	Increased liver weight
Species	rat	rat	rat
Basis	NOAEC (DEGBE): 100 mg/m³ (14 ppm)	NOAEC (EGHE): 245 mg/m³ (41 ppm) NOAEC (DEGHE): 325 mg/m³	NOAEC (EGHE): 245 mg/m³ (41 ppm) NOAEC (DEGHE): 325 mg/m³
Adjusted for cont. exposure	- Value derived using "preferred value approach" (67 mg/m³ (10 ppm) for DEGBE)	6h/24h	6h/8h, and different respiratory rates under light activity (6.7m³/10m³)
Extrapolation factors Time LOAEC to NOAEC Interspecies Intraspecies Total	 - - - - 100 (was used as default factor)	 2 - - 10 20	 2 - - 5 10

2.6.2 Derivation of an EU-LCI value

The data basis for DEGHE is very limited. However, additional data is available from a number of studies with various structurally related glycol ethers.

No data are available on the toxicity of DEGHE in humans or via inhalation in animals. In a subacute oral toxicity study according to OECD 422 DEGHE led to liver and body weight effects in the highest tested dose of 1000 mg/(kg bw x d). Therefore a NOAEL of 300 mg/(kg bw x d) was derived. After repeated dermal exposure to DEGHE no adverse systemic effects were observed in rabbits.

A subchronic inhalation study with EGHE in rats observed increased absolute and/or relative kidney and liver weights in the highest concentration tested without any findings in gross pathology or histology. Nevertheless, the mid concentration of 41 ppm was derived as a NOAEC.

Inhalation studies with DEGBE in rats only revealed a slight increase in liver weight, histological changes in females of all concentration groups, and lung effects after subacute exposure. The observed effects could not be seen after subchronic exposure.

DEGHE provided no evidence for genotoxic effects in *in vitro* assays performed in prokaryotes and mammalian cells. Furthermore, DEGHE was not clastogenic in *in vivo* tests in mice.

Carcinogenicity studies are not available for DEGHE or its read-across substances.

A few studies showed that fertility, reproduction and development of offspring was not affected by DEGHE or its read-across substances.

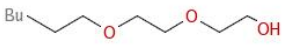
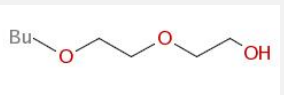
Due to the lack of inhalation toxicity data for DEGHE the inhalation data of the read-across substance, DEGBE, is considered as suitable for the derivation of an EU-LCI value for DEGHE.

The rationale for read-across with DEGBE are:

- Within the chemical class of 'diethylene glycol ethers', DEGBE is the closest homologue compound with an EU-LCI value. Two additional CH_2 groups in the aliphatic chain (see Table 14) of DEGHE are the only difference between the two substances.
- The key assumption underlying the read-across of the EU-LCI value from DEGBE to DEGHE is that both compounds have the same critical endpoint (irritation) and this is caused by the common functional group (and not by the additional CH_2 groups).
- Difference in chain length between the two homologue compounds is not larger than two CH_2 groups per aliphatic chain.

Furthermore, DEGBE was also used as a suitable read-across substance for DEGHE in assessments performed by OECD (2005) and AgBB (2012; 2018), thus supporting the applied read-across approach for the derivation of an EU-LCI value for DEGHE.

Table 14: Substance information of 2-(2-hexyloxyethoxy)-ethanol (DEGHE) and 2-(2-butoxyethoxy)ethanol (DEGBE) for deriving an EU-LCI value (ECHA Dissemination, 2019b)

Compound	Structure	Molar mass [g/mol]	EU-LCI value
2-(2-hexyloxyethoxy)-ethanol (DEGHE)		190.28	400 µg/m³ (proposed) (read-across to DEGBE)
2-(2-butoxyethoxy)ethanol (DEGBE)		162.23	Newly derived EU-LCI value according to concept of the European Commission: 335.7 µg/m³* 670 µg/m³ (Ascribed EU-LCI value, adopted 2013)

* As POD a NOEL from a subchronic inhalation study (94 mg/m³) was used. As assessment factors 2.5 (remaining interspecies differences in inhalation studies), 10 (intraspecies variance), 2 (time extrapolation from subchronic to chronic), and 5.6 (adjustment for exposure duration) were applied (total 280).

For the calculation of an EU-LCI value for DEGHE, the unrounded EU-LCI value for DEGBE (335.7 µg/m^3) was used. By applying molar adjustment, the differences in molar masses of DEGBE and DEGHE were considered, therefore the newly derived EU-LCI of DEGBE was multiplied by a factor of 1.173 (190.28 g/mol (DEGHE)/162.23 g/mol (DEGBE)) and results in an EU-LCI value for DEGHE of 393.7 µg/m^3, which is rounded to 400 µg/m^3 (see Table 14).

A higher value may be derived from a combined repeated dose and reproduction / developmental screening study with oral exposure (OECD 422) with DEGHE in which a NOAEL of 300 mg/(kg bw x d) was derived (see chapter 2.5.2), based on observed liver and body weight effects in the highest tested dose. A route-to-route extrapolation from oral to inhalation route

needs to be performed in order to derive an EU-LCI value. In accordance to ECHA guidance (2012) and under the assumption of 50% oral and 100% inhalation absorption the NOAEL was converted into a human equivalent inhalation dose of 300 mg/(kg bw x d) / 1.15 m^3/kg bw x 50% / 100% = 130.4 mg/m^3. Assessment factors of 2.5 (remaining interspecies differences in inhalation studies), 10 (intraspecies variance), and 6 (time extrapolation from subacute to chronic) were applied (total 150), resulting in a value of 0.87 mg/m^3 (= 870 µg/m^3).

The derived value of 870 µg/m^3 for DEGHE from an oral study with subacute exposure (OECD 422) is higher than the proposed EU-LCI value of rounded 400 µg/m^3 based on the read-across approach with DEGBE. Since data on DEGHE is limited (only an oral study with subacute exposure (OECD 422) is available), and the proposed EU-LCI value from a read-across approach is lower, 400 µg/m^3 is proposed as an EU-LCI for DEGHE.

An EU-LCI value (rounded) for DEGHE of 400 µg/m^3 is proposed.

DEGHE is reported to have a mild odour. However, data on odour thresholds are not available.

2.7 List of references

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2.8 Fact and data sheet for 2-(2-hexyloxyethoxy)-ethanol (DEGHE)

Table 15: Data collection sheet for 2-(2-hexyloxyethoxy)-ethanol

Compound	2-(2-Hexyloxyethoxy)-ethanol (DEGHE)	*Data collection sheet*
N° CAS 112-59-4	**EU-Classification: -**	
1 ppm = 6.732 mg/m³	**CLP:** harmonised classification, Acute Tox. 4 * (H312), Eye Dam. 1 (H318) *minimum classification	
Organisation name	AgBB	REACH registrants
Risk value name	NIK ('Lowest Concentration of Interest')	DNEL
Risk value (mg/m³)	740 µg/m³ (read-across from DEGBE)	4.1 mg/m³ (read-across from EGHE)
Reference period	Chronic (general population)	Chronic (general population)
Risk value (mg/m³) Short term (15 min)	-	-
Year	2008	2018
Key study	Study report from BASF (1992) mentioned by SCOEL (2002)	Study report from 1985 reported as „key" study for repeated dose inhalation
Study type	Inhalation study (0; 13; 40 or 94 mg/m³, whole body) with DEGBE (read-across, CAS: 112-34-5)	Inhalation study, similar OECD 413 (mean concentrations: 0, 20, 41, or 71 ppm, whole body) with EGHE (read-across, CAS: 112-25-4)
Species	Rat	Fischer 344 rats (n=20/sex/group)
Duration of exposure in key study	6 h/d, for 90 d	6 h/d, 5 d/w for 14 weeks
Critical effect	No critical effect	Increased liver weight
Critical dose value	NOEL (DEGBE): 94 mg/m³ (14 ppm)	NOAEC (EGHE): 245 mg/m³ (41 ppm) NOAEC (DEGHE): 325 mg/m³
Adjusted critical dose	Value derived using "preferred value approach"[§] is 67.5 mg/m³ (10 ppm) for DEGBE	325 mg/m³ x 6/24 = 81.25 mg/m³
Single assessment factors	EU OEL (adopted from SCOEL) /100 = 67,500 µg/m³/100 = 675 µg/m³	UF_H 10 x UF_A 1 x UF_S 2 = 20
Other effects		
Remarks	Read-across was applied and DEGBE was used as test item instead of DEGHE. The derived NIK value for DEGBE was transformed into a NIK value for DEGHE by considering a molar adjustment.	Read-across was applied and EGHE was used as test item instead of DEGHE. The NOAEC for EGHE was transformed into a NOAEC for DEGHE by considering a molar adjustment. No interspecies factor was applied by the registrant, because increase in liver weight was regarded as an unspecific effect not significantly differing between species (ECHA Dissemination, 2019)

AgBB = Ausschuss zur gesundheitlichen Bewertung von Bauprodukten

UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study

DEGBE = 2-(2-butoxyethoxy)ethanol (CAS: 112-34-5)

EGHE = ethylene glycol monohexyl ether (CAS: 112-25-4)

[§] Preferred value approach means that OELs will be rounded up or down to decimals of the integers 1, 2 or 5 ppm. For example, SCOEL recommends to use 0.05, 0.1, 0.2, 0.5, 1, 2, 5, 10 or 50 ppm and to refrain from discriminating any further, except if scientific data or reasons suggest a more specific value (SCOEL, 2013).

Table 16: Fact sheet 2-(2-butoxyethoxy)ethanol (DEGBE)

Compound	**2-(2-Butoxyethoxy)ethanol (DEGBE)**		***Factsheet***
Parameter	**Note**	Comments	Value / descriptor
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	350*
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2019
General information			
CLP-Index No.	4	INDEX	603-096-00-8
EC-No.	5	EINECS	203-961-6
CAS-No.	6	Chemical Abstract Service number	112-34-5
Harmonised CLP classification	7	Human health risk related classification	Eye Irrit. 2 (H319)
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	162.23 1 ppm = 6.732 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	Study report, BASF AG, 1992 (cited from SCOEL, 2002)
Read across compound	10	Where applicable	-
Species	11	Rat	rat
Route / type of study	12	Inhalation, oral feed, etc.	inhalation
Study length	13	Days, subchronic, chronic, etc.	Subchronic (90 d)
Exposure duration	14	h/d, d/w	6 h/d, 5 d/w
Critical endpoint	15	Effect (s), site of	No critical effect
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOEL
POD value	17	[mg/m³] or ppm or [mg/kg_{BW}×d]	94 mg/m³ (14 ppm)
Assessment factors (AF)	18		
Adjustment for exposure duration	19	Study exposure h/d, d/w	5.6
Study length	20	sa→sc→c	2
Route-to-route extrapolation factor	21	-	1
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	1
	22b	Severity of effect (R8 6d)	1
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	1
	23b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		1
Other adjustment factors Quality of database	26		1
Result			
Summary of assessment factors	27	Total Assessment Factor	280
POD/TAF	28	Calculated value [µg/m³ and ppb]	335.71 µg/m³ (53.57 ppb)
Molar adjustment factor	29		-
Rounded value	30	[µg/m³]	350
Additional comments	31		
Rationale section	32		

* newly derived EU-LCI value according to the current EU-LCI concept (EC, 2013). The current EU-LCI value of 670 µg/m³ is an ascribed EU-LCI value and was calculated by dividing the OEL with a default factor of 100.

Rationale for derivation of EU-LCI

Inhalation studies with DEGBE in rats only revealed a slight increase in liver weight, histological changes in females of all concentration groups, and lung effects after subacute exposure. These effects could not be observed after subchronic exposure. The NOEL from a subchronic inhalation study (94 mg/m³) was used as POD. As assessment factors 2.5 (remaining interspecies differences in inhalation studies), 10 (intraspecies variance), 2 (time extrapolation from subchronic to chronic), and 5.6 (adjustment for exposure duration) were applied (total 280). Thus the newly derived EU-LCI value for DEGBE is 335.71 µg/m³.

References

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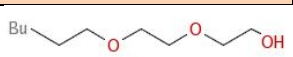
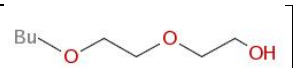
Table 17: Fact sheet 2-(2-hexyloxyethoxy)-ethanol (DEGHE)

Compound	**2-(2-Hexyloxyethoxy)-ethanol (DEGHE)**		***Factsheet***
Parameter	**Note**	Comments	Value / descriptor
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	400
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2019
General information			
CLP-Index No.	4	INDEX	603-175-00-7
EC-No.	5	EINECS	203-988-3
CAS-No.	6	Chemical Abstract Service number	112-59-4
Harmonised CLP classification	7	Human health risk related classification	Acute Tox. 4 (H312), Eye Dam. 1 (H318)
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	190.28 1 ppm = 7.83 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	2-(2-butoxyethoxy)ethanol (DEGBE)
Species	11	Rat	
Route / type of study	12	Inhalation, oral feed, etc.	
Study length	13	Days, subchronic, chronic, etc.	
Exposure duration	14	h/d, d/w	
Critical endpoint	15	Effect (s), site of	
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	
POD value	17	[mg/m³] or ppm or [mg/kg_{BW}×d]	POD/TAF from the DEGBE fact sheet: 0.335 mg/m³
Assessment factors (AF)	18		
Adjustment for exposure duration	19	Study exposure h/d, d/w	-
Study length	20	sa→sc→c	-
Route-to-route extrapolation factor	21	-	-
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	-
	22b	Severity of effect (R8 6d)	-
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	-
	23b	Kinetic + dynamic	-
Intraspecies differences	24	Kinetic + dynamic General population	-
AF (sensitive population)	25		-
Other adjustment factors Quality of database	26		-
Result			
Summary of assessment factors	27	Total Assessment Factor	
POD/TAF	28	Calculated value [µg/m³ and ppb]	335.71 µg/m³ (53.57 ppb)
Molar adjustment factor	29		1.173 (= 190.28 / 162.23)
Rounded value	30	[µg/m³] (335.71 µg/m³ x 1.173 = 393.7 µg/m³)	400

Additional comments	31		
Rationale section	32		

Rationale for read-across

- Data poor compound: no adequate toxicological data for DEGHE; *de novo* derivation of EU-LCI for DEGHE is not possible.
- Read-across from EU-LCI value of DEGBE (adopted in 2013): within the chemical class 'diethylene glycol ethers', DEGBE is the closest homologue compound with an EU-LCI value. Two additional CH_2 groups in the aliphatic chain of DEGHE are the only difference between the two substances.
- Toxicological critical endpoint for DEGBE: irritation of eyes and mucous membranes. These local effects cannot be detected by route-to-route extrapolation, which speaks in favour of a read-across approach from an inhalation study.
- The key assumption underlying the read-across of the EU-LCI value from DEGBE to DEGHE is that both compounds have the same critical endpoint (irritation) and this is caused by the common functional group (and not by the additional CH_2 groups). Furthermore, DEGBE was also regarded as a suitable read-across substance for DEGHE in assessments performed by OECD (OECD SIDS, 2005) and AgBB (2012, 2018), thus supporting the applied read-across approach for the derivation of an EU-LCI value for DEGHE.

Compound	Structure	Molar mass [g/mol]	EU-LCI value
2-(2-hexyloxyethoxy)-ethanol (DEGHE)		190.28	(read-across to DEGBE) *Rounded value: 400 µg/m³*
2-(2-butoxyethoxy)ethanol (DEGBE)		162.23	Newly derived EU-LCI value according to concept of the European Commission: 335.7 µg/m³ 670 µg/m³ (Ascribed LCI value, adopted 2013)

- EU-LCI value for DEGBE derived by applying default assessment factors: 335.7 µg/m³ to be used for read-across for calculating the EU-LCI of DEGHE.
- No cut-off rule in place: difference in chain length between the two homologue compounds is not larger than two CH_2 groups per aliphatic chain.
- When applying the EU-LCI value for DEGBE of 335.7 µg/m^3 and performing MW conversion: EU-LCI of DEGBE = 335.7 µg/m³ x 1.173 = 393.7 µg/m³ is rounded to 400 µg/m³.

Comparison of proposed EU-LCI with a derived EU-LCI value from a subacute oral study

In the registration dossier of DEGHE a combined repeated dose and reproduction / developmental screening study is described (according to OECD 422 and GLP) as key study for repeated oral exposure (ECHA, Dissemination 2019). Rats (n=12/sex/dose) were exposed to 0, 100, 300, or 1000 mg DEGHE/(kg bw x d) in diet for in total 33 d (males) or 39 – 52 d (females). Based on liver and body weight effects observed in the highest tested dose, a NOAEL of 300 mg/(kg bw x d) was derived. For deriving an EU-LCI value, a route-to-route extrapolation from oral to inhalation route needs to be performed. In accordance to ECHA guidance (2012) and under the assumption of 50 % oral and 100 % inhalation absorption the NOAEL was converted into a human equivalent inhalation dose of 300 mg/kg bw/d / 1.15 m³/kg bw x 50% / 100% = 130.4 mg/m³. Assessment factors of 2.5 (remaining interspecies differences in inhalation studies), 10 (intraspecies variance), and 6 (time extrapolation from subacute to chronic) were applied (total 150), resulting in a value of 0.87 mg/m³ (= 870 µg/m³).

The derived value of 870 µg/m³ for DEGHE from an oral study with subacute exposure (OECD 422) is higher than the proposed EU-LCI value of 400 µg/m³ based on read-across approach with DEGBE and applying default assessment factors. The value derived in this way therefore protects against systemic effects of DEGHE when comparing the derived values, since route-to-route extrapolation results in a higher LCI. Thus, the proposed EU-LCI value for DEGHE is 400 µg/m³.

