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Final report

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

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Toxikologische Beratung, Müllheim im Markgräfler Land

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

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

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

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

References

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

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

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

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

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

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

Quellen

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

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Table of content

List of figures

List of tables

List of abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
AgBB	Ausschuss zur gesundheitlichen Bewertung von Bauprodukten (Committee for Health-related Evaluation of Building Products)
AGÖF	Arbeitsgemeinschaft ökologischer Forschungsinstitute e.V. (Association of Ecological Research Institutes e.V.)
AGS	Ausschuss für Gefahrstoffe (Committee on Hazardous Substances)
AGW	Arbeitsplatzgrenzwert (Occupational Exposure Limit)
ANSES	Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail (French Agency for Food, Environmental and Occupational Health and Safety)
BG Chemie	Berufsgenossenschaft Chemie (Institution for Statutory Accident Insurance and Prevention in the Chemical Industry)
bw	Body weight
CAS	Chemical abstract service
CIR	Cosmetic Ingredient Review
CLH	Harmonised Classification and Labelling
CLP	Classification, labelling and packaging
C_{max}	Maximum plasma concentrations
CNS	Central nervous system
CO_2	Carbon dioxide
DFG	Deutsche Forschungsgemeinschaft (German Research Foundation)
DGUV	Deutsche gesetzliche Unfallversicherung (German Social Accident Insurance)
DNEL	Derived no effect level
ECHA	European Chemicals Agency
EFSA	European Food Safety Authority
EFSA ANS	EFSA Panel on Food Additives and Nutrient Sources added to Food
EFSA CEF	The EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids
EU	European Union
F	Female(s)
FVC	Forced Vital Capacity
FEV1	Forced expiratory volume in 1 second
FOB	Functional observational battery
GABA	γ-Aminobutyric acid
GBL	γ-Butyrolactone
GD	Gestation day
GHB	γ-Hydroxybutyrate
GLP	Good laboratory practice
GPMT	Guinea pig maximisation test
HPV	High Production Volume

ACGIH	American Conference of Governmental Industrial Hygienists
IOEL	Indicative Occupational Exposure Limit
K_P	Permeability Coefficient
LCI	Lowest concentration of interest
LO(A)EC/L	Lowest observed (adverse) effect concentration
LoD	Limit of detection
Log Pow	Logarithm of octanol/water partition coefficient
LOQ	Limit of quantification
M	Male(s)
MA	Motor activity
MAK	Maximale Arbeitsplatzkonzentration (Maximum workplace concentration)
MDMA	3,4-methylenedioxymethamphetamine
MIBC	Methyl isobutyl carbinol
MIBK	Methyl isobutyl ketone
MSDI	Maximised Survey-derived Daily Intake
mTAMDI	modified Theoretical Added Maximum Daily Intake
MTD	Maximum tolerated dose
MW	Molecular weight/mass
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
NICNAS	National Industrial Chemicals Notification and Assessment Scheme
NIK	Niedrigste Interessierende Konzentration (Lowest concentration of interest)
NLM	National Library of Medicine
NO(A)EC/L	No observed (adverse) effect concentration/level
NTP	National Toxicology Program
OECD	Organization for economic cooperation and development
OEL	Occupational exposure limit
PND	Postnatal day
POD	Point of departure
REACH	Registration, evaluation, authorization, and restriction of chemicals
SCCS	Scientific Committee on Consumer Safety
SCOEL	Scientific Committee on Occupational Exposure Limits
TG	Test guideline
URT	Upper respiratory tract

Summary

Substance profile and proposed EU-LCI value for 4-hydroxy-4-methylpentan-2-one (diacetone alcohol)

4-Hydroxy-4-methylpentan-2-one (diacetone alcohol) is a colourless liquid with a sweet odour and belongs to the group of beta-hydroxy ketones. The substance occurs naturally in some plants (e.g. *Camellia sinensis, Angelica gigas*). The technical grade of diacetone alcohol can contain up to 15 % acetone. Diacetone alcohol is primarily used as a solvent in a wide range of products, e.g. coatings, biocides, fillers, plasters, adhesives and sealants, putties, and modelling clay. In the European Union, the substance is approved as a fragrance in cosmetics and as a flavouring substance for food.

Diacetone alcohol may be released into the indoor air from consumer products (e.g. air fresheners, fragrances, detergents or other inhouse-products) and long-term household items (e.g. flooring, furniture, construction materials).The concentrations measured in indoor air were low as they were below the detection limit.