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3 Toxicological evaluation of 1-propenylbenzene as basis for the derivation of an EU-LCI value

(Note: 1-propenylbenzene (ß-methylstyrene) is a data-poor compound. Read-across is performed for most of the substance effects to its structural isomer 2-phenylpropene (α-methylstyrene). An EU-LCI report with data and fact sheets including the derivation of an EU-LCI value has been prepared (Voss, 2018). Brief summaries of the results for the read-across compound are presented here. For more detailed information on the read-across compound the reader is referred to the mentioned report.)

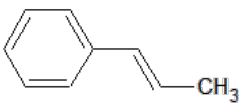
3.1 Substance identification

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

The substance may occur as two isomers: cis- and trans- 1-propenylbenzene. However, no physicochemical or toxicological data could be identified for the cis-isomer. If not explicitly stated otherwise, data presented in this report refer to the trans-isomer of 1-propenylbenzene.

1-Propenylbenzene (ß-methylstyrene) is a pale yellow liquid with an annoying odour. It is a by-product in the synthesis of 2-phenylpropene (α-methylstyrene) and may be present as an impurity in 2-phenylpropene. 1-phenylpropene occurs in two isomeric forms (cis and trans) (WHO, 2017).

Table 18: Substance identification of 1-propenylbenzene

CAS-No. EU-No. CLP-Index-No.	Systematic name, common names	Summary formula	Structural formula
CAS-No. 637-50-3 (cis) CAS-No. 873-66-5 (trans) EU-No. 211-287-9 (cis) EU-No. 212-848-0 (trans)	1-propenylbenzene, ß-methylstyrene	C_9H_{10}	

3.2 Substance properties and uses

The substance may be present as an impurity in 2-phenylpropene (about 0.5 % by weight) (HSDB, 2002). No data on the use of this substance could be identified in the available literature.

Table 19: Physicochemical properties of 1-propenylbenzene (IFA, 2019a; WHO, 2017)

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa) (at 25°C)	Density (g/cm³)	log Pow	Solubility in water (g/L) (at 20°C)
118.18	-27 °C*	172 – 173 °C*		0.91*	3.35*	near insoluble* 0.014 g/100 ml

* Data for trans-isomer. No data for the cis-isomer were available.

3.3 Exposure

3.3.1 Indoor air

There are no data available.

3.3.2 Other sources

There are no data available.

3.4 Toxicokinetics

Few data are available on the toxicokinetics of this compound. In a study with rats, cinnamyl alcohol was identified in urine metabolite of 1-propenylbenzene. This alcohol may be formed by hydroxylation of the methyl group (Peele and Oswald, 1977). Cinnamyl alcohol may be further oxidised but no further information on the toxicokinetics of 1-propenylbenzene could be identified in the available literature.

Read-across: 2-phenylpropene

Systemic effects observed after inhalation or oral exposure show that the substance is absorbed via these pathways. However, no reliable quantitative data are available. It was reported that about two thirds of the vapour was retained in the respiratory tract of humans during an 8 h inhalation (ECHA Dissemination, 2018). For structurally related compounds (C_9-C_{15} alkylbenzenes) uptake of 50-70% was reported in studies with humans (Ad-hoc AG, 2012).

The distribution, metabolism, and excretion of 2-phenylpropene was studied in male F344 rats after intravenous administration of ^{14}C-labelled 2-phenylpropene (11 mg/kg bw) and also from limited additional experiments with inhalation (300 or 900 ppm, 6 h, nose only) and oral exposure (1000 mg/kg bw) (De Costa et al., 2001; DFG, 2004; ECHA Dissemination, 2018; NICNAS, 2017). 2-Phenylpropene was rapidly eliminated. 72 h after administration, only 0.3% of the administered activity was still present in tissues, the highest values were observed in spleen, followed by kidney, bladder, lung, liver, heart and skin and adipose tissue. The lowest values were found in muscle, testis and brain. The elimination half-life of 2-phenylpropene was calculated to be 3-5 h after inhalation exposure (De Costa et al., 2001). Depletion of hepatic glutathione was observed in another study after inhalation exposure of rats to 2-phenylpropene (Morgan et al., 1999). About 76 % of the administered activity was excreted in urine within 24 h and about 90% in 72 h, only small amounts were excreted in faeces and breath (1-3%) (De Costa et al., 2001).

3.5 Health effects

3.5.1 Acute toxicity, sensory irritation and local effects

1-Propenylbenzene is reported to be irritating to skin, eyes, and mucous membranes (WHO, 2017). Without details, an oral LD50 value of 3600 mg/kg bw has been reported for rats (IFA, 2019a). No further data were identified in the available literature.

Read-across: 2-phenylpropene

In a study with human volunteers, subjects briefly exposed to 2-phenylpropene reported no response to the odour below 10 ppm (49 mg/m^3). At 50 ppm (245 mg/m^3), the odour was detectable, but no mucous membrane irritation was noted by the subjects. At 100 ppm (490

mg/m^3), the odour was strong, but considered as tolerable, at 200 ppm (975 mg/m^3), the odour became strong and objectionable, and slight eye irritation was noted. At ≥ 600 ppm (2920 mg/m^3), the subjects noted a very strong odour and strong eye and nasal irritation (Wolf et al., 1956).

An RD_{50} of 273 ppm (1330 mg/m^3) is reported for Swiss mice (no details available) (DFG, 2004).

3.5.2 Repeated dose toxicity

There are no data available for effects following repeated exposure of humans or animals against 1-propenylbenzene, except for the following observation:

Some aromatic solvents are known to cause ototoxicity in rats. A comparison of the ototoxicity of 21 different compounds was performed by Gagnaire and Langlais (2005). Sprague-Dawley rats were exposed by gavage to 8.47 mmol/(kg bw x d) of the test compound trans-1-propenylbenzene for 5 d/week for 2 weeks (i.e. 1000 mg/(kg bw x d)). Eight compounds including 1-propenylbenzene, 2-phenylpropene and styrene showed some ototoxicity as seen in morphological investigations of the cochlea. However, 1-propenylbenzene and 2-phenylpropene (together with toluene) were the least active compounds tested in this assay (Gagnaire and Langlais, 2005).

Read-across: 2-phenylpropene

The critical effect of 2-phenylpropene inhalation in animal experiments is respiratory tract irritation. In a chronic inhalation study with rats (50 M + 50 F/concentration, 0, 100, 300 or 1000 ppm 2-phenylpropene (0, 487, 1460 or 4870 mg/m^3), 6 h/d, 5 d/week for a total of 105 weeks), incidences of basal cell hyperplasia were significantly increased in all exposed groups of males and females, and the incidences of degeneration of the olfactory epithelium were increased in 1470 mg/m^3 (300 ppm) females and 4900 mg/m^3 (1000 ppm) males and females. No olfactory epithelial degeneration was observed in rats at 490 mg/m^3 (100 ppm). In the parallel study with mice, the incidences of olfactory epithelial metaplasia and hyperplasia of the glands overlying the olfactory epithelium were significantly increased in all exposed groups of males and females. In addition, atrophy of the olfactory epithelium was significantly increased in 300 and 600 ppm males. Increased incidences of exposure-related nasal lesions, including atrophy and hyperplasia of Bowman's glands and atrophy and metaplasia of the olfactory epithelium, were also observed in all exposed groups of male and female mice after subchronic inhalation for 14 weeks (LOAEC: 368 mg/m^3, 75 ppm). No nasal epithelial lesions were observed in rats after subchronic inhalation at concentrations ranging from 368 to 4900 mg/m^3 (75 -1000 ppm) (NTP, 2007).

In the study with chronic exposure, renal tubule lesions and an increased incidence of renal tubule tumours in male rats were also observed. This effect is related to the α2u-globulin associated nephropathy in male rats and is not relevant for risk assessment in humans. Similarly, the observed increased incidence of hepatocellular tumours in the used strain of mice is considered not relevant for risk assessment. No increased incidences of neoplastic lesions were observed in the nasal epithelia of rats and mice (NTP, 2007).

3.5.3 Genotoxicity and carcinogenicity

Genotoxicity

Read-across: trans-1-propenylbenzene epoxide

The epoxide of trans-1-propenylbenzene, which is expected to be formed by the oxidative metabolism of 1-propenylbenzene, was tested for mutagenicity in bacteria and for the induction of sister chromatid exchanges (SCE) in cultured human lymphocytes. This epoxide was not mutagenic in bacteria. It increased the rate of SCE formation but not of gene mutations in mammalian cells (IFA, 2019a; Norppa and Vainio, 1983).

Read-across: 2-phenylpropene

In vitro, 2-phenylpropene was not mutagenic in several bacterial mutation assays with and without exogenous metabolic activation system. In mammalian cells, the substance did not induce mutations or chromosomal aberrations with and without metabolic activation. 2-phenyl-propene induced sister chromatid exchanges (SCE) in the presence but not in the absence of metabolic activation. A further study in human lymphocytes showed a weakly positive result (increase of SCE less than twofold) (ECHA Dissemination, 2018).

In vivo, inhalation exposure of mice with up to 1000 ppm (4900 mg/m^3) 2-phenylpropene for 13 weeks did not induce micronuclei in erythrocytes in peripheral blood. A significant increase in micronucleated normochromatic erythrocytes (NCE) was observed in female mice at the highest exposure concentration. 2 of the 10 female mice died at this concentration indicating that the exposure was in the lethally toxic range. No increase in micronucleated polychromatic immature erythrocytes (PCE) was observed in males or females, indicating that the observed effect in NCE was reflective of long-term accumulation of damage and was not detectable immediately after exposure by analysing PCE (ECHA Dissemination, 2018; NTP, 2007).

Carcinogenicity

No data are available for this endpoint for 1-propenylbenzene.

Read-across: 2-phenylpropene

Accumulation of hyaline droplets in renal tubules, renal tubule lesions and, after chronic exposure, an increased incidence of renal tubule tumours were observed in male F344 rats exposed to 2-phenylpropene (Morgan et al., 1999; NTP, 2007). This effect is related to the α2u-globulin associated nephropathy in male rats and is not relevant for risk assessment in humans (Swenberg and Lehman-McKeeman, 1999). Similarly, the observed increased incidence of hepatocellular tumours in the used strain of mice (NTP, 2007) is generally considered not relevant for risk assessment (Voss, 2018).

3.5.4 Toxicity to reproduction

There are no studies available with exposure to 1-propenylbenzene.

Read-across: 2-phenylpropene

A combined repeated dose toxicity study with the reproduction/developmental toxicity screening test (according to OECD Guideline 422) was performed with Sprague-Dawley rats (ECHA Dissemination, 2018). The animals were exposed to 0, 40, 200 or 1000 mg/(kg bw x d) of 2-phenylpropene by gavage from 14 d prior to mating for a total of 43 d (M) or (F), including the mating period, until day 3 of lactation. Parental toxicity was observed at the highest and at the mid-dose. The test substance had no effects on any reproductive parameter, but two dams at the highest dose lost all their offspring during the lactation period. Neonates from the highest dose group showed a decrease of body weight and a slightly lower viability index on PND 4 due to the

total litter losses of the two dams. No significant differences in other developmental parameters or on clinical signs, body weight gain after birth or at necropsy were observed in the offspring.

A LOAEL for repeated dose toxicity of 200 mg/(kg bw x d) can be derived from this study (NOAEL 40 mg/(kg bw x d)). For reproductive and developmental toxicity, a LOAEL of 1000 mg/(kg bw x d) can be derived (NOAEL 200 mg/(kg bw x d)).

3.5.5 Odour perception

The substance is reported to have an annoying odour. However, no data on the odour threshold are available for 1-propenylbenzene.

Read-across: 2-phenylpropene

2-phenylpropene and also styrene have a very annoying odour which can be detected at very low concentrations. It may be expected that the odour of 1-propenylbenzene may also be detected at low concentrations.

3.6 Evaluation

3.6.1 Existing regulations and classifications

There is no harmonised classification for 1-propenylbenzene (ECHA C&L Inventory, 2019). There were no OELs available for 1-propenylbenzene (IFA, 2019b). Furthermore, no other existing guide values for 1-propenylbenzene in air were identified in the available literature except for a NIK value reported by AgBB (AGBB, 2018). However, no substance-specific data were used. Instead, the NIK-value for 1-propenylbenzene is based on read-across using data and the EU-LCI value for 1-phenylpropene.

3.6.2 Derivation of an EU-LCI value

The data basis for 1-propenylbenzene (ß-methylstyrene) is very limited. Additional data can be obtained by read-across from studies with 2-phenylpropene (α-methylstyrene).

No data are available on the toxicity of 1-propenylbenzene in humans or via inhalation in animals. A study comparing the ototoxicity of several alkyl and alkenyl benzenes after oral administration of rats indicated that the ototoxicity of 1-propenylbenzene was as low as that of 2-phenylpropene and the lowest of all studied compounds which showed at least some activity (Gagnaire and Langlais, 2005).

1-propenylbenzene epoxide was mot mutagenic in bacteria or mammalian cells but induced SCE in the latter (IFA, 2019a; Norppa and Vainio, 1983).

The critical effect of 2-phenylpropene inhalation in animal experiments is respiratory tract irritation. In a chronic inhalation study with rats, a LOAEC of 100 ppm for increased incidences of basal cell hyperplasia was obtained for rats. In mice, the incidences of olfactory epithelial metaplasia and hyperplasia of the glands overlying the olfactory epithelium were also significantly increased (NTP, 2007). Renal tubule lesions and an increased incidence of renal tubule tumours in male rats were also observed. This effect is related to the α2u-globulin associated nephropathy in male rats and is not relevant for risk assessment in humans. Similarly, the observed increased incidence of hepatocellular tumours in the used strain of mice is considered not relevant for risk assessment. No increased incidences of neoplastic lesions were observed in the nasal epithelia of rats and mice (NTP, 2007).

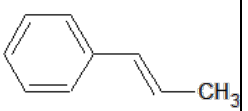
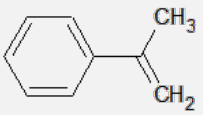
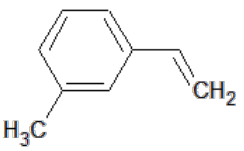
From a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test with Sprague-Dawley rats, a NOAEL for repeated dose toxicity of 40 mg/(kg bw x d) can be derived. For reproductive and developmental toxicity, a NOAEL of 200 mg/(kg bw x d) can be derived for 2-phenylpropene (ECHA Dissemination, 2018).

Due to the lack of toxicity data for 1-propenylbenzene, the inhalation data of the read-across substance, 2-phenylpropene, are considered as suitable for the derivation of an EU-LCI value for 1-propenylbenzene.

The rationale for read-across with 2-phenylpropene are:

- Within the chemical class of propenylbenzenes, 2-phenylpropene is the closest homologue compound with an EU-LCI value. Both compounds are structural isomers with the same molar mass differing only in the position of the methyl group in the side-chain.
- It is noted that both compounds differ in that 1-propenylbenzene has a straight alkenyl side-chain while that of 2-phenylpropene is branched. This may affect the metabolism and the toxicity of these compounds. However, the key assumption underlying the read-across of the EU-LCI value from 2-phenylpropene to 1-propenylbenzene still holds that both compounds will have the same critical endpoint (irritation) caused by the similar structure. This assumption is further strengthened by the observation that vinyltoluenes, structurally related isomers of 2- and 1-phenylpropene with an unbranched side-chain, also lead to similar lesions of the nasal epithelia of rats, and that a numerical identical EU-LCI value as for 2-phenylpropene was also proposed and adopted for vinyl toluenes (EU-LCI Working Group, 2018; Voss, 2018). Moreover, the same approach was followed in the derivation of a NIK value for 1-phenylpropene by the AgBB (2018).

Table 20: Substance information for 1-propenylbenzene and 2-phenylpropene

Compound	Structure	Molar mass [g/mol]	EU-LCI value
1-propenylbenzene, ß-methylstyrene		118.2	1200 µg/m³ (read-across to 2-phenylpropene)
2-phenylpropene, α-methylstyrene		118.2	1200 µg/m³ (derived EU-LCI value*, adopted 2018) (EU-LCI Working Group, 2018)
m-vinyl toluene (3-methyl-styrene) (one of three isomers differing only in the position of the ring methyl group)		118.2	1200 µg/m³ (all isomers) (derived EU-LCI value*, adopted 2018) (EU-LCI Working Group, 2018)

* As POD a LOAEC of 100 ppm (490 mg/m³) from a chronic inhalation study with rats was used. As assessment factors 3 (extrapolation of a NAEC from a LOAEC), 2.5 (remaining interspecies differences in inhalation studies), 10 (intraspecies variance), and 5.6 (adjustment for continuous exposure duration) were applied (total 420) (Voss, 2018).

As 1-propenylbenzene is a structural isomer of 2-phenylpronene, both compounds share the same molar mass. Thus, the molar adjustment factor is 1 leading to a proposed EU-LCI value for 1-propylene benzene of 1200 µg/m³.

An EU-LCI value for 1-propenylbenzene of 1200 µg/m³ is proposed.

1-propenylbenzene is reported to have an annoying odour. However, data on odour thresholds are not available.

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3.8 Fact and data sheet for 1-propenylbenzene (ß-methylstyrene)

Table 21: Data collection sheet 1-propenylbenzene (ß-methylstyrene)

Compound	1-Propenylbenzene	*Data collection sheet*
N° CAS 637-50-3 (cis) **N° CAS 873-66-5 (trans)** 1 ppm = 4.9 mg/m³	**EU-Classification:** **CLP:** -	
Organisation name	AgBB	
Risk value name	NIK ('Lowest Concentration of Interest')	
Risk value (mg/m³)	1.2 mg/m³	
Reference period	Chronic (general population)	
Risk value (mg/m³) Short term (15 min)	-	
Year	2018	
Key study	NTP (2007)	
Study type	Chronic inhalation study (0, 100, 300, 1000 ppm) with 2-phenylpropene	
Species	Rat	
Duration of exposure in key study	6 h/d, 5 d/week, 105 weeks	
Critical effect	Lesions of nasal olfactory epithelium	
Critical dose value	LOAEC (2-phenylpropene): 490 mg/m³ (100 ppm)	
Adjusted critical dose	6/24 x 5/7 => 87.5 mg/m³	
Single assessment factors		
Other effects		
Remarks	Read-across was applied and α-methylstyrene (2-phenylpropene) was used as test item instead of 1-phenylpropene. No molar adjustment is necessary because both compounds are structural isomers with the same molar mass.	
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study UF_D data deficiencies		

Table 22: Fact sheet 2-propenylbenzene (2-phenylpropene, α-methylstyrene) (Voss, 2018)

Compound	**2-Phenylpropene**		***Factsheet***
Parameter	**Note**	Comments	Value / descriptor
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m³]	1200
EU-LCI status	2	Draft/Final	Final
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2018
General information			
CLP-Index No.	4	INDEX	601-027-00-6
EC-No.	5	EINECS	202-705-0
CAS-No.	6	Chemical Abstract Service number	98-83-9
Harmonised CLP classification	7	Human health risk related classification	Eye Irrit. 2 (H319); STOT SE 3 (H335)
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	118.2 1 ppm = 4.9 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	NTP (2007)
Read across compound	10	Where applicable	
Species	11	Rat	Sprague-Dawley rats and B6C3F1 mice
Route / type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic, etc.	Chronic (2 years)
Exposure duration	14	h/d, d/w	6 h/d, 5 d/week
Critical endpoint	15	Effect (s), site of	Lesions of nasal olfactory epithelium
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	LOAEC
POD value	17	[mg/m³] or [ppm] or [mg/kg_{BW}×d]	490 mg/m³ (100 ppm)
Assessment factors (AF)	18		
Adjustment for exposure duration	19	Study exposure h/d, d/w	5.6
Study length	20	sa→sc→c	1
Route-to-route extrapolation factor	21		1
Dose-response	22a	Reliability of dose-response, LOAEL to NAEL	3
	22b	Severity of effect (R8 6d)	1
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	1
	23b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		1
Other adjustment factors Quality of database	26		1
Result			
Summary of assessment factors	27	Total Assessment Factor	420
POD/TAF	28	Calculated value [µg/m³ and ppb]	1166 µg/m³ and 240 ppb
Molar adjustment factor	29		
Rounded value	30	[µg/m³]	1200
Additional comments	31		
Rationale section	32		

Rationale for critical effects

In a study with human volunteers, brief exposures to a concentration of 975 mg/m³ (200 ppm) was reported to have an unpleasant odour and to cause eye irritation, higher concentrations also caused strong nasal irritation. No irritation was reported at 245 mg/m³ (50 ppm), but the odour is detectable below 5 mg/m³ (1 ppm).

The critical effect of 2-phenylpropene inhalation is respiratory tract irritation. In a chronic inhalation study with rats (50 M + 50 F/concentration, 0, 100, 300 or 1000 ppm 2-phenylpropene (0, 487, 1460 or 4870 mg/m³), 6 h/d, 5 d/week for a total of 105 weeks), incidences of basal cell hyperplasia were significantly increased in all exposed groups of males and females, and the incidences of degeneration of the olfactory epithelium were increased in 1470 mg/m³ (300 ppm) females and 4900 mg/m³ (1000 ppm) males and females. No olfactory epithelial degeneration was observed in rats at 490 mg/m³ (100 ppm). In the parallel study with mice, the incidences of olfactory epithelial metaplasia and hyperplasia of the glands overlying the olfactory epithelium were significantly increased in all exposed groups of males and females. In addition, atrophy of the olfactory epithelium was significantly increased in 300 and 600 ppm males. Increased incidences of exposure-related nasal lesions, including atrophy and hyperplasia of Bowman's glands and atrophy and metaplasia of the olfactory epithelium, were also observed in all exposed groups of male and female mice after subchronic inhalation for 14 weeks (LOAEC: 368 mg/m³, 75 ppm). No nasal epithelial lesions were observed in rats after subchronic inhalation at concentrations ranging from 368 to 4900 mg/m³ (75 -1000 ppm).

In the study with chronic exposure, renal tubule lesions and an increased incidence of renal tubule tumours in male rats were also observed. This effect is related to the α2u-globulin associated nephropathy in male rats and is not relevant for risk assessment in humans. Similarly, the observed increased incidence of hepatocellular tumours in the used strain of mice is considered not relevant for risk assessment. No increased incidences of neoplastic lesions were observed in the nasal epithelia of rats and mice.

There is no clear evidence of genotoxicity of 2-phenylpropene. At non-parentally toxic doses, 2-phenylpropene had no effect on reproductive and developmental parameters in a one-generation study with rats.

Rationale for starting point

The derivation of the EU-LCI value is based on the observed lesions of the nasal epithelia in rats, at the same concentration, similar effects were also observed in mice. Slight effects were already observed at 490 mg/m³, the lowest concentration tested. This LOAEC serves as the starting point for the derivation of the LCI.

Rationale for extrapolation factors

- Factor for adjustment for exposure duration: 5.6
- Adjusted study length factor: 1 (chronic exposure)
- LOAEC → NOAEC extrapolation: 3
- Interspecies differences: 2.5 (According to the ECA report No. 29, no correction has to be made for differences in systemic metabolism when the POD is related to local effects. For remaining uncertainties, a value of 1 is used for remaining specific differences for effects on skin, eye and GI tract if the mode of action implies only a simple destruction of membranes, and a default value of 2.5 is used for effects on the skin, eye and GI tract if local metabolism or receptor binding reactions are involved. A factor of 2.5 for 2-phenylpropene is used, because metabolism is known to be involved in the toxicity of structurally related compounds (Ad-hoc AG, 2012; DFG, 2004) and likely so for 2-phenylpropene.)
- Intraspecies differences: 10

Total extrapolation factor is: 420, leading to a value of 490 000 µg/m³ : 420 = 1200 µg/m³.

The following EU-LCI is proposed for 2-phenylpropene (α-methylstyrene): 1200 µg/m³. The derived EU-LCI is within the reported wide range of odour thresholds of 0.1-244 mg/m³ (0.02 – 49.7 ppm) reported by AIHA (2013) and, according to SCOEL (1995), the penetrating and unpleasant odour of 2-phenylpropene is detectable below 5 mg/m³ (1 ppm). Thus, odour perception and annoyance cannot be excluded at the proposed EU-LCI.

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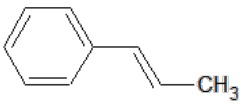
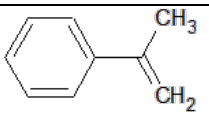
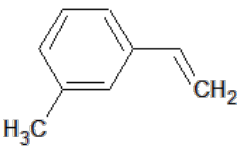
Table 23: Fact sheet 1-Propenylbenzene (ß-methylstyrene)

Compound	**1-Propenylbenzene**		***Factsheet***
Parameter	**Note**	Comments	Value / descriptor
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m³]	1200
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2019
General information			
CLP-Index No.	4	INDEX	-
EC-No.	5	EINECS	211-287-9 (cis), 212-848-0 (trans)
CAS-No.	6	Chemical Abstract Service number	637-50-3 (cis), 873-66-5 (trans)
Harmonised CLP classification	7	Human health risk related classification	
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	118.2 1 ppm = 4.9 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	2-phenylpropene (α-methylstyrene)
Species	11	Rat	
Route / type of study	12	Inhalation, oral feed, etc.	
Study length	13	Days, subchronic, chronic, etc.	
Exposure duration	14	h/d, d/w	
Critical endpoint	15	Effect (s), site of	
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	
POD value	17	[mg/m³] or [ppm] or [mg/kg_{BW}×d]	POD/TAF from the fact sheet for 2-phenylpropene: 1.166 mg/m³
Assessment factors (AF)	18		
Adjustment for exposure duration	19	Study exposure h/d, d/w	-
Study length	20	sa→sc→c	-
Route-to-route extrapolation factor	21		-
Dose-response	22a	Reliability of dose-response, LOAEL to NAEL	-
	22b	Severity of effect (R8 6d)	-
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	-
	23b	Kinetic + dynamic	-
Intraspecies differences	24	Kinetic + dynamic General population	-
AF (sensitive population)	25		-
Other adjustment factors Quality of database	26		-
Result			
Summary of assessment factors	27	Total Assessment Factor	
POD/TAF	28	Calculated value [µg/m³ and ppb]	1166 µg/m³ (240 ppb)
Molar adjustment factor	29		1
Rounded value	30	[µg/m³]	1200
Additional comments	31		
Rationale section	32		

Rationale for read-across

- Data poor compound: no adequate toxicological data for 1-propenylbenzene; de novo derivation of EU-LCI is not possible.
- Read-across from EU-LCI value of 2-phenylpropene (adopted in 2018): 2-phenylpropene shows structural and physicochemial similarities to 1-propenylbenzene, both compounds are isomers differing only in the position of the methyl group of the side chain.
- Toxicological critical endpoint for 2-phenylpropene: lesions of olfactory nasal epithelium
- The key assumption underlying the read-across of the EU-LCI value from 2-phenylpropene to 1-propenylbenzene is that both compounds have the same critical endpoint (local epithelial damage) and this is caused by the structural similarity. The same approach was followed in the derivation of a NIK value for 1-propenylbenzene by the AgBB (2018). The key assumption is further strengthened by the observation that vinyltoluenes, structurally related isomers of 2- and 1-propenylbenzene with an unbranched side-chain as 1-propylene benzene, also lead to lesions of the nasal epithelia of rats (NTP 1990).

Compound	Structure	MW [g/mol]	EU-LCI value (µg/m³)
1-propenylbenzene (ß-methylstyrene) (trans-form)		118.2	1 200 (proposed)
2-phenylpropene (α-methylstyrene)		118.2	1 200 (final)
m-vinyl toluene (3-methylstyrene) (one of three isomers)		118.2	1 200 (final)

Data for 1-propenylbenzene (ß-methylstyrene)

1-Propenylbenzene is pale yellow liquid with an annoying odour. It is a by-product in the synthesis of 2-phenylpropene (α-methylstyrene) and may be present as an impurity (up to 0.5 %) in 2-phenylpropene. 1-propenylbenzene occurs in two isomeric forms (cis and trans).

Very few data are available about the toxicity of 1-propenylbenzene. 1-propenylbenzene is metabolised with the formation of cinnamyl alcohol (Peele, 1977). Acute exposure is reported to be irritating to eyes, mucous membranes, and skin (IPCS, 2006). A comparative study of the ototoxicity of various aromatic solvents in rats revealed that trans-1-propenylbenzene does produce ototoxic effects; however, its potency is not higher than that of 2-phenylpropene and lower than that of styrene (Gagnaire und Langlais, 2005). In vitro data indicate that the epoxide of trans-1-propenylbenzene induces sister chromatid exchange but not gene mutations in mammalian cells and was not mutagenic in bacteria (GESTIS, 2014). Further genotoxicity or other toxicity studies are not available. No data on the toxicity of the cis-form were identified in the available literature.

The derivation of the EU-LCI value for the read-across compound, 2-phenylpropene, is based on the observed lesions of the nasal epithelia in rats, at the same concentration, similar effects were also observed in mice. Since both compounds, 1-propenylbenzene and 2-phenylpropene, are structural isomers, the molar adjustment factor is one leading to the same EU-LCI value of 1200 µg/m^3 for 1-propenylbenzene.

The substance is reported to have an annoying odour. However, no data on odour thresholds are available.

References

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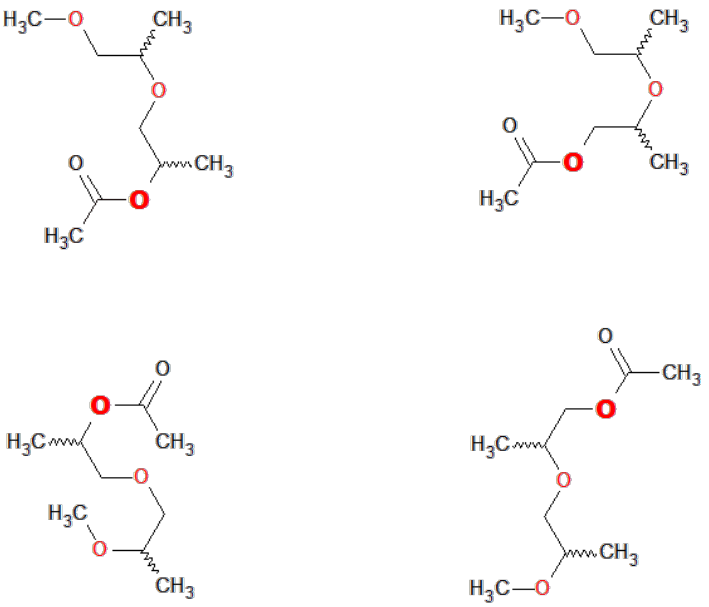
4 Toxicological evaluation of dipropylene glycol mono methyl ether acetate as basis for the derivation of an EU-LCI value

4.1 Substance identification

Generally, propylene (and also dipropylene) glycol ethers may appear in two isomeric forms. The predominant form, which is thermodynamically favoured during synthesis, consists of a secondary alcohol (also referred to as the α-isomer) and a minor form (the ß-isomer), consisting of a primary alcohol. Commercial products of propylene glycol ethers are thus mixtures, consisting of predominantly α-isomers (OECD SIDS, 2003b).

Unless otherwise stated, data reported in this evaluation pertain to commercial products. Commercial dipropylene glycol mono methyl ether acetate (DPGMEA) (CAS No. 88917-22-0) is a mixture of four isomers (Figure 1): (2-(2-methoxy-1-methyl)ethoxy)-1-methylethyl acetate; (2-(2-methoxy-2-methyl)ethoxy)-1-methylethyl acetate; (2-(2-methoxy-2-methyl)ethoxy)-2-methylethyl acetate; and (2-(2-methoxy-1-methyl)ethoxy)-2-methylethyl acetate (ECHA Dissemination, 2019f). Each of these structural isomers are racemates of the RR and RS isomers[2].

Figure 1: Structural isomers of dipropylene glycol mono methyl ether acetate (DPGMEA)



(Source: ECHA Dissemination, 2019f)

Two of these isomers (those on the right in the figure above) are derivatives of the ß-isomer form, i.e. of a primary alcohol. After hydrolysis, such a primary alcohol may be directly oxidised to the corresponding alkoxy propionic acid. However, it is reported that these two isomers are usually present in the racemic mixture at concentrations below 5 % (CARB, 2010).

DPGMEA is produced by esterification of dipropylene glycol methyl ether (DPGME) with acetic acid. According to the manufacturers specification of DPGME, the respective fractions of the structural isomers are 40-50 % 1-(2-methoxypropoxy)propanol-2, 40 -45 % 1-(2-methoxy-1-

[2] Each propylene glycol moiety contains a chiral center. The commercial product is a racemic mixture of the optic isomers. No studies are available with defined enantiomers.

methylethoxy)propanol-2 , 2-5 % 2-(2-methoxypropoxy)propanol-1, and 3-5 % 2-(2-methoxy-1-methylethoxy)propanol-1 (OECD SIDS, 2003a). Thus, a low amount of DPGMEA isomers with primary hydroxyl groups can also be deduced from the composition of the non-esterified DPGME.

4.2 Substance properties and uses

Substance physicochemical properties of dipropylene glycol mono methyl ether acetate (DPGMEA) are shown in Table 24.

DPGMEA is a clear colourless liquid with an ether-like odour. No natural sources of these substances are known. More than 100 tonnes of DPGMEA are manufactured and/or imported into the European Economic Area annually (ECHA Dissemination, 2019f).

DPGMEA may be used as in consumer products in cleaning agents, as solvent in air refreshener and in coatings. Uses by professional workers and at industrial sites additionally include ink mixing and printing processes (ECHA Dissemination, 2019f).

Table 24: Physicochemical properties of DPGMEA (OECD SIDS, 2003b)

Molar mass (g/mol) and sum formula	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa) (at 25°C)	Density (g/cm³)	log Pow	Solubility in water (g/L) (at 20°C)
190.3 $C_9H_{18}O_4$	< -25.2	209	0.17	0.976	0.803	160

4.3 Exposure

4.3.1 Indoor air

Few data are available regarding the occurrence of DPGMEA in indoor air (see Table 25). The substance could only be detected at low concentrations and in less than 1 % of all samples from offices, homes and (pre)schools in Germany (Hofmann and Plieninger, 2008). According to another evaluation based on 2267 measurements, concentrations exceeding 1.5 µg/m^3 may be considered as “conspicuous value” (corresponding to the 95th percentile of measured concentrations) (AGÖF, 2013).

4.3.2 Other sources

There are no data available.