Available toxicokinetic data in rats after inhalation of diacetone vapour indicate that the substance is rapidly and extensively absorbed through the respiratory tract. The potential for diacetone alcohol accumulation in the body is a valid concern, as the elimination rate was found to be dependent on the initial exposure concentration. A study in mice observed that diacetone alcohol can cross the blood-brain-barrier. Diacetone alcohol is primarily excreted as sulphate and glucuronide conjugates via the renal pathway and, to a lesser extent, as carbon dioxide via the respiratory system.

In humans, the acute inhalation exposure to 457 mg/m^3 (100 ppm) diacetone alcohol in a chamber test caused symptoms such as headaches, nausea and vomiting. At 100 ppm, diacetone alcohol was irritating to the eyes, nose and throat but not skin irritating after the application of a coin-sized amount of the substance on the back of the hands. In animals, the acute toxicity of diacetone alcohol was relatively low. Slight nasal and eye irritation occurred in an older study in rats with exposure to 1500 ppm. In rabbits, undiluted diacetone alcohol caused eye irritation and was minimally irritating to abraded skin but was not irritating to intact skin after repeated exposure. In guinea pig maximisation tests according to OECD TG 406, the substance showed no skin sensitising effects.

With regard to repeated dose toxicity, there is one case report describing a 59-year-old man who developed subacute proliferative glomerulonephritis 40 days after exposure to diacetone alcohol and an unknown ethanolic solvent for three days.

In a subacute inhalation study equivalent to OECD TG 412, rats were exposed to 0, 233, 1041 or 4685 mg/m^3 (50, 225 or 1000 ppm) undiluted diacetone alcohol vapours for 6 h/d, 5 d/w for 6 weeks. No mortality occurred, but slight lethargy, changes in body weight, and organ weight alterations, particularly in the liver and kidneys, were noted. Male rats exhibited species-specific kidney effects (eosinophilic hyaline droplets) irrelevant to humans. Based on liver and kidney effects, different NOEL/LOEL and NOEC/NOAEC values were reported by the MAK commission and in the registration dossier due to variations in the interpretation of liver weight changes. The authors of this evaluation regard the highest concentration group as LOAEC due to a liver weight increase of +23 %. In a subchronic oral study following OECD TG 408, rats were exposed to up to 600 mg/(kg bw x d) diacetone alcohol via gavage for 13 weeks. A NOAEL of 600 mg/(kg bw x d) was derived based on reduced body weight, haematological findings and biochemical changes observed in the highest dose group.

In vitro studies have provided no evidence of genotoxic effects of diacetone alcohol in bacteria, yeast and mammalian cells. *In vivo* studies with diacetone alcohol are not available.

Carcinogenicity studies with diacetone alcohol are not available. The available data from *in vitro* genotoxicity studies and repeated dose toxicity studies do not provide evidence of concern for carcinogenic effects of the substance.

The reproductive toxicity of diacetone alcohol was assessed in several studies. In an extended one-generation reproductive toxicity study with oral exposure of rats (OECD TG 443) for the F0 and the F1 generation, a NOAEL of 200 mg/(kg bw x d) was derived for male rats based on increased severity of hyaline droplets accumulation associated with nephropathy, while female rats showed no adverse effects up to the highest tested dose of 600 mg/(kg bw x d). Based on the increase in post-natal loss observed in both parental generations at 600 mg/(kg bw x d) a NOAEL of 200 mg/(kg bw x d) for both sexes was derived for the F2 generation. Developmental toxicity studies according to OECD TG 414 have been performed in rats and rabbits. In rats, no adverse effects on maternal health or foetal development were observed up to the highest tested dose of 1000 mg/(kg bw x d) (=NOAEL). In rabbits, higher doses (800 mg/(kg bw x d)) resulted in reduced food intake, transient weight loss, and one prematurely euthanised female due to poor health, and some foetuses showing external, visceral and/or skeletal malformations, leading to a derived NOAEL for maternal toxicity of 300 mg/(kg bw x d) and a NOAEL for developmental toxicity of 100 mg/(kg bw x d).