Table 25: Data on the occurrence of DPGMEA in indoor air from homes, schools, children day care centres and offices

Rooms	N	LoD (µg/m³)	N > LoD (% > LoD)	Median (µg/m³)	P95 (µg/m³)	Maximum (µg/m³)	Source
Offices, homes, (pre)-schools, Germany	735	0.7 – 3.0 (mean: 1.0)	2 (0.3)	0.5	1.5	15	(Hofmann and Plieninger, 2008)
Indoor air (not further specified), Germany	2267	not reported		< 1	< 1.5		(AGÖF, 2013)

4.4 Toxicokinetics

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

The metabolism of glycol ethers follows two main oxidative pathways. One pathway involves oxidation by microsomal cytochrome P450 monooxygenases at the ether bond via O dealkylation. This leads to the production of the corresponding glycol (dipropylene glycol in case of DPGnBE) and is the main pathway for dipropylene glycols. Dipropylene glycol may undergo further metabolism with oxidative cleavage of ether bonds and final oxidation of the carbon chain to carbon dioxide. Alternatively, propylene glycol ethers or their partially metabolized products may be conjugated with glucuronide or sulfate and excreted via the kidneys into the urine (OECD SIDS, 2003b). The other pathway involves oxidation by alcohol dehydrogenase and further oxidation by aldehyde dehydrogenase with the formation of alkoxyalkanoic acids. This pathway requires a primary hydroxyl (OH) group and thus is observed with the alpha isomers. Beta-isomers, which do not contain a primary but a secondary free hydroxyl group, cannot be oxidised via this pathway to alkoxyalkanoic acids but only to the corresponding ketones which are further oxidised by other pathways (ECETOC, 2005; OECD SIDS, 2003b).

A summary of toxicokinetic data for DPGMEA is presented in the REACH registration dossier (ECHA Dissemination, 2019f).

The absorption, metabolism, and elimination of DPGMEA was studied in female Sprague-Dawley rats (2/dose) following 4 daily repeated oral gavage doses of 329 and 659 mg/(kg bw x d), respectively. After the first dose, blood was collected at 0.08, 0.17, 0.25, 0.5, 1, 2, 4, 6, 10, 24, 48, and 72 h post-dosing. After the 4th day dosing, blood was collected at 0.17, 0.5, 1 and 2 h post-dosing. The results indicated that DPGMEA was rapidly absorbed without any apparent lag time based on blood concentrations of DPGMEA, DPGME and MPA (2-methoxypropionic acid). Blood concentrations declined rapidly during the elimination phase (half-life 1.5 - 3.5 h) for both metabolites. Kinetic parameters could not be calculated for the parent compound due to a limited number of samples with quantifiable levels. However a comparison of estimated AUC for DPGMEA vs. the sum of DPGME isomers plus MPA, show that ≤ 2 % of the parent test material was systemically bioavailable (ECHA Dissemination, 2019f).

Within the scope of an oral developmental toxicity study with DPGMEA (see chapter 4.5.4), blood samples were collected to compare the toxicokinetic profile and systemic exposure of

DPGMEA and the primary metabolites, DPGME and MPA (2-methoxypropionic acid). Pregnant Sprague-Dawley rats (6/group) received 0, 110, 329, 659 and 1000 mg/(kg bw x d) on GD19-21. Blood samples were collected just after dosing on GD 19, and then after 24 h, 27 h, and 32 h for calculation of daily systemic exposure. Blood samples were also collected at a single time point from all dams and their fetuses (pooled for each litter) at the time of terminal sacrifice on GD 21. In summary, the data indicated that DPGMEA was rapidly absorbed and highly metabolised to dipropylene glycol methyl ether (DPGME) and MPA. DPGMEA itself was present at concentrations above the analytical lower limit of quantitation in only a few blood samples from dams and fetuses, primarily in the higher dose groups, and only early after dosing. In contrast, DPGME and MPA were present at quantifiable levels in most of the blood samples from exposed animals. DPGME was the major metabolite and was present in blood at all time points in adult females and fetuses, except just prior to dosing, consistent with the rapid formation and relatively short elimination half-life of this compound. MPA was present in blood at all time points in adults and fetuses at levels of about 7-20 % those of DPGME, consistent with the slower formation and slightly longer elimination half-life of MPA. Fetus blood concentrations of DPGME and MPA were generally equivalent to dam blood concentrations. Blood levels of all analytes were dose-proportional, where measurable (ECHA Dissemination, 2019f).

Read-across:

The rate of *in vitro* hydrolysis of **DPGMEA** in rat whole blood and rat liver S9 fraction was measured and compared with its shorter-chain analog, propylene glycol methyl ether acetate (**PGMEA**). Two concentrations (38 and 380 µM) of both compounds were incubated separately with rat whole blood or rat liver S9 fraction under physiological conditions. The rate of hydrolysis was determined by the disappearance of the two major isomers of both compounds over a period of 60 minutes. Hydrolysis of PGMEA was rapid, both from the rat whole blood and rat liver S9 fraction, without any dose dependency and with half-lives of disappearance between 11 and 18 min. The half-life of hydrolysis in blood of both of the major isomers of DPGMEA was 10-12 min and 13-17 min, similar to what was observed for PGMEA. Hydrolysis of DPGMEA from rat liver S9 was 3-5fold slower (40-50 min and 58-82 min) than that of PGMEA. On the basis of these results, DPGMEA is expected to rapidly hydrolyse in blood after absorption, similar to PGMEA. Although DPGMEA was slowly hydrolysed by the liver S9, the overall impact of this slow hydrolysis will likely be limited due to its low tissue partition coefficient and restriction of the absorbed dipropylene glycol methyl ether mostly to the blood, where it is rapidly hydrolysed (ECHA Dissemination, 2019f).

In the same study, plasma binding was estimated to be only 7-21 %. Similarly, all three test materials had low volume of distribution (Vd = 1.0-1.2 L/kg) (ECHA Dissemination, 2019f).

The rate of hydrolysis of **PGMEA** *in vivo* was determined following intravenous administration of 14.7 or 147 mg/(kg bw x d) in F344 rats. Half-lives of PGMEA elimination were calculated to be 1.6 and 2.3 min at the two dose levels. Once hydrolysed, the kinetics for PGME derived from PGMEA was identical to that for directly applied PGME as observed in the same study. Further studies were conducted to compare the rate of *in vitro* hydrolysis of PGMEA in blood and liver homogenate from rats and humans at two concentrations of 5 and 50 µg/ml, respectively. The rate of loss of PGMEA was more rapid in rat blood than in human blood, with hydrolysis half-lives 16 and 15 min in rat blood compared to 36 and 34 min in human blood. No such differences were observed for the rate of loss of PGMEA in human and rat liver homogenate incubations (27–30 min and 34 min, respectively) (Domoradzki et al., 2003).

The results of this study show that the acetate ester of PGME is more rapidly hydrolysed *in vivo* than expected on the basis of *in vitro* data. It is known that *in vivo* there are numerous sites of

esterase activity in the body, including blood, liver, skin, nasal mucosa, heart, muscle, adipose tissue and kidney. Evaluation of esterase activity from any single tissue source, such as liver or blood, would therefore underestimate metabolic fate that occurs *in vivo* (ECHA Dissemination, 2019f).

4.5 Health effects

4.5.1 Acute toxicity, sensory irritation and local effects

The acute toxicity of DPGMEA to animals is low. No deaths occurred in an acute inhalation study with 4 hour exposure of rats at nominal vapour concentration of 5700 mg/m^3 (CARB, 2010; ECHA Dissemination, 2019f). The oral LD50 is > 5000 mg/kg bw and the dermal LD50 > 2000 mg/kg bw (ECHA Dissemination, 2019f).

No skin irritation (erythema or oedema) was observed in a guideline study (OECD 404) on the skin of rabbits (n=3) after semi-occlusive application of DPGMEA. In a second, similar study with rabbits (n=6), application of the undiluted test material to intact and freshly abraded skin resulted in only very slight redness in one of the animals immediately at the end of the treatment but not later on. In an eye irritation test according to OECD guideline 405, slight conjunctival redness, slight chemosis and a slight discharge were noted 1 h post instillation in the eyes of rabbits (n=3). All responses were reversible by 24 h. No corneal and iridial responses were noted. In a second study, instillation of the undiluted material of rabbits (n=9) resulted in moderate discomfort and slight conjunctival redness, which reverted to normal 3 d following exposure (ECHA Dissemination, 2019f).

No sensitisation was observed in a Magnusson-Kligman Maximisation Test with guinea pigs (ECHA Dissemination, 2019f).

Read-across:

Dipropylene glycol mono methyl ether (DPGME) produced no evidence of primary irritation or skin sensitisation in humans in a patch test with 200 and in another tests with 50 participants. In these studies, the test substance had been applied to skin of the back for 5 or 10 days and reapplied to the same area after three weeks for up to 48 h (OECD SIDS, 2003a).

4.5.2 Repeated dose toxicity

There are no data available for effects of DPGMEA following repeated exposure of humans.

Inhalation exposure

Inhalation studies with repeated exposure of animals to DPGMEA are not available.

Read-across:

In a short-term repeated inhalation toxicity study (comparable to OECD guideline 412), F344 rats and B6C3F1 mice (5 M + 5 F/group) were exposed “whole body” to analytically confirmed vapour concentrations of 0, 300, 1000, or 3000 ppm **PGMEA** for 6 h/d, 5 d/week, 2 weeks (a total of 9 exposures). The highest concentration approached the saturated vapour concentration (4950 ppm PGMEA) (Miller et al., 1984).

In rats, no lethality was observed, and all animals appeared normal. Body weights and weight gain of exposed animals were similar to those of controls. The relative liver weight of high-dose females was significantly increased (by about 5 %) without any gross or histopathological changes. Slight kidney changes (slightly reticulated, pale appearance) were observed in all high-dose and in 11/5 mid-dose males and in 2/5 high-dose females. The mean urinary specific

gravity of high-dose males and females tended to be slightly lower than those for controls (Miller et al., 1984).

Regarding local effects, an exposure-related slight to moderate degeneration of the olfactory epithelium was observed in the nasal cavities of 3/5 males and 1/5 high-dose females. The changes were characterised by loss of cells in the neuron layer and flattening of the sustentacular cell layer, resulting in decreased thickness of the neuroepithelium. As such changes are not a common finding in young rats, the changes noted were attributed to the exposure to vapours of PGMEA. The ciliated respiratory epithelium remained unaffected (Miller et al., 1984).

In mice, the only histopathologic changes attributable to exposure occurred in the nasal cavities. Degeneration of the olfactory epithelium, similar to that described for rats, was present to some degree in all male and female mice in all PGMEA exposed groups. This acute degenerative change occurred in a dose-related manner and was generally more severe and more extensive in animals exposed to 3000 ppm. However, even at 300 ppm, slight changes were generally present in the dorsomedial aspects of the ethmoid recess in addition to those in the more anterior portions of the olfactory epithelium in the nasal cavity proper. Most animals at the two higher concentrations and 1/5 of female mice in the 300-ppm group had slight focal areas of "respiratory metaplasia," a condition in which the compromised olfactory epithelium is replaced by ciliated respiratory epithelium similar to that normally present throughout the rest of the respiratory tree. An acute inflammatory exudate was present in the lumen of the nasal cavities in some animals of the two higher doses (Miller et al., 1984). A LOAEC of 300 ppm PGMEA can be derived from these data.

A subchronic inhalation study was performed with dipropylene glycol monomethyl ether **(DPGME)** in which F344 rats (10 M + 10 F/group) were exposed to 0, 15, 50 and 200 ppm (0, 91, 303 and 1212 mg/m^3) for 6 h/d, 5 d/week for 13 weeks. DPGME exposure had no related adverse effects on body weights. There were no statistically significant differences from control body weight means, no exposure related adverse effects on haematology, clinical chemistry or urinary parameters in either sex of rat. There were no statistically significant differences in organ weights, except for a slight decrease in mean relative liver weight males at 50 ppm. There were no histopathological effects in the liver or other organs of exposed animals. A NOAEC for DPGME of 200 ppm can be derived from this study (ECHA Dissemination, 2019e).

A similar study with **DPGME** was performed with New Zealand White rabbits (7 M + 7 F/group). The animals were exposed to 0, 15, 50 and 200 ppm (0, 91, 303 and 1212 mg/m^3) 6 h/d, 5 d/week for 13 weeks. As in rats, there were no substance-related adverse effects at any concentrations on any parameter. An observed increase in mean relative kidney weight of female rabbits exposed to 200 ppm and of absolute mean kidney weights of 50 and 200 ppm exposed female rabbits were within the range of historical control values. Additionally, there was no evidence of nephrotoxicity. Thus, the increased kidney weights in the female rabbits were considered unrelated to treatment (ECHA Dissemination, 2019e). A NOAEC of 200 ppm can be derived from this study.

Group of rats (strain not specified, 20 M + 20 F/group) were exposed 7 h/d, 5 d/week for 28 weeks to an atmosphere essentially saturated with DPGME at 400 ppm nominal concentration. There were no exposure related adverse effects on body weights, organ weights, hematology or macroscopic and microscopic organ pathology. Based on the results of this study, the NOAEL for inhalation exposure to DPGME was > 400 ppm nominal (> 300 ppm, analytical) (ECHA Dissemination, 2019d).

Oral exposure

In a subacute study Sprague- Dawley rats (5 M + 5 F/group) were gavaged with 0,100, 250, 1000 mg DPGMEA/(kg bw x d) for 28 d. Increased breathing and subdued behaviour were evident in the majority of animals of both sexes, but there were no deaths during the exposure period. Body weights and feed consumption, haematology and clinical chemistry did not show intergroup differences in either sex. There was a slight increase in liver weight in high dose females. Gross pathology and microscopic findings did not show changes considered to be due to administration of the test material. Based on the results of this study a dose of 1000 mg/(kg bw x d) was identified as NOAEL. Based on a slight increase in liver weight (without histopathologic changes) in females, the NOEL is 250 mg/(kg bw x d) (ECHA Dissemination, 2019f).

4.5.3 Genotoxicity and carcinogenicity

Genotoxicity

In vitro, DPGMEA was not mutagenic in two bacterial mutation assays with and without exogenous metabolic activation system (S9 mix from rat liver) in all tested strains of Salmonella typhimurium (TA98, TA100, TA1535, TA1537, TA1538) and in Escherichia coli WP2uvrA (ECHA Dissemination, 2019f). DPGMEA was also not mutagenic in a mammalian cell gene mutation assay (HGPRT assay with CHO cells) and not clastogenic in a cytogenicity/chromosome aberration assay with CHO cells, both in the absence or presence of exogenous metabolic activation system (S9 mix from rat liver) (ECHA Dissemination, 2019f).

In vivo data are not available for DPGMEA.

Read-across:

DPGME was also negative in a cytogenetic assay in CHO cells with and without metabolic activation (OECD SIDS, 2003b).

No genotoxicity was observed *in vivo* with two structurally related propylene glycol ethers:

Propylene glycol -butyl ether (PGnBE) was not clastogenic in a micronucleus test in male and female CD-1 mice at doses up to 2500 mg/kg bw, the highest dose causing lethality in both sexes (ECHA Dissemination, 2019a; OECD SIDS, 2003b). Also, PGME at doses up to 6000 mg/kg bw administered to mice did not increase the frequency of micronuclei in polychromatic erythrocytes harvested from bone marrow (OECD SIDS, 2003a).

Also, diethylene glycol mono ethyl ether acetate (2-(2-ethoxyethoxy)ethyl acetate) was not clastogenic in an *in vivo* micronucleus assay after inhalation exposure of male and female rats to 0.05, 0.15 and 0.5 ppm (50, 150 and 500 mg/m^3) on 6 h/d, 5 d/week for 90 d. (ECHA Dissemination, 2019b).

Carcinogenicity

No data are available for this endpoint for DPGMEA.

Read-across:

No evidence of carcinogenicity was observed in a two-year carcinogenicity study (according to OECD guideline 453) with inhalation exposure of F344 rats (50 M + 50 F/group) to **PGME** (propylene glycol monomethyl ether, CAS No. 107-98-2) up to the highest concentration tested (3000 ppm). Non-neoplastic effects observed in this study included decreased activity, incoordination, and transient sedation during and immediately after exposure to 3000 ppm. Body weights were also decreased at the 3000 ppm exposure level. Liver and kidney weights were increased at 3000 ppm in both sexes. Dark foci in the liver were observable in male rats

exposed to 1000 and 3000 ppm PGME after 24 months. These animals also exhibited eosinophilic hepatocellular foci and cystic degeneration microscopically that was not reported in female rats. In the kidney, histopathology revealed that male rats had α2u-globulin nephropathy. The incidence and severity of this condition was increased in males exposed to 1000 and 3000 ppm PGME compared to controls. A NOAEC of 300 ppm based on altered hepatocellular foci in males can be derived from this study (OECD SIDS, 2003b).

4.5.4 Toxicity to reproduction

Fertility

No data are available from fertility studies with DPGMEA.

Read-across:

A two-generation reproductive toxicity study (according to OECD guideline) was performed with propylene glycol methyl ether **(PGME)** (99% 1-methoxy-2-hydroxypropane or propylene glycol methyl ether (alpha isomer), CAS No. 107-98-2 and 1.9% 2-methoxy-1-hydroxypropane or propylene glycol methyl ether (beta isomer)). Sprague-Dawley rats (30 M + 30 F/group) were exposed to 0, 300, 1000 or 3000 ppm PGME (0, 1110, 3710, 11170 mg/m^3) via inhalation, for 6 h/d, 5 d/week prior to mating and 6 h/d, 7 d/week during mating, gestation and lactation for two generations (Carney et al., 1999; OECD SIDS, 2003b).

Inhalation exposure of adult male and female rats to 1000 (females only) and 3000 (males and females) ppm PGME resulted in dose-related parental effects. Toxicity in 3000 ppm PGME P1 and P2 males and females was evidenced primarily as an increased incidence of sedation for several weeks early in the exposure regimen and significant decreases in body weights. Decreased body weights in the P1 and P2 high concentration females generally persisted throughout the pre-breeding, gestation and lactation phases of the study. Additional effects noted among P1 and P2 adult females exposed to 3000 ppm PGME included lengthened estrous cycles, decreased fertility, decreased ovary weights and an increased incidence of histologic ovarian atrophy. The effects on fertility, estrous cyclicity and ovarian weight/histology appeared to be interrelated and associated with the significant decreases in 3000 ppm PGME female body weights and general toxicity/nutritional stress throughout the test period. No treatment-related differences in sperm counts or motility were observed among P1 or P2 adult males. Neonatal effects observed at 3000 ppm PGME consisted of decreased pup body weights, reduced pup survival and litter size, increased time to vaginal opening or preputial separation, and histopathologic observations in the liver and thymus of weanling rats. These neonatal effects were considered secondary to maternal toxicity. In the 1000 ppm PGME group, mild parental toxicity was evidenced by slightly decreased pre-mating body weights among P1 and P2 females, but was not accompanied by any statistically significant effects on parental reproduction or neonatal survival, growth or development. There were no treatment-related parental or neonatal effects related to exposure of rats to 300 ppm PGME. In conclusion, the no-observed-effect-level (NOEL) for fertility and reproductive effects in this two-generation inhalation reproduction study was 1000 ppm (3710 mg/m^3) PGME. Mild parental toxicity was noted at this concentration (Carney et al., 1999; ECHA Dissemination, 2019c; OECD SIDS, 2003b).

Development

A study (following OECD guideline 414) was conducted with oral exposure of rats to DPGMEA. The test substance was applied to pregnant Sprague-Dawley rats (n=24/group) by gavage as solution in distilled water at doses of 0, 100, 300 or 1000 mg/(kg bw x d) on GD6-21. There were no treatment-related effects in dams regarding clinical observations, body weight and weight gain, feed consumption, or gross pathology in any treated group. Histopathological examination revealed a treatment-related increase in the incidence of very slight centrilobular to midzonal hepatocellular hypertrophy with increased cytoplasmic eosinophilia at the highest dose in 12/22 animals. These changes corresponded to treatment-related increases in absolute and relative liver weights (about 13 %) in the high-dose group compared to controls. Slightly increased absolute and relative liver weights (but within recent historical control values) were also observed at the mid dose. There were no treatment-related effects on pregnancy rates, resorption rates, litter size, numbers of corpora lutea or implantations, percent preimplantation loss, percent postimplantation loss, fetal sex ratios, fetal body weights or gravid uterine weights at any dose level. No indications of embryo- or fetotoxicity were observed. There were no treatment-related differences in the incidence of any fetal alteration in any of the treated groups compared to controls. The small number of alterations observed in fetuses from dams administered DPGMEA either occurred at low frequencies and/or were not dose-related. The NOAEL for maternal toxicity and for developmental toxicity was 1000 mg/(kg bw x d), the highest dose tested. The same NOAEL was obtained in a range-finding study performed prior to the full study described (ECHA Dissemination, 2019f).

Read-across:

The developmental toxicity of **DPGME** was studied in rats and rabbits via the inhalation route of exposure at concentrations of 0, 50, 150, or 300 ppm (0, 303, 909, or 2728 mg/m^3). Mated F344 rats (32-37/group) were exposed for 6 h/d on GD 6-15. On GD21, all animals were killed prior to caesarean section and examined. No treatment-related effects were observed on any of the maternal, embryonal and foetal parameters evaluated.

In a similar study, New Zealand rabbits (16 mated F/group) were exposed for 6 h/d on GD 7-19. On day 28 of gestation, all animals were euthanised and examined. No treatment related effects were observed on any of the maternal and embryonal/foetal parameters evaluated at any exposure level.

Thus, the highest vapour concentration of 300 ppm (2728 mg/m^3) which was practically attainable at normal room temperature represents a NOAEC for DPGME for the studies in both species (Breslin, 1990; OECD SIDS, 2003b).

4.5.5 Odour perception

DPGMEA is described to have an ether-like odour. No data on odour thresholds are available.

4.6 Evaluation

4.6.1 Existing regulations and classifications

There is no harmonised classification for DPGMEA (ECHA C&L Inventory, 2019).

Existing guide values for DPGMEA in air are summarised in Table 26.

A NIK (Lowest Concentration of Interest) value of 3900 µg/m^3 is reported for DPGMEA. This value was adopted from the EU-LCI value for dipropylene glycol monomethyl ether (DPGME) of

3100 µg/m³ (AGBB, 2018). This EU-LCI value for DPGME is an "ascribed EU-LCI value" (EU-LCI Working Group, 2018).

Table 26: Guide values for DPGMEA in air (for explanation, see text)

Guidance value Parameter/ Organisation	AgBB (2018)	ECHA Dissemination (2019)	CARB (2010)
Name (reference period)	NIK Value (2018)	DNEL (chronic, general population)	Draft interim 8-hr REL*
Value (mg/m³)	3.9	46	0.08
Organ/critical effect			Kidney weight
Species			Rats and rabbits
Basis			NOAEC for DPGME: 15 ppm
Adjusted for cont. exposure			6 h/8 h, 5 d/7 d, leading to 8 ppm
Extrapolation factors		Intraspecies: 2	Time: $10^{0.5}$; Interspecies 2 x $10^{0.5}$; Intraspecies: 10 x $10^{0.5}$, total: 600
Remarks	The EU-LCI value of 3100 µg/m³ for DPGME was adopted. The EU-LCI value for DDPGME is an "ascribed EU-LCI-value". The NIK value for DPGMEA was calculated by molar adjustment.	"The dose descriptor used was the worker-DNEL-long term for the inhalation route which was corrected for the differences in duration of exposure between worker and consumer (24 h per day, 7 days per week) and the intraspecies difference."	Read-across was performed using data from a subchronic inhalation study with rats and rabbits.

* A Reference Exposure Level (REL) is the concentration level at or below which no adverse non-cancer health effects are anticipated for the specified exposure duration. RELs are designed to protect the most sensitive individuals in the population by the inclusion of factors that account for uncertainties as well as individual differences in human susceptibility to chemical exposures. The factors used in the calculation of RELs are meant to err on the side of public health protection in order to avoid underestimation of non-cancer hazards. Exceeding the REL does not automatically indicate an adverse health impact. However, increasing concentrations above the REL value increases the likelihood that the health effect will occur (OEHHA, 2015).

General population

In the registration dossier for DPGMEA, a DNEL of 46 mg/m³ for the protection of the general population via the inhalation route has been derived. The dose descriptor used was the worker-DNEL-long term for the inhalation route (see below) which was corrected for the differences in duration of exposure between worker and consumer (24h per day, 7 days per week) and the intraspecies difference (ECHA Dissemination, 2019f).

A DNEL of 1.67 mg/(kg bw x d) for the protection of the general population via the oral exposure route has also been derived in the dossier. The value is based on the NOAEL of 1000 mg/(kg bw x d) from a subacute gavage study in rats, using an overall assessment factor of 600 (no further details, but probably 6 for time extrapolation and 10 each for inter- and intraspecies extrapolation) (ECHA Dissemination, 2019f). It should be noted that a route-to-route

extrapolation (70 kg bw, 10 m^3/d, and assuming the same resorption via oral and inhalation uptake) based on this $DNEL_{oral}$ would lead to a value of 11.7 mg/m^3, which is a factor of four lower than the $DNEL_{ihl}$ reported in the dossier.

A "draft interim 8-hr REL" (Reference Exposure Level) of 0.08 mg/m^3 (0.013 ppm) has been derived for DPGMEA (CARB, 2010). The derivation is based on a subchronic toxicity study with rabbits and rats. According to CARB; "among the seven female rabbits, a significant ($p < 0.05$) increase in kidney weights at 50 and 200 ppm was reported. The authors suggest that since there was no attendant evidence of nephrotoxicity and the kidney weights were within the range for historical controls, these effects were unrelated to treatment. However, in the context of this experiment, these results suggest potentially pathological changes that may impair kidney function." Thus, CARB rated the lowest experimental concentration of 15 ppm as a NOAEC for DPGME.

The German Ad-hoc Working Group on Indoor Guidelines has evaluated the toxicity of glycol ethers and glycol esters and derived substance-specific guide values for substances with sufficient data. No substance-specific value was derived by the working group for DPGMEA. A default guide value I of 0.005 ppm was recommended for glycol ethers and glycol esters with insufficient data basis (Ad-hoc AG, 2013). This recommendation was based on a statistical analysis of the available data of all glycol ethers, not taking into account substance-specific structural criteria for individual compounds. In case of DPGMEA, the recommended guide value I of 0.005 ppm corresponds to a mass-based concentration of 39 µg/m^3.

Workplace

An inhalation DNEL for workers of 50 ppm is reported in the REACH registration dossier for DPGMEA (ECHA Dissemination, 2019f). The value is based on a read-across taking into account the data for dipropylene glycol methyl ether. A NOAEC of ≥ 200 ppm has been derived in a 13-week inhalation toxicity study with dipropylene glycol methyl ether in rats. Based on analogy with the toxicological profile of dipropylene glycol methyl ether and the toxicokinetic behaviour of dipropylene glycol methyl ether acetate (rapid hydrolysis in the blood to dipropylene glycol methyl ether), the workplace exposure level of 50 ppm for dipropylene glycol methyl ether established by the German MAK Commission and by SCOEL was adopted (ECHA Dissemination, 2019f).

A value of 50 ppm would be equivalent to a concentration of 390 mg DPGMEA/m^3. However, a DNEL of 1556 mg/m^3 and an overall assessment factor of 3 are also mentioned in the registration dossier (ECHA Dissemination, 2019f). No further details and no explanation are given in the dossier for the differences between this and the other reported value.

4.6.2 Derivation of an EU-LCI value

The data basis for DPGMEA is limited. Additional data are available from studies with structurally related propylene glycol ethers and ether acetates.

No data are available on the toxicity of DPGMEA in humans. Also, no inhalation studies with repeated exposure of animals to DPGMEA are available.

In a subacute inhalation study with PGMEA, a degeneration with metaplasia of the olfactory nasal epithelium was observed in rats at 3000 ppm (NOAEC 1000 ppm) and in mice at all exposure concentrations (LOAEC: 300 ppm, no NOAEC) (Miller et al., 1984).

Similar lesions of the olfactory nasal epithelium of rats or mice have been described in a number of subacute or subchronic inhalation studies in which the animals had been exposed to other aliphatic esters of alkanoic acids: methyl acetate, ethyl acetate, n-butyl acetate, vinyl acetate, n-

amyl acetate, n-butyl propanoate, or methyl methacrylate. The concentrations at which such effects were observed were in the range of 350 – 2500 ppm, similar to that of PGMEA. The epithelial lesions are attributed to the formation of acetic, propanoic or methacrylic acid, leading to cytotoxicity when the specific intracellular buffer capacity of the cells is exceeded and exhausted (Hardisty et al., 1999).

Studies on the toxic effects and the toxicokinetic of PGMEA and the non-esterified PGME clearly indicated that both are essentially toxicologically equivalent, with the exception of nasal irritation, which were only observed in inhalation studies with PGMEA but not with PGME despite the high absorption of both chemicals by this tissue (Domoradzki et al., 2003).

Similar conclusions can be drawn in case of DPGMEA and DPGME. Studies with DPGMEA indicate a low systemic toxicity, similar to that of the non-esterified DPGME. The similarity of those two compounds regarding systemic effects is corroborated by toxicokinetic data showing that DPGMEA is rapidly hydrolysed *in vivo* with the formation of DPGME (and acetate)[3].

For DPGME, subchronic toxicity studies with rats and rabbits provided a NOAEC of 200 ppm, the highest concentrations tested (ECHA Dissemination, 2019e). DPGMEA was not genotoxic *in vitro,* and no genotoxicity was observed with structurally related glycol ethers (PGME) or ether acetates (DEGMEA) *in vivo* (ECHA Dissemination, 2019e; OECD SIDS, 2003a). Carcinogenicity data are not available for DPGME(A), but PGME was not carcinogenic in a two-year carcinogenicity study with rats (OECD SIDS, 2003b).

No fertility study is available for DPGMEA. The no-observed-effect-level (NOEL) for fertility and reproductive effects of PGME in a two-generation inhalation reproduction study was 1000 ppm (3710 mg/m^3). Mild parental toxicity was noted at this concentration (ECHA Dissemination, 2019c). Developmental toxicity studies have been carried with both DPGMEA and DPGME. No developmental toxicity was observed with DPGMEA up to the highest oral dose of 1000 mg/(kg bw x d) in rats (ECHA Dissemination, 2019f) and up to the highest inhalation concentration of 300 ppm DPGME in rats and rabbits (Breslin, 1990; OECD SIDS, 2003b).

Overall, the data for DPGMEA and DPGME as well as for other propylene glycol ethers indicate a low systemic toxicity. At the same time, data for PGMEA show that this acetate ester – as structurally similar to other aliphatic esters – produces local irritation effects in the olfactory nasal epithelium of rodents which are not observed at similar concentrations with the non-esterified glycol ether.

Thus, it is concluded that data for DPGME and other propylene glycol ethers do not provide a suitable basis for the derivation of an EU-LCI value for DPGMEA. Instead, read-across with data for the structurally-related PGMEA will be used for the derivation of an EU-LCI value for DPGMEA.

The subacute inhalation toxicity study with propylene glycol mono methyl ether acetate (PGMEA) in rats and mice (Miller et al., 1984) is considered a suitable key study for the derivation of an EU-LCI value for DPGMEA, performing a read across.

The LOAEC of 300 ppm observed for mice in that study is used as POD for the calculation.

[3] In case of ethyl acetate, calculations indicate that no change of blood pH or systemic acidosis is to be expected by the small amounts of acetic acid formed by the enzymatic hydrolysis of the ester at airborne concentrations of 400 ppm during an 8-hr work shift (Ad-hoc AG, 2014). Moreover, the amount of acetate produced via hydrolysis of the ester is very small compared to the daily uptake and the internal metabolic production of acetic acid (Voss, 2018). These considerations also apply in case of DPGMEA.

The following adjustment factors are used:

- Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6
- Adjusted study length factor (subacute exposure study): 6
- LOAEC to NAEC extrapolation: 3
- Interspecies extrapolation:
  allometry: 1 (inhalation exposure, local effect)
  remaining differences: 2.5
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 2520. This leads to a concentration of 300 ppm : 2520 = 0.119 ppm.

It is proposed to adopt this value for DPGMEA on a molar basis:

1 ppm DPGMEA = 7.82 mg/m^3, leading to a proposed EU-LCI value of 931 µg/m^3 (rounded to 950 µg/m^3).

Table 27: Derivation of EU-LCI-value for DPGMEA (for explanation, see text)

Organ/endpoint	POD	LOAEC to NAEC	Exposure duration	Time	Inter-species	Intra-species	Value	Reference
Read-across data from PGMEA, nasal epithelial lesions in rats	LOAEC 300 ppm	3	5.6	6	2.5	10	0.119 ppm	(Miller et al., 1984)

A developmental toxicity study with oral exposure of rats to DPGMEA indicated a NOAEL of 1000 mg/(kg bw x d) for maternal and developmental toxicity. Toxicokinetic data *in vivo* indicate a rapid and nearly complete absorption of DPGMEA after oral administration. No substance-specific data are available regarding absorption after inhalation; however, glycol ethers in general are known to be well absorbed by inhalation (ECETOC, 2005; OECD SIDS, 2003b). Therefore, similar oral and inhalation absorption may be assumed when performing a route-to-route extrapolation.

Considering the maternal toxicity, the study length (GD6-21) can be considered as of "subacute" duration. Using standard extrapolation factors (EC, 2013; ECHA, 2012):

- Route-to-route extrapolation (rats): 1.15 m^3(kg b.w. x d)
- Adjusted study length factor (subacute exposure study): 6
- Allometric scaling: already included in route-to-route extrapolation
- Interspecies extrapolation: 2.5
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 172.5 m^3/(kg b.w. x d). This leads to a concentration of 1000 mg/(kg bw x d): 172.5 m^3/(kg b.w. x d) = 5.797 mg/m^3 (0.74 ppm). This value is about

6fold higher than that derived on the basis of local effects in the respiratory tract observed after inhalation exposure to DPGMEA. It is concluded that the latter value will also offer protection against systemic effects of DPGMEA.

A comparison may also be performed with the derivation of a value for DPGMEA based on a read-across using data from inhalation studies with dipropylene glycol mono methyl ether (DPGME). In two subchronic studies with rats or rabbits, respectively, no adverse effects were observed up to the highest concentration of 200 ppm (see chapter 4.5.2.). Using standard extrapolation factors, i. e.:

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

Total assessment factor: 280. This leads to a concentration of 200 ppm : 280 = 0.714 ppm.

Performing a molar adjustment with 1 ppm DPGMEA = 7.82 mg/m^3, this leads to a value of 5583 µg/m^3. This value is also about 6fold higher than the proposed EU-LCI value based on local effects of the acetate ester of propylene glycol as derived above.

It is concluded that the derivation of the EU-LCI value should be based on the local effects observed in an inhalation study with PGMEA, performing a read-across. The so-derived value is regarded as also protective against systemic effects of DPGMEA.

An EU-LCI value (rounded) for DPGMEA of 950 µg/m^3 is proposed.

DPGMEA is reported to have a mild odour. However, data on odour thresholds are not available.