The most critical effects of diacetone alcohol exposure are the developmental adverse effects such as post-natal lethality and malformations observed in several developmental toxicity studies. Therefore, the prenatal development toxicity study (OECD TG 414) in rabbits is regarded as valid and suitable for the derivation of an EU-LCI value. The NOAEL of 100 mg/(kg bw x d) is corrected via route-to-route extrapolation to a NOAEC of 145.83 mg/m^3 (100 mg/(kg bw x d)/ 2.4 x 70 kg bw/ 20 m^3/person). In light of the severity of the effects, an assessment factor of three was taken into account.

Adjustments for continuous exposure and study length are not applied as the pregnant animals were exposed daily throughout the critical time window of pregnancy.

The following assessment factors are used:

- Adjustment study length factor: 1
- Allometric scaling: already included in route-to-route extrapolation
- Interspecies extrapolation: 2.5
- Intraspecies extrapolation (interindividual variability, general population): 10
- Other (severity of effects): 3

Total assessment factor: 75 leading to a value of 145.83 mg/m^3 : 75 = 1.94 mg/m^3 (rounded to 1900 µg/m^3).

An EU-LCI value of (rounded) 1900 µg/m^3 is proposed for diacetone alcohol.

An odour threshold value between 0.28 ppm and 100 ppm (1338 µg/m^3 and 478,000 µg/m^3) has been reported in the literature. While the lower threshold (0.28 ppm) falls below the the proposed EU-LCI value, the upper threshold (100 ppm) significantly exceeds the proposed EU-LCI value for diacetone alcohol, suggesting that it should not be expected that the odour will be percieved at the proposed EU-LCI value.

Substance profile and proposed EU-LCI-value for 1,4-butanediol

The primary alcohol, 1,4-butanediol (1,4-BD), is a colourless, odourless liquid at room temperature. The substance does not occur naturally. It is mainly used in the production of polyurethanes and poly(butylene terephthalate), but also as raw material for plastics, resins and other industrial chemicals, as cosmetic ingredient (e.g. as a supplement in deodorants) and in cleaning and household care products (e.g. glass cleaner). According to the few data available on measured concentrations in indoor air, 1,4-BD is detected at low concentrations, with a median < 0.001 mg/m^3.

No quantitative data are available on the uptake of 1,4-BD through the respiratory tract. A study in rats showed that the substance is rapidly absorbed and within 2 h ca. 50 % of the administered dose was excreted as carbon dioxide in the exhaled breath and only a minor amount in the urine (4 %) and faces (0.6 %). 1,4-BD can cross the blood-brain barrier and placental barriers. 1,4-BD is metabolised to γ-hydroxybutyrate (GHB), which is further metabolised via succinic semialdehyde to γ-aminobutyric acid (GABA). Succinic semialdehyde is metabolised to succinic acid, and finally via the tricarboxylic acid cycle to carbon dioxide.

The acute toxicity of 1,4-BD in rats was determined as moderate in acute toxicity studies (4 h LC50: > 5100 µg/m^3). In humans, the lethal oral dose is reported to be 60 mg/kg bw. Human patch tests showed no irritant or sensitising effects of 1,4-BD. In rabbits, undiluted 1,4-BD was not irritating to the skin but caused slight and reversible effects (within 48 h) to the eyes. No skin sensitising potential of 1,4-BD was observed in guinea pigs (GPMT tests).

Most human poisoning cases describe acute accidental ingestion of 1,4-BD by the oral route. The main symptoms are central nervous system effects, including sedation up to coma, which are mostly reversible within hours.

In a subacute inhalation study equivalent or similar to OECD TG 412 (including a recovery group), rats were exposed nose-only to 1,4-BD aerosol of 0.20, 1.1 or 5.2 mg/L (200, 1100 or 5200 mg/m^3) for 6 h/d, 5 d/week for two weeks. There were no clinical signs, but the body weight gain of the high-concentration group was significantly lower (28 %) compared to controls during the exposure period. No pathological changes were observed in the lungs of rats in the high concentration group. Further effects observed in the highest concentration group included changes in clinical chemistry, haematological parameters and histopathological findings (thymic tissue atrophy) that were either biological variations, reversible, or not present in the recovery group. The NOAEC was set at 1100 mg/m^3. Rats were exposed to 1500 – 2000 mg 1,4-BD/m^3 for 2 h/d for 4 months in a briefly reported subchronic inhalation study. Local irritation (e.g. extensive pulmonary emphysema, mild pulmonary oedema) and clinical signs including inactivity and drowsiness which were reversible within 10 to 20 min after the end of exposure were observed. A LOAEC of 1500 – 2000 mg/m^3 was derived for central nervous system (CNS) effects. In a non-guideline study in male rats no effects were observed up to the highest concentration tested of 500 mg 1,4-BD/m^3 for 2 h/d, 6 d/week for 4 months.