4.7 List of references

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4.8 Fact and data sheet for dipropylene glycol mono ethyl ether acetate (DPGMEA)

Table 28: Data collection sheet for propylene glycol mono methyl ether acetate (PGMEA)

Compound	**Propylene glycol mono methyl ether acetate**	***Data collection sheet***
N° CAS 108-65-6 1 ppm = 5.4 mg/m³ at 23 °C	**EU-Classification: -** **CLP,** harmonised classification: none with respect to toxicity	
Organisation name	AgBB	Reach registrants
Risk value name	NIK ('Lowest Concentration of Interest')	DNEL
Risk value (mg/m³)	2.7 mg/m³	33 mg/m³
Reference period	Chronic (general population)	Chronic (general population)
Risk value (mg/m³) Short term (15 min)	-	-
Year	2015	2019
Key study		Study report from 1981 reported as key study for repeated dose inhalation
Study type		Inhalation study with 0, 300, 1000, 2000 ppm PGMEA, "whole body"
Species		B6C3F1 mice (n=5 M + 5 F/concentration)
Duration of exposure in key study		6 h/d, 4-5 d/week, 2 weeks (9 exposures)
Critical effect		Irritation
Critical dose value		LOAEC: 300 ppm
Adjusted critical dose		6/24 x 5/7
Single assessment factors		Overall factor: see below
Other effects		
Remarks	The EU-LCI value of 2700 µg/m³ for PGMEA was adopted. The EU-LCI value for DPGME is an "ascribed EU-LCI-value".	The dose descriptor used was the worker-DNEL-long term for the inhalation route (50 ppm, 275 mg/m³) derived by SCOEL. This was corrected for the differences in duration of exposure between worker and consumer (24 h/d, 7 d/week vs. 8 h/d, 5 d/week) and the intraspecies differences (worker/general population: 2). This DNEL based on local effects is also considered to be sufficiently protective for systemic effects.
AgBB = Ausschuss zur gesundheitlichen Bewertung von Bauprodukten UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study UF_D data deficiencies.		

Table 29: Fact sheet propylene glycol mono methyl ether acetate (PGMEA)

Compound	**Propylene glycol mono methyl ether acetate (PGMEA, 2-methoxy-1-methylethyl acetate)**		***Factsheet***
Parameter	**Note**	Comments	Value / descriptor
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2019
General information			
CLP-Index No.	4	INDEX	203-603-9
EC-No.	5	EINECS	607-195-00-7
CAS-No.	6	Chemical Abstract Service number	108-65-6
Harmonised CLP classification	7	Human health risk related classification	-
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	132.16 1 ppm = 5.4 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	Miller et al. (1984)
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	B6C3F1 mice
Route / type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic, etc.	2 weeks
Exposure duration	14	h/d, d/w	6 h/d, 5 d/week, 2 weeks (11 exposures)
Critical endpoint	15	Effect (s), site of	Lesions of nasal olfactory epithelium
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	LOAEC
POD value	17	[mg/m³] or ppm or [mg/kg_{BW}×d]	1632 mg/m³ (300 ppm)
Assessment factors (AF)	18		
Adjustment for exposure duration	19	Study exposure h/d, d/w	5.6
Study length	20	sa→sc→c	6 (subacute to chronic)
Route-to-route extrapolation factor	21	-	1
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	3
	22b	Severity of effect (R8 6d)	1
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	1
	23b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		1
Other adjustment factors Quality of database	26		1
Result			
Summary of assessment factors	27	Total Assessment Factor	2520
POD/TAF	28	Calculated value [µg/m³ and ppb]	643 µg/m³ (119 ppb)
Molar adjustment factor	29		
Rounded value	30	[µg/m³]	650
Additional comments	31		

Rationale section	32		

- **Rationale for critical effects**

In a short-term repeated inhalation toxicity study (comparable to OECD guideline 412), F344 rats and B6C3F1 mice (5 M + 5 F/group) were exposed "whole body" to analytically confirmed vapour concentrations of 0, 300, 1000, or 3000 ppm PGMEA for 6 h/d, 5 d/week, 2 weeks (a total of 9 exposures). The highest concentration approached the saturated vapour concentration (4950 ppm PGMEA) (Miller et al., 1984, ECHA Dissemination, 2019).

In rats, no lethality was observed, and all animals appeared normal. Body weights and weight gain of exposed animals were similar to those of controls. The relative liver weight of hig-dose females was significantly increased (by about 5 %) without any gross or histopathological changes. Slight kidney changes (slightly reticulated, pale appearance) were observed in all high-dose and in 11/5 mid-dose males and in 2/5 high-dose females. The mean urinary specific gravity of high-dose males and females tended to be slightly lower than those for controls (Miller et al., 1984, ECHA Dissemination, 2019).

Regarding local effects, an exposure-related slight to moderate degeneration of the olfactory epithelium was observed in the nasal cavities of 3/5 males and 1/5 high-dose females. The changes were characterised by loss of cells in the neuron layer and flattening of the sustentacular cell layer, resulting in decreased thickness of the neuroepithelium. As such changes are not a common finding in young rats, the changes noted were attributed to the exposure with vapours of PGMEA. The ciliated respiratory epithelium remained unaffected (Miller et al., 1984, ECHA Dissemination, 2019).

In mice, the only histopathologic changes attributable to exposure occurred in the nasal cavities. Degeneration (metaplasia) of the olfactory epithelium, similar to that described for rats, was present to some degree in all male and female mice in all PGMEA exposed groups. This acute degenerative change occurred in a dose-related manner and was generally more severe and more extensive in animals exposed to 3000 ppm. However, even at 300 ppm, slight changes were generally present in the dorsomedial aspects of the ethmoid recess in addition to those in the more anterior portions of the olfactory epithelium in the nasal cavity proper. Most animals at the two higher concentrations and 1/5 of female mice in the 300 ppm group had slight focal areas of "respiratory metaplasia," a condition in which the compromised olfactory epithelium is replaced by ciliated respiratory epithelium similar to that normally present throughout the rest of the respiratory tree. An acute inflammatory exudate was present in the lumen of the nasal cavities in some animals of the two higher doses (Miller et al., 1984, ECHA Dissemination, 2019).

A LOAEC of 300 ppm PGMEA can be derived from these data.

Rationale for starting point

The LOAEC for effects on the nasal epithelium of mice at 300 ppm PGMEA served as the POD for the derivation of the EU-LCI.

Rationale for extrapolation factors

- Factor for adjustment for exposure duration: 5.6
- Adjusted study length factor: 6 (subacute exposure)
- LOAEC → NAEC extrapolation: 3
- Interspecies differences:
  allometry 1 (inhalation exposure, local effect)
  remaining differences 2.5 (According to the ECA report No. 29, no correction has to be made for differences in systemic metabolism when the POD is related to local effects. For remaining uncertainties, a value of 1 is used for remaining specific differences for effects on skin, eye and GI tract if the mode of action implies only a simple destruction of membranes, and a default value of 2.5 is used for effects on the skin, eye and GI tract if local metabolism or receptor binding reactions are involved. Since acetate esters are metabolically hydrolysed in the nasal epithelium, the factor of 2.5 is retained.)
- Intraspecies differences: 10

Total extrapolation factor: 2520, leading to a value of 300 ppm : 2520 = 0.119 ppm for PGMEA.
1 ppm PGMEA = 5.4 mg/m³, leading to a value for PGMEA of 643 µg/m³.

An EU LCI value for PGMEA of 650 µg/m³ is proposed.

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Table 30: Data collection sheet for dipropylene glycol mono methyl ether acetate (DPGMEA)

Compound	**Dipropylene glycol mono methyl ether acetate**	***Data collection sheet***	
N° CAS 88917-22-0 1 ppm = 7.82 mg/m³ at 23 °C	**EU-Classification: -** **CLP,** harmonised classification: none with respect to toxicity		
Organisation name	AgBB	CARB	
Risk value name	NIK ('Lowest Concentration of Interest')	8-hr REL	
Risk value (mg/m³)	3.9 mg/m³ (read-across from DPGME)	0.08	
Reference period	Chronic (general population)	Acute (8 h)	
Risk value (mg/m³) Short term (15 min)	-	-	
Year	2018	2010	
Key study		Landry and Yano, 1984	
Study type		Inhalation study with 0, 15, 50, 200 ppm DPM	
Species		rats, rabbits	
Duration of exposure in key study		6 h/d, 5 d/week, 13 weeks	
Critical effect		Kidney weight	
Critical dose value		NOAEC: 15 ppm	
Adjusted critical dose		15 ppm x 6 h/8 h x 5 d/7 d = 8 ppm	
Single assessment factors		UF_S $10^{0.5}$ x UF_A 2 x $10^{0.5}$ x UF_H 10 x $10^{0.5}$ = 600	
Other effects			
Remarks	The EU-LCI value of 3100 µg/m³ for DPGME was adopted. The EU-LCI value for DPGME is an "ascribed EU-LCI-value". The NIK value for DPGMEA was calculated by molar adjustment.	Read-across was performed: The derivation is based on data from a subchronic inhalation study with dipropylene glycol methyl ether	

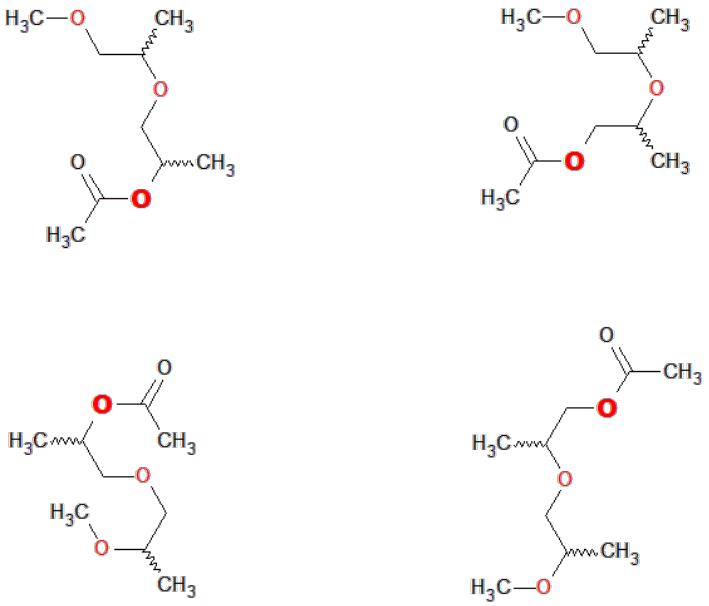
AgBB = Ausschuss zur gesundheitlichen Bewertung von Bauprodukten
UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study UF_D data deficiencies.

Table 31: Fact sheet dipropylene glycol mono methyl ether acetate (DPGMEA)

Compound	**Dipropylene glycol mono methyl ether acetate (DPGMEA)**		***Factsheet***
Parameter	**Note**	Comments	Value / descriptor
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2019
General information			
CLP-Index No.	4	INDEX	-
EC-No.	5	EINECS	406-880-6
CAS-No.	6	Chemical Abstract Service number	88917-22-0 (mixture of isomers)
Harmonised CLP classification	7	Human health risk related classification	-
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	190.3 1 ppm = 7.83 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	Propylene glycol methyl ether acetate (PGMEA)
Species	11	Rat, human, etc.	
Route / type of study	12	Inhalation, oral feed, etc.	
Study length	13	Days, subchronic, chronic, etc.	
Exposure duration	14	h/d, d/w	
Critical endpoint	15	Effect (s), site of	
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	
POD value	17	[mg/m³] or ppm or [mg/kg_{BW}×d]	POD/TAF from the fact sheet for PGMEA: 0.643 mg/m³
Assessment factors (AF)	18		
Adjustment for exposure duration	19	Study exposure h/d, d/w	-
Study length	20	sa→sc→c	-
Route-to-route extrapolation factor	21	-	-
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	-
	22b	Severity of effect (R8 6d)	-
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	-
	23b	Kinetic + dynamic	-
Intraspecies differences	24	Kinetic + dynamic General population	-
AF (sensitive population)	25		-
Other adjustment factors Quality of database	26		-
Result			
Summary of assessment factors	27	Total Assessment Factor	
POD/TAF	28	Calculated value [µg/m³ and ppb]	643 µg/m³ (119 ppb)
Molar adjustment factor	29		0.694 (= 132.16 / 190.3)
Rounded value	30	[µg/m³]	950
Additional comments	31		

Rationale section	32		

Dipropylene glycol monomethyl ether acetate (DPGMEA) (CAS No. 88917-22-0) is a mixture of four isomers (each of these in itself are a racemate of the RR and RS isomers): (2-(2-methoxy-1-methyl)ethoxy)-1-methylethyl acetate; (2-(2-methoxy-2-methyl)ethoxy)-1-methylethyl acetate; (2-(2-methoxy-2-methyl)ethoxy)-2-methylethyl acetate; and (2-(2-methoxy-1-methyl)ethoxy)-2-methylethyl acetate:



Two of these isomers (those on the right in the figure above) are derivatives of the beta-isomer form, i.e. of a primary alcohol. After hydrolysis, this alcohol may be directly oxidised to the corresponding alkoxy propionic acid. However, it is reported that theses isomers is usually present in the racemic mixture at concentrations below 5 % (CARB, 2010).

- **Rationale for read-across**

The data basis for DPGMEA is limited. Inhalation studies with repeated exposure to DPGMEA are not available.

Additional data are available from studies with structurally related propylene glycol ethers and ether acetate.

In a subacute inhalation study with propylene glycol mono methyl ether acetate(PGMEA), a degeneration with metaplasia of the olfactory nasal epithelium was observed in rats at 3000 ppm (NOAEC 1000 ppm) and in mice at all exposure concentrations (LOAEC: 300 ppm, no NOAEC) (Miller et al., 1984).

Similar lesions of the olfactory nasal epithelium of rats or mice have been described in a number of subacute or subchronic inhalation studies in which the animals had been exposed to other aliphatic esters of alkanoic acids: methyl acetate, ethyl acetate, n-butyl acetate, vinyl acetate, n-amyl acetate, n-butyl propanoate, or methyl methacrylate. The concentrations at which such effects were observed were in the range of 350 – 2500 ppm, similar to that of PGMEA. The epithelial lesions are attributed to the formation of acetic, propanoic or methacrylic acid, leading to cytotoxicity when the specific intracellular buffer capacity of the cells is exceeded and exhausted (Hardisty et al., 1999).

Studies on the toxic effects and the toxicokinetic of PGMEA and the non-esterified PGME clearly indicated that both are essentially toxicologically equivalent, with the exception of nasal irritation, which were only observed in inhalation studies with PGMEA but not with PGME despite the high absorption of both chemicals by this tissue (Domoradzki et al., 2003).

Similar conclusions can be drawn in case of DPGMEA and DPGME. Studies with DPGMEA indicate a low systemic toxicity, similar to that of the non-esterified DPGME. The similarity of those two compounds regarding systemic effects is corroborated by toxicokinetic data showing that DPGMEA is rapidly hydrolysed *in vivo* with the formation of DPGME (and acetate).

For DPGME, subchronic toxicity studies with rats and rabbits provided a NOAEC of 200 ppm, the highest concentrations

tested (ECHA Dissemination, 2019e). DPGMEA was not genotoxic in vitro, and no genotoxicity was observed with structurally related glycol ethers (PGME) or ether acetates (DEGMEA) in vivo (ECHA Dissemination, 2019e; OECD SIDS, 2003a). Carcinogenicity data are not available for DPGME(A), but PGME was not carcinogenic in a two-year carcinogenicity study with rats (OECD SIDS, 2003b).

No fertility study is available for DPGMEA. The no-observed-effect-level (NOEL) for fertility and reproductive effects of PGME in a two-generation inhalation reproduction study was 1000 ppm (3710 mg/m³). Mild parental toxicity was noted at this concentration (ECHA Dissemination, 2019c). Developmental toxicity studies have been carried with both DPGMEA and DPGME. No developmental toxicity was observed with DPGMEA up to the highest oral dose of 1000 mg/(kg bw x d) in rats (ECHA Dissemination, 2019) and up to the highest inhalation concentration of 300 ppm DPGME in rats and rabbits (Breslin, 1990; OECD SIDS, 2003b).

Overall, the data for DPGMEA and DPGME as well as for other propylene glycol ethers indicate a low systemic toxicity. At the same time, data for PGMEA show that this acetate ester ¬– as structurally similar to other aliphatic esters – produces local irritation effects in the olfactory nasal epithelium of rodents which are not observed at similar concentrations with the non-esterified glycol ether.

Thus, it is concluded that data for DPGME and other propylene glycol ethers do not provide a suitable basis for the derivation of an EU-LCI value for DPGMEA. Instead, read-across with data for the structurally-related PGMEA will be used for the derivation of an EU-LCI value for DPGMEA.

The subacute inhalation toxicity study with PGMEA in rats and mice (Miller et al., 1984) is considered a suitable key study for the derivation of an EU-LCI value for DPGMEA, performing a read across. This leads to a value for DPGMEA of 932 µg/m³.

A developmental toxicity study with oral exposure of rats to DPGMEA indicated a NOAEL of 1000 mg/(kg bw x d) for maternal and developmental toxicity. Toxicokinetic data in vivo indicate a rapid and nearly complete absorption of DPGMEA after oral administration. No substance-specific data are available regarding absorption after inhalation; however, glycol ethers in general are known to be well absorbed by inhalation (ECETOC, 2005; OECD SIDS, 2003b). Therefore, similar oral and inhalation absorption may be assumed when performing a route-to-route extrapolation.

Considering the maternal toxicity, the study length (GD6-21) can be regarded as of “subacute” duration. Using standard extrapolation factors (EC, 2013; ECHA, 2012):

- Route-to-route extrapolation (rats): 1.15 m³(kg b.w. x d)
- Adjusted study length factor (subacute exposure study): 6
- Allometric scaling: already included in route-to-route extrapolation
- Interspecies extrapolation: 2.5
- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 172.5 m³/(kg b.w. x d). This leads to a concentration of 1000 mg/(kg bw x d): 172.5 m³/(kg b.w. x d) = 5.797 mg/m³ (0.74 ppm). This value is about 6fold higher than that derived (from read-across) on the basis of local effects in the respiratory tract after inhalation exposure. It is concluded that the latter value will also offer protection against systemic effects of DPGMEA.

A comparison may also be performed with the derivation of a value for DPGMEA based on a read-across using data from inhalation studies with dipropylene glycol mono methyl ether (DPGME). In two subchronic studies with rats or rabbits, respectively, no adverse effects were observed up to the highest concentration of 200 ppm (see chapter 4.5.2.). Using standard extrapolation factors, i. e.:

- Adjustment for continuous exposure (6 h/d, 5 d/week): 5.6
- Adjusted study length factor (subchronic exposure study): 2
- Interspecies extrapolation:
  allometry: 1 (inhalation exposure, local effect)
  remaining differences: 2.5

- Intraspecies extrapolation (interindividual variability, general population): 10

Total assessment factor: 280. This leads to a concentration of 200 ppm : 280 = 0.714 ppm.

Performing a molar adjustment with 1 ppm DPGMEA = 7.82 mg/m³, this leads to a value of 5583 µg/m³. This value is also about 6fold higher than the proposed EU-LCI value based on local effects of the acetate ester of propylene glycol as derived above.

It is concluded that the derivation of the EU-LCI value should be based on the local effects observed in an inhalation study with PGMEA, performing a read-across. The so-derived value is regarded as also protective against systemic effects of DPGMEA.

An EU LCI value for DPGMEA of 950 µg/m³ is proposed.

DPGMEA is reported to have a mild odour. However, data on odour thresholds are not available.

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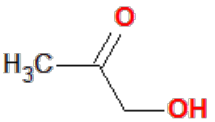
5 Toxicological evaluation of hydroxyacetone (acetol) as basis for the derivation of an EU-LCI value

(Note: Hydroxyacetone (acetol) is a data-poor compound. Read-across is performed for most of the substance effects to the structurally related compound propylene glycol (propane-1,2-diol). For this compound, an EU-LCI has been derived and the data basis for the derivation of the EU-LCI value has been published (EU-LCI Working Group, 2018). Brief summaries of the results for the read-across compound are presented here. For more detailed information on the read-across compound the reader is referred to the fact sheet for propylene glycol (see chapter5.8).

5.1 Substance identification

Substance identification data and physicochemical properties of hydroxyacetone are shown in Table 32 and Table 33. Hydroxyacetone is an oily liquid which is completely miscible with water. The substance is reported to have a characteristic odour which, however, is not further described.

Table 32: Substance identification of hydroxyacetone (IFA, 2019a; NLM, 2019a)

CAS-No. EU-No. CLP-Index-No.	Systematic name, common names	Summary formula	Structural formula
CAS-No. 116-06-6 EU-No. 204-124-8	hydroxyacetone, 1-hydroxy-propane-2-one	$C_3H_6O_2$	

5.2 Substance properties and uses

10 – 100 tonnes of hydroxyacetone are manufactured and/or imported into the European Economic Area annually. No uses at industrial sites, by professional workers, or consumer uses are listed in the registration dossier (ECHA Dissemination, 2019a). Hydroxyacetone is considered to be generally recognised as safe (GRAS) with no safety concern as a food additive (JECFA, 2010; Smith et al., 2009). No further data on the use of this substance could be identified in the available literature.

Table 33: Physicochemical properties of hydroxaacetone (IFA, 2019a)

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa) (at 20°C)	Density (g/cm³)	log Pow	Solubility in water (g/L) (at 20°C)
74.08	-17 °C*	decomposition	7.5	1.08	-0.78 (estimated)	miscible

5.3 Exposure

5.3.1 Indoor air

There are no data available.

5.3.2 Other sources

Hydroxyacetone occurs naturally in foodstuffs and is an intermediate in the metabolism of the protein amino acids glycine, serine and threonine metabolism and hence a normal constituent of the human body. It is also generated from methylglyoxal by the enzymatic reaction of oxidoreductases. Hydroxyacetone is also the first oxidation product in the metabolism of (endogenously produced or taken up from exogenous sources) acetone and of propane-1,2-diol (EFSA, 2017; NLM, 2019b; TGSC, 2018; U.S.EPA, 2003).

5.4 Toxicokinetics

Few data are available on the toxicokinetics of this compound.

Enzymatic reduction of hydroxyacetone to L-propane-1,2-diol has been demonstrated by human aldose reductase from muscle and placenta. L-propane-1,2-diol is further oxidised via L-lact-aldehyde to L-lactic acid and to pyruvic acid which is a centrepiece of the normal intermediary metabolism in mammalian cells. Hydroxyacetone, on the other hand, can be oxidised by acetol monooxygenase to methylglyoxal (2-oxopropanal) which is converted by a glutathione-dependent reaction to D-lactic acid. This compound is further oxidised to pyruvic acid. Alternatively, methylglyoxal may be directly oxidised to pyruvic acid as well. In summary, sharing metabolic pathways of propane-1,2-diol metabolism, hydroxylacetone may be oxidised via several metabolic pathways to pyruvic acid and consequently enter various intermediary pathways (especially citric acid cycle, gluconeogenesis, fatty acid synthesis) (ATSDR, 1997; JECFA, 2010; Kalapos, 1999).

5.5 Health effects

5.5.1 Acute toxicity, sensory irritation and local effects

The acute toxicity of hydroxyacetone is low. An 8-hour exposure of rats to 6150 mg/m^3 did not lead to lethal effects, and systemic effects after massive vapour inhalation were not observed in animal experiments (no further details available). An LD50 value of 2200 mg/kg bw was found in an animal experiment with rats. Dermal exposure to hydroxyacetone (17.3 g/kg bw) did not entail any fatalities in rabbits. Hydroxyacetone did not show a sensitising potential in guinea pigs. Direct eye contact with liquid hydroxyacetone lead to irritative to weak corrosive effects in animal experiments (IFA, 2019a).

Hydroxyacetone was negative in the Reconstructed human Epidermis (RhE), as well as in the Reconstructed human Cornea-like Epithelium (RhCE) test method. Thus, hydroxyacetone is considered non-irritant to skin and eyes (ECHA Dissemination, 2019a). No information was identified in the available literature regarding *in vivo* irritative effects of hydroxyacetone on the mucosae of the eyes and the upper respiratory tract. However, such a potential can be deduced from a read-across to propane-1,2-diol for which such effects have been studied and described.

Read-across: propane-1,2-diol

In a human volunteer study, 27 individuals exposed to 176 – 851 mg propane-1,2-diol /m^3 in an aircraft simulator for 1 min reported sore and dry eyes, throat dryness and irritative cough were reported. A decrease in tear film stability was also described (Wieslander et al., 2001).

In an acute inhalation assay with rats, nose-only exposure for 4 hours to fully respirable vapor-aerosol mixtures led to slight localised irritation (bleeding around the eyes and nose) and temporarily reduced weight gain (Werley et al., 2011).

In another acute "nose-only" inhalation study with rats, no treatment-related clinical effects were noted up to the highest concentration of 41 mg/L (Werley et al., 2011).

In an acute assay with beagle dogs, animals were exposed via face mask to an ascending dose phase and a 7-day repeated dose phase. Aerosols were fully respirable and the concentrations and exposure times were 1.5 – 30 mg/l for 8 – 60 min in the ascending phase and 5 mg/l for 60 min in the 7 d day repeated dose phase. In the ascending dose phase, dogs were generally intolerant (e.g. showing restlessness) of high exposure concentrations (15 and 30 mg/L). There was an inverse relationship between the tolerable exposure concentration and the time of exposure (Werley et al., 2011).

5.5.2 Repeated dose toxicity

There are no data available from toxicological studies regarding effects following repeated exposure of humans or animals against hydroxyacetone.

Read-across: propane-1,2-diol

Inhalation

In a more subacute (28 d) study, rats were exposed "nose only" to propylene glycol aerosols (highly respirable particles) (Werley et al., 2011). The animals were exposed to 30 mg propylene glycol/l for up to 120 min/d in order to obtain deposited lung doses of 7.2, 21.6, 72 and 216 mg/(kg bw x d). The only biologically relevant findings included clinical signs of ocular and nasal irritation indicated by minor bleeding around the eyes and nose, and minimal laryngeal squamous metaplasia at 72 and 216 mg/(kg bw x d).

In a corresponding study, dogs were exposed via a face mask with an oropharyngeal tube to aerosol concentrations of 5 mg/l for 3 – 31 min and 37 – 49 min in the high-dose group in order to obtain deposited lung doses of 3, 6, 18 and 60 mg/(kg bw x d). No local effects of statistical significance were identified. Treatment-related decreases in haemoglobin, red blood cells and haematocrit were observed in the two highest exposure groups, equivalent to approximately 18 and 60 mg/(kg bw x d) (NOEL 6 mg/(kg bw x d)) (Werley et al., 2011).

This study in rats and dogs substantiates the effects observed in other studies (local ocular and respiratory irritation in rats, mild haematotoxicity in dogs). However, its value in identifying a dose descriptor for deriving an emission threshold is limited, since daily exposure times were varied in order to obtain targeted deposited lung doses (EU-LCI Working Group, 2018).

Oral exposure

No adverse effects were observed in rats in a chronic toxicity feeding study with oral exposure levels up to 1700 and 2100 mg propane-1,2-diol/(kg KG x d) for male and female animals, respectively (Gaunt et al., 1972).

Slight, reversible haematotoxicity was observed in a chronic feeding study with dogs at a dose levels of 5000 but not at 2000 mg/(kg bw x d) (Weil et al., 1971). Cats appear to be more sensitive to haematotoxic effects of propylene glycol. In a subchronic (94 d) study with dietary exposure of male cats, a dose-dependent increase in Heinz bodies was reported. A NOAEL was identified of 443 mg/(kg bw x d) based on a secondary increase in haemosiderin deposits in liver and spleen. Heinz bodies represent membranous protein aggregations, which in certain cases represent the most sensitive endpoint of haematotoxicity; however, they are generally not considered to be adverse (ECHA Dissemination, 2019b).

5.5.3 Genotoxicity and carcinogenicity

Genotoxicity

A weak mutagenic potential of hydroxyacetone has been proposed from the results of several *in vitro* tests. However, it was presumed that the mutagenic potential can chiefly be ascribed to contaminations of the substance with methylglyoxal (IFA, 2019a).

Read-across: propane-1,2-diol

No studies were located regarding in vivo genotoxic effects in humans.

Based on the negative results of several bacterial mutagenicity assays, *in vitro* chromosomal aberrations tests and an *in vivo* dominant lethal assay with mice, a mouse micronucleous test and a chromosome aberration test with rats (ECHA Dissemination, 2019b; NTP, 2004), there is no concern for genotoxicity of propane-1,2-diol.

Carcinogenicity

No data are available for this endpoint for hydroxyacetone.

Read-across: propane-1,2-diol

NTP summarised the results of 2-year bioassay with rats. The animals were fed diets with up to 5 % (2,500 mg/(kg bw x d)) propane-1,2-diol in their diet. No treatment-related neoplasms were noted (NTP, 2004).

5.5.4 Toxicity to reproduction

There are no studies available with exposure to hydroxyacetone.

Read-across: propane-1,2-diol

No adverse effects on fertility were found in a continuous breeding study with mice. In this study, animals received propylene glycol at levels up to 10100 mg/(kg bw x d) for 7 days before mating, followed by cohabitation and continuous treatment for 98 days. The NOAEL for reproductive toxicity was established to exceed 10100 mg/(kg bw x d). Also, no adverse effects on development were noted in mice treated with propylene glycol doses up to 10400 mg/(kg bw x d) on GD 6-15 (ECHA Dissemination, 2019b; NTP, 2004).

5.5.5 Odour perception

The substance is reported to have a characteristic odour (IFA, 2019a). However, no data on the odour threshold are available.

5.6 Evaluation

5.6.1 Existing regulations and classifications

There is no harmonised classification for hydroxyacetone (ECHA C&L Inventory, 2019). There were no OELs available for hydroxyacetone (IFA, 2019b). Furthermore, no other existing guide values for hydroxyacetone in air were identified in the available literature except for a NIK value reported by AgBB (AGBB, 2018). However, no substance-specific data were used. Instead, the NIK-value for hydroxyacetone is based on read-across using data and the EU-LCI value for propylene glycol.

5.6.2 Derivation of an EU-LCI value

The data basis for hydroxyacetone is very limited.

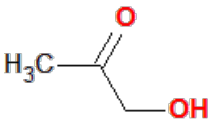
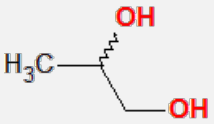
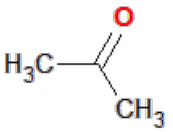
No data are available on the toxicity of hydroxyacetone in humans. Reported acute toxicity data from animal studies indicate a low toxicity of hydroxyacetone. Hydroxyacetone occurs naturally in foodstuffs and is an intermediate in the metabolism of the protein amino acids glycine, serine and threonine metabolism and hence a normal constituent of the human body. Hydroxyacetone is also the first metabolite in the metabolism of acetone in the human body. Hydroxyacetone is metabolised to pyruvic acid, entering and sharing the metabolic pathways of propane-1,2-diol (propylene glycol) to pyruvic acid, and finally thus entering various intermediary pathways (especially citric acid cycle, gluconeogenesis, fatty acid synthesis) (ATSDR, 1997; JECFA, 2010; Kalapos, 1999). The weak mutagenic potential of hydroxyacetone observed in some *in vitro* studies may be attributed to contaminations with methylglyoxal (IFA, 2019a). Carcinogenicity and reproductive toxicity studies with hydroxyacetone are not available.

Due to the lack of toxicity data for hydroxyacetone, the inhalation data of the read-across substance, propane-1,2-diol (propylene glycol), are considered as suitable for the derivation of an EU-LCI value for hydroxyacetone.

The rationale for read-across with propane-1,2-diol (propylene glycol) are:

- Propane-1,2-diol is a compound which is structurally closely related to 1-hydroxy-acetone, differing only in that the secondary hydroxyl group of propane-1,2-diol is oxidised to a keto group. Both compounds also provide similar physicochemical properties (water solubility, high viscosity due to hydrogen bonds) and share the same metabolic pathways in mammals.
- Based on the structural and physicochemical similarities, the key assumption is that both compounds will have the same critical endpoint (irritation) as was observed in inhalation studies with propane-1,2-diol. The same approach was followed in the derivation of a NIK value for hydroxyacetone by the AgBB (2018).
- The first step in acetone metabolism leads to the formation of hydroxyacetone, so there is also a metabolic similarity for acetone and hydroxyacetone. However, acetone lacks a hydroxyl group and is a much more volatile compound than hydroxyacetone. The local irritation of acetone to eyes and mucous membranes in inhalation studies is very low. Read-across using data from inhalation studies with acetone would lead to a much higher LCI value than that derived from read-across with data for propylene glycol. Thus, read-across performed with data for propylene glycol is a more conservative approach and is based on greater structural similarity of this compound with hydroxyacetone as compared to acetone.

Table 34: Substance information for hydroxyacetone and propylene glycol (propane-1,2-diol)

Compound	Structure	Molar mass [g/mol]	EU-LCI value
hydroxyacetone, acetol		74.08	2100 µg/m³ (read-across to propane-1,2-diol)
propane-1,2-diol		76.09	2100 µg/m³ (derived EU-LCI value*, adopted 2016) (EU-LCI Working Group, 2018)
Acetone		58.08	120 000 (proposed)

* As POD a LOAEC of 160 mg/m³ from a subchronic inhalation study with rats was used. As assessment factors 3 (extrapolation of a NAEC from a LOAEC), 1 (study length: no increase in severity of effects with prolonged exposure to be expected), 2.5 (remaining interspecies differences in inhalation studies), 10 (intraspecies variance), and 1 (i. e., no adjustment for continuous exposure duration) were applied (total 420) (EU-LCI Working Group, 2018).

A molar adjustment factor of 74.08/76.09 = 0.97 is used leading to a proposed EU-LCI value for hydroxyacetone of 2100 µg/m³.

An EU-LCI value for hydroxyacetone of 2100 µg/m³ is proposed.

Hydroxyacetone is described as having a distinct odour. Data on odour thresholds are not available.

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5.8 Fact and data sheet for hydroxyacetone (acetol)

Table 35: Data collection sheet for hydroxyacetone (acetol)

Compound	Hydroxyacetone	*Data collection sheet*
N° CAS 116-09-6	**EU-Classification: -**	
1 ppm = 3.05 mg/m³	**CLP:** no harmonised classification	
Organisation name	AgBB	
Risk value name	NIK ('Lowest Concentration of Interest')	
Risk value (mg/m³)	2100 µg/m³ (read-across from propane-1,2-diol)	
Reference period	Chronic (general population)	
Risk value (mg/m³) Short term (15 min)	-	
Year	2016	
Key study	Suber et al. (1989)	
Study type	Subchronic inhalation study (0, 160, 1000 or 2200 mg/m³, aerosol, nose only) with propylene glycol (read-across, CAS: 57-55-6)	
Species	Rat	
Duration of exposure in key study	6 h/d, 5 d/week, for 90 d	
Critical effect	Local ocular and respiratory tract (nasal) irritation	
Critical dose value	LOAEC (propylene glycol): 160 mg/m³ (51.4 ppm)	
Adjusted critical dose	None (local effect, completely reversible)	
Single assessment factors	UF_S 1 x UF_L 3 x UF_A 2.5* x UF_H 10 x UF_D 1 = 75	
Other effects	-	
Remarks	Read-across was applied and propane-1,2-diol (propylene glycol) was used as test item instead of hydroxyacetone. The derived NIK value for propylene glycol was transformed into a NIK value for hydroxyacetone by considering a molar adjustment.	