No repeated dose oral or inhalation toxicity studies with subchronic/chronic exposure durations are available for 1,4-BD.

1,4-BD was not genotoxic *in vitro* in assays with bacteria (Ames test) and mammalian cells (gene mutation assay) and did not induce chromosomal aberrations in mammalian cells (chromosome aberration test). Neither *in vivo* genetic toxicity data nor carcinogenicity studies are available for 1,4-BD.

A combined repeated dose toxicity study with reproduction/developmental screening (according to OECD TG 422) in rats dosed with 200, 400 and 800 mg 1,4-BD/(kg bw x d)

observed no impairment of reproductive performance was observed in parental (F0) animals. Systemic parental effects included reduced body-weight gain, pathological changes in the urinary bladder at the mid- and high dose groups and a dose-related slight decrease in blood glucose from 200 mg/(kg bw x d) onwards. A NOAEL for parental effects was derived at 200 mg/(kg bw x d). No reduction in viability or signs of morphological abnormalities were observed in pups up to the highest dose tested. Reduced pup body weights were evaluated as a secondary effect of maternal toxicity. The NOAEL for fertility, reproductive performance and developmental toxicity was 800 mg/(kg bw x d).

For the derivation of an EU-LCI value, the subacute inhalation toxicity study in rats with a NOAEC of 1100 mg/m³ is considered valid and suitable.

The following assessment factors are used:

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

Total assessment factor: 840. This leads to a value of 1100 mg/m³: 840 = 1.31 mg/m³ for 1,4-BD (rounded to 1300 µg/m³).

An EU-LCI value of 1300 µg/m³ is proposed for 1,4-BD.

Since no odour threshold is available for 1,4-BD, no conclusions can be drawn regarding olfactory perception of the substance at the proposed EU-LCI value.

Substance profile and proposed EU-LCI-value for acetophenone

Acetophenone (phenylethanone, methylphenylketone) is a colourless, low-volatility, low-melting solid at room temperature. The odour is described as sweetish and pungent, but also as almond-like, orange and jasmine scented or reminiscent of river water.

Acetophenone is a large-scale industrial product (tonnage band in the EU 10000 to 100000 tonnes/year). The use of acetophenone includes coatings, cements and fillers, modelling clay, lubricants and greases, detergents and cleaning agents, air fresheners and finger paints. The substance also occurs naturally as a component of vegetable essential oils and in food, e. g. in honey, hazelnuts, nectarines, or cheese.

Data on the occurrence of acetophenone in indoor air from studies carried out in Germany showed that the substance could be detected in about 33 % of the samples, normally at low concentrations around 2 µg/m³ but reaching 2300 µg/m³ in extreme cases. A possible source of acetophenone in indoor air is polystyrene-based insulation materials, which can cause acetophenone emissions.

Systemic effects after oral and dermal exposure and excretion of metabolites after oral administration demonstrate the bioavailability after exposure to acetophenone via these pathways. Bioavailability after inhalation exposure is to be assumed. However, more precise quantitative data on absorption availability are not available.

Acetophenone was marketed around the turn of the 20th century as a hypnotic (brand name "Hypnon") because of the sedative-hypnotic effect ascribed to it; however, this effect has also

been called questionable. There are no usable human data available for the health assessment of repeated inhalation exposure to acetophenone.

There is little information available from animal experiments on the inhalation toxicity of acetophenone. Studies on mice on the respiratory irritant effect of acetophenone provided RD50 in the range of 500 mg/m^3 (100 ppm).

In a subacute inhalation study in mice, inhalation for two weeks at the only tested concentration of 1500 mg/m^3 did not lead to histologically detectable damage in the nasal epithelia or in deeper sections of the respiratory tract; other tissues and organs were not examined. Another inhalation study in rats reported that histological changes of mitral cells in the olfactory bulb occur after continuous subacute exposure to 8.9 mg/m^3. However, the adversity of these changes cannot be clarified from the information provided in the study.

Oral exposure of rats was associated with central nervous system effects, which manifested as movement disorders immediately following gavage, i.e. bolus administration. The effective oral doses were in the range of 500-700 mg/kg bw and thus in the same dose range as intraperitoneally administered doses (400-500 mg/kg bw), which produced corresponding central nervous effects in mice.

With continued oral exposure, non-specific effects such as reduced weight gain and changes in haematological or clinical chemical parameters occurred. These were of mild nature and partly in the range of historical controls. Increased liver weight was also observed without histologically detectable cytological damage. A NOAEL of 250 mg/(kg KG x d) can be obtained from a subchronic toxicity study. However, considering the dose-dependent increase in the relative liver weight at this concentration as adverse, the NOAEL could be set to 125 mg/(kg bw x d).

The available results of *in vitro* and *in vivo* genotoxicity studies do not indicate concern for such effects, with the exception of a weakly positive finding on the induction of chromosomal aberrations in the presence of exogenous metabolising system. There are no studies available on the carcinogenic effect of acetophenone. A study carried out within the framework of the NTP with 1-phenyl-ethan-1-ol, which is metabolised to acetophenone, showed an increased nephropathy and hyperplasia of the renal tubule cells in male rats and an increased incidence of tumours of the renal tubules. Acetophenone caused hyaline inclusions in the kidney of male rats with detection of α2u microglubulin in a subchronic feeding study. This form of α2u nephropathy and the associated formation of renal tumours is considered a species- and sex-specific process that is not relevant for risk assessment in humans.

In an extended one-generation reproductive toxicity study (EOGRTS, OECD guideline 443), rats received 0, 75, 225 or 500 mg acetophenone/(kg bw x d) by gavage. At the beginning of the mating period, the parent animals had already been exposed for ten weeks. Exposure continued during the two-week mating period (females only until successful mating) and then both sexes were exposed for a further 6 weeks until the end of the lactation period. The cohorts of offspring 1A, 1B and 2A were also exposed directly from the 22nd day (weaning phase). Cohort 2B was not directly exposed. Clinical signs of effects on the CNS were observed at all doses in the parental animals and in the subsequent generations. Organ weight changes included an increased relative and absolute liver weight at the medium and high dose. At all doses, histopathology showed dose-dependent hepatocellular hypertrophy. At the highest dose, effects noted included follicular cell hypertrophy in the thyroid gland, an increased incidence of vaginal enlargement. Three females at the low dose, one at the middle and three at the high dose had to be sacrificed prematurely between GD 23 and 26 as they had difficulty giving birth (dystocia). In these potential litters, 1 out of 11 and 6 out of 15 foetuses were dead. There were three females with

dead litters in the medium dose and eleven in the highest dose group. It was noted that the substance did not cause marked systemic toxicity, and that only the dystocia was the trigger of the sacrifices of the females at delivery. The lowest dose of 75 mg/(kg bw x d) is considered to be the LOAEL (P0 females, sexual function and fertility), due to the clear evidence of dystocia (difficulty to deliver).

This LOAEL is used as the key study for the derivation of an EU-LCI value for acetophenone.

Toxicokinetic data indicate that qualitatively and quantitatively comparable metabolite patterns occur with oral and intraperitoneal administration. It is concluded that the metabolism of acetophenone is not subject to a pronounced first-pass effects in the liver. Thus, the present findings do not provide evidence against a route-to-route extrapolation.

The key study provided a LOAEL, but not a NOAEL. Therefore, a LOAEL-to-NOAEL extrapolation was performed. Overall, the following assessment factors are used:

- Route-to-route extrapolation: 1.15 m^3/kg bw x d
- Standard factor for differences between inhalation and oral absorption: 2
- LOAEL to NOAEL: 3
- Severity of effect: 3 (because the critical effect is a severe outcome: foetal lethality)
- Adjusted study length factor: 2
- Interspecies extrapolation: 2.5
- Intraspecies extrapolation (interindividual variability, general population): 10

Route-to-route extrapolation of LOAEL: 75 mg/(kg bw x d) : 1.15 m^3/(kg bw x d) : 2 = 32.6 mg/m^3

Total assessment factor: 450, leading to a value of 0.072 mg/m^3 (rounded to 70 µg/m^3).

An EU-LCI value of 70 µg/m^3 is proposed for acetophenone.

An odour threshold of 2.9 µg/m^3 is reported for acetophenone. Therefore, it is expected that the odour will be perceivable