AgBB = Ausschuss zur gesundheitlichen Bewertung von Bauprodukten; *: remaining differences interspecies toxicodynamics factor

UF_L Used LOAEL; UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study; UF_D data deficiencies

Fact sheet propylene glycol (propane-1,2-diol) (EU-LCI Working Group (2018))

Compound	**Propylene glycol (propane-1,2-diol)**		***Factsheet***
Parameter	**Note**	Comments	Value / descriptor
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	2100
EU-LCI status	2	Draft/Final	Final
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2016
General information			
CLP-Index No.	4	INDEX	-
EC-No.	5	EINECS	200-338-0
CAS-No.	6	Chemical Abstract Service number	57-55-6
Harmonised CLP classification	7	Human health risk related classification	-
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	76.09 1 ppm = 3.11 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	Suber et al. (1989)
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	Rat
Route / type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic, etc.	Subchronic (90 d)
Exposure duration	14	h/d, d/w	6 h/d, 5 d/week
Critical endpoint	15	Effect (s), site of	Local ocular and respiratory tract irritation
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	LOAEC
POD value	17	[mg/m³] or ppm or [mg/kg_{BW}×d]	160 mg/m³
Assessment factors (AF)	18		
Adjustment for exposure duration	19	Study exposure h/d, d/w	1
Study length	20	sa→sc→c	1
Route-to-route extrapolation factor	21	-	N/A
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	3
	22b	Severity of effect (R8 6d)	1
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	1
	23b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		1
Other adjustment factors Quality of database	26		1
Result			
Summary of assessment factors	27	Total Assessment Factor	75
POD/TAF	28	Calculated value [µg/m³ and ppb]	2133 µg/m³ [681 ppb]
Molar adjustment factor	29		
Rounded value	30	[µg/m³] (2133 µg/m³ x 0.97 = 2069 µg/m³)	2100
Additional comments	31		

Rationale section	32		

- **Rationale for critical effects**

Inhalation exposure to propylene glycol (PG) may result in local ocular and respiratory tract irritation in experimental animals and human volunteers.

Acute exposure of human volunteers for 1 minute to PG atmospheres of 176-851 mg/m3 resulted in sore dry eyes, throat dryness, irritative cough and a mild decrease in tear film stability (Wieslander et al., 2001). In a subchronic (90-day) repeated exposure study with rats, a LOAEC of 160 mg/m^3 was identified based on a slightly increased incidence in nasal haemorrhaging (in the absence of a histopathological correlate at this dose level) and ocular discharge (Suber et al., 1989).

The LOAEL of 160 mg/m^3 from the subchronic study is the most relevant dose descriptor for the derivation of a limit value for local effects, and the weight of evidence from the human volunteer study substantiates its reliability.

Assessment factors

Adjustment for exposure duration: 1 (local effect, and completely reversible at weekends)
Exposure duration factor (subchronic/chronic): 1
LOAELNOAEL: 3 (slight effect without histopathological correlate)
Allometry: 1 (inhalation exposure, local effect)
Remaining differences interspecies toxicodynamics factor (rat-to-human): 2.5
Intraspecies factor (general population): 10
Quality of database factor: 1 (weight of evidence of animal and human data)

The TAF is 75. The calculated EU-LCI value for propylene glycol is POD/TAF = 160 mg/m^3/75=2133 µg/m^3 (681 ppb). After rounding, the EU-LCI-value is 2100 µg/m^3.

Extrapolation of a vapour threshold based on data for the aerosol bears a significant uncertainty.

Appendix / background

Propylene glycol is a naturally occurring chemical in foods. The FDA and the Joint FAO/WHO Expert Committee on Food Additives (JEFCA) consider PG to be generally recognised as safe (GRAS) and approved as a food additive for all food categories up to 2 %.

The WHO Joint Expert Committee on Food Additives (JECFA) has established an ADI of 0-25 mg/kg/day (FAO/WHO Expert Committee, 1974).

The FDA Center for Drug Evaluation and Research (FDA CDER, 1996, www.fda.gov) has included PG on the revised'Inactive Ingredients for Currently Marketed Drug Products' list for use in 'inhalation solution' and 'metered nasal spray', where the specific potency and formulation range for PG remains unspecified at this time. The vapour pressure of PG is 0.2 hPa at 25 °C, resulting in a calculated saturated vapour concentration of 0.63 mg/l (= 630 mg/m^3).

Acute toxicity

Propylene glycol is not acutely toxic via the oral or dermal route of exposure.

In an acute inhalation assay, rats were nose-only exposed for 4 hours to single atmospheres of 14.4, 30.5, and 44.9 mg/L of fully respirable PG. Treatment-related clinical signs included slight localised bleeding around the eyes and nose at day 7. On study days 1–3 post-exposure, there were 5-10 % decreases in body weight, which were fully reversible by study day 7 (Werley et al., 2011).

In another acute inhalation assay, rats were exposed nose-only for 4 hours/day for seven consecutive days. Groups of 5 animals/sex/concentration were exposed to either 20.8 or 41.0 mg/L fully respirable PG aerosol. There were no treatment-related clinical observations. Since no treatment-related effects were observed, the NOEL was > 41 mg/L

(Werley et al., 2011).

In an acute assay with beagle dogs, 2 male and 2 female animals were exposed via face mask to an ascending dose phase and a 7-day repeated dose phase. PG aerosols were fully respirable and the concentrations and exposure times were 1.5-30 mg/l for 8-60 minutes in the ascending phase and 5 mg/l for 60 minutes in the 7-day repeated dose phase.

In the ascending dose phase, dogs were generally intolerant (e.g. showing restlessness) of high exposure concentrations (15 and 30 mg/L). There was an inverse relationship between the tolerable exposure concentration and the time of exposure.

In the 7-day repeated dose study, 5 mg/L for up to 60 minutes duration was well tolerated (Werley et al., 2011).

PG is essentially non-irritating to the skin, mildly irritating to the eyes and not sensitising. In addition, the substance is not mutagenic.

Repeated dose toxicity — oral

Chronic oral exposure of rats did not result in adverse effects at and up to dose levels of 1.7 and 2.1 g/kg bw/day in feed for male and female animals, respectively (OECD limit dose 1 g/kg bw/day) for exposure periods up to 2 years (Gaunt et al., 1972).

In a chronic study of dogs, groups of 5 male and 5 female animals were fed diets containing PG dose levels of 5 and 2 g/kg bw/day for 104 weeks. Slight, reversible haematotoxicity was observed in the high dose group, characterised by slight decrease in haemoglobin, haematocrit, total erythrocyte count and reticulocytes (NOAEL 2 g/kg bw/day) (Weil et al., 1971).

Cats appear to be more sensitive to PG haematotoxicity. Male animals were subchronically exposed via the diet to dose levels of 443 and 4239 mg/kg bw/day for 94 days and 80, 675 and 1763 mg/kg bw/day for 69 days.

A species-specific and dose-dependent increase in Heinz bodies was reported. The NOAEL was identified as 443 mg/kg bw/day based on a secondary increase in haemosiderin deposits in liver and spleen. Heinz bodies represent membranous protein aggregations, which in certain cases represent the most sensitive endpoint of haematotoxicity; however, they are generally not considered to be adverse (Toxicology Research Laboratory 1979).

In a further cat study, induction of Heinz bodies was noted, albeit at higher dose levels of 2400 mg/kg bw/day or higher when gavaged for 17 weeks (Weiss et al., 1990).

Repeated dose toxicity — inhalation

In a subchronic inhalation study, rats were exposed to PG aerosol at dose levels of 0, 0.16, 1, and 2.2 mg/l for 6h/day, 5 days/week for 90 days.

Reversible, treatment-related nasal haemorrhaging was observed in 1, 64, 74 and 75 % of males and in 1, 14, 71 and 71 % of females in the control, low-, medium-, and high-exposure group, respectively. Similar trends were observed for ocular discharge (5, 16, and 40 % in males, and 8, 14, 28, and 35 % in females).

Microscopic examination of the nasal cavity showed a thickening of the respiratory epithelium (an increased number of goblet cells or an increase in the mucin content of goblet cells) in the medium and high dose groups only. In the absence of a histopathological correlate in the low-dose group, 160 mg/m3 is considered to be an acceptable LOAEL for local effects for the risk assessment.

The increased number of goblet cells and/or increased mucin content appear to be an adaptive response. Minimal local irritation and histopathological changes in the nasal cavity are well known unspecific observations which are commonly observed with high aerosol concentrations. Indeed this dosimetry and interpretation is fully supported by the proceedings of an international expert workshop of the European Society of Toxicology (Kaufmann et al., 2009). Accordingly, such lesions might be assessed as ‘non-adverse’.

The observed nasal haemorrhage might be explained by pigment/porphyrin staining following an increase in lacrimal secretion caused by the mildly irritating or drying effect of propylene glycol aerosol on mucous membranes (Suber et

al., 1989).

In a more recent subacute (28 day) study, PG aerosols were generated in a novel capillary aerosol generator resulting in highly respirable particles. The aerosols were nose-only exposed to rats and via a face mask with an oropharyngeal tube to dogs (Werley S.W. et al., 2011).

In the rat study, 31 animals/sex/group were exposed to concentrations of 30 mg/l respirable PG for up to 120 minutes/day in order to obtain deposited lung doses of 7.2, 21.6, 72 and 216 mg/kg/day.

The only biologically relevant findings included clinical signs of ocular and nasal irritation indicated by minor bleeding around the eyes and nose, and minimal laryngeal squamous metaplasia in the 72 and 216 mg/kg/day dose groups (NOEL approx. 20 mg/kg bw). This finding is commonly observed in inhalation studies in rats, and is likely related to the unique sensitivity of the tissue but also to the circuitous airflow pathway through the larynx, which increases particle deposition.

In the dog study, 4 animals/sex/group were exposed to aerosol concentrations of 5 mg/l for 3-31 minutes and 37 to 49 minutes in the high-dose group in order to obtain deposited lung doses of 3, 6, 18 and 60 mg/kg bw/day.

No local effects of statistical significance were identified. Treatment-related decreases in haemoglobin, red blood cells and haematocrit were observed in the two highest exposure groups, equivalent to approximately 18 and 60 mg/kg/day (NOEL 6 mg/kg bw/day). In male dogs from the high dose group, similar small (albeit non-statistically significant) decreases were observed in these haematological markers as well.

This study in rats and dogs substantiates the effects observed in other studies (local ocular and respiratory irritation in rats, mild haematotoxicity in dogs). However, its value in identifying a dose descriptor for deriving an emission threshold is limited, since daily exposure times were varied in order to obtain targeted deposited lung doses.

No toxicity to reproduction was identified in a continuous breeding study with mice (NOAEL 10.1 g/kg bw/day; NTP 1985) or in a prenatal developmental toxicity study in mice (NOAEL 10.4 g/kg bw/day; Bushy Run Center 1993).

Systemically available propylene glycol is converted to lactate involving alcohol dehydrogenase. Lactate is efficiently excreted or detoxified via gluconeogenesis (NTP 2004).

Human evidence

In a human volunteer study, 27 individuals were exposed to PG atmospheres of 176-851 mg/m^3 in an aircraft simulator for 1 minute. Sensations of sore and dry eyes, throat dryness and irritative cough were reported. In addition, a decrease in tear film stability was found (Wieslander et al., 2001).

Due to significant co-exposures, paint emission studies and studies with theatrical smokes were not taken into account since no reliable dose descriptors can be derived (Wieslander & Norbäck, 2010; Ernstgard et al., 2007; NIOSH, 1992; Moline et al., 2000).

Alternative derivation of an EU-LCI for systemic effects

Propylene glycol has a low potential to cause systemic effects following acute or repeated inhalation. The biological relevance of haematological changes in cats and dogs at high dose levels is unclear. However, an alternative derivation of an EU-LCI for systemic effects is presented for plausibility:

NOAEL: 443 mg/kg bw from a subchronic cat study

EU-LCI: Route-to-route extrapolation:

NOAEC = NOAEL x 1/sRVcat x ABSoral/ABSinhal
= 443 mg/kg bw x 1/0.2 x 1 = 2215 mg/m^3
Exposure duration factor (subchronic/chronic): 2
Allometry (cat/human): 1 (reflected in route-to-route extrapolation)
Remaining differences interspecies toxicodynamics factor (rat-to-human): 2.5
Intraspecies factor (general population): 10

Quality of database factor: 1

EU-LCI = 2215 mg/m³ /(2 × 2.5 × 10) = 44.3 mg/m³ = 44 000 µg/m³

Respiratory volume for cats 0.2 l/min/kg bw

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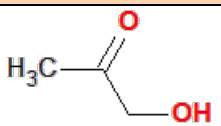
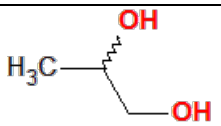
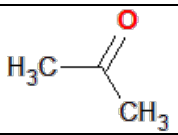
Table 36: Fact sheet hydroxyacetone (acetol)

Compound	**Hydroxyacetone**		***Factsheet***
Parameter	**Note**	Comments	Value / descriptor
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	2100
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2019
General information			
CLP-Index No.	4	INDEX	-
EC-No.	5	EINECS	204-124-8
CAS-No.	6	Chemical Abstract Service number	116-09-6
Harmonised CLP classification	7	Human health risk related classification	-
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	74.08 1 ppm = 3.05 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	propylene glycol (propane-1,2-diol)
Species	11	Rat, human, etc.	
Route / type of study	12	Inhalation, oral feed, etc.	
Study length	13	Days, subchronic, chronic, etc.	
Exposure duration	14	h/d, d/w	
Critical endpoint	15	Effect (s), site of	
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	
POD value	17	[mg/m³] or ppm or [mg/kg_{BW}×d]	POD/TAF from the fact sheet of propylene glycol: 2.133 mg/m³
Assessment factors (AF)	18		
Adjustment for exposure duration	19	Study exposure h/d, d/w	-
Study length	20	sa→sc→c	-
Route-to-route extrapolation factor	21	-	-
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	-
	22b	Severity of effect (R8 6d)	-
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	-
	23b	Kinetic + dynamic	-
Intraspecies differences	24	Kinetic + dynamic General population	-
AF (sensitive population)	25		-
Other adjustment factors Quality of database	26		-
Result			
Summary of assessment factors	27	Total Assessment Factor	
POD/TAF	28	Calculated value [µg/m³ and ppb]	2133 µg/m³ and 700 ppb
Molar adjustment factor	29		0.97 (= 74.08 / 76.09)
Rounded value	30	[µg/m³] (2133 µg/m³ x 0.97 = 2069 µg/m³)	2100
Additional comments	31		

Rationale section	32		

Rationale for read-across

- Data poor compound: no adequate toxicological data for hydroxyacetone; *de novo* derivation of EU-LCI is not possible.
- Read-across from EU-LCI value of propylene glycol (adopted in 2016): hydroxyacetone (1-hydroxypropane-2-one) shows structural, physicochemical and metabolic similarities to propylene glycol (1,2-dihydroxypropane). Hydroxyacetone and propylene glycol share common metabolic pathways in the metabolism of C_3-compounds.
- Toxicological critical endpoint for propylene glycol: local nasal and ocular irritation.
- The key assumption underlying the read-across of the EU-LCI value from propylene glycol to hydroxyacetone is that both compounds have the same critical endpoint (local irritation) and this is caused by the structural similarity. The same approach was followed in the derivation of a NIK value for hydroxyacetone by the AgBB (2018).
- The first step in acetone metabolism leads to the formation of hydroxyacetone, so there is also a metabolic similarity for acetone and hydroxyacetone. However, acetone lacks a hydroxyl group and is a much more volatile compound than hydroxyacetone. The local irritation of acetone to eyes and mucous membranes in inhalation studies is very low. Read-across using data from inhalation studies with acetone would lead to a much higher LCI value than that derived from read-across with data for propylene glycol. Thus, read-across performed with data for propylene glycol represents a more conservative approach and is based on greater structural similarity of this compound with hydroxyacetone as compared to acetone.

Compound	Structure	MW [g/mol]	EU-LCI value (µg/m³)
Hydroxyacetone		74.08	2 100 (proposed)
Propane-1,2-diol (racemate)		76.09	2 100 (final)
Acetone		58.08	120 000 (final)

Data for hydroxyacetone

Hydroxyacetone is a non-volatile oily, water-soluble liquid with a distinct odour. It occurs naturally in food. In the human body, hydroxyacetone occurs as an intermediate in the metabolism of the protein amino acids glycine, serine and threonine metabolism. It is also generated from methylglyoxal by the enzymatic reaction of oxidoreductases (NLM, 2019). Hydroxyacetone is the first metabolite in the metabolism of acetone and may also be formed by the oxidation of propylene glycol. The metabolism of hydroxyacetone is described to follow to two routes: one, preferentially in the liver, leading to methylglyoxal, the other, extrahepatic pathway, leading to propylene glycol (Kalapos, 1999). Both metabolites are subsequently further oxidised via different pathways to the same metabolite, pyruvic acid, which is a central metabolite in the normal intermediary cellular metabolism of carbohydrates. Pyruvic acid (or pyruvate) will be used in different metabolic pathways, e. g. citric acid cycle, gluconeogenesis and synthesis of fatty acids.

Hydroxyacetone is assumed to be of low toxicity. However, the data base is extremely limited. No deaths were reported following the 8-hour exposure of rats with 6150 mg/m³ hydroxyacetone (GESTIS, 1996). The acute oral toxicity is low: LD50 rat 2200 mg/(kg bw x d) (Smyth and Carpenter, 1948). Weak mutagenic effects noted in some studies were attributed to contamination with methylglyoxal (GESTIS, 1996). Further data are not available.

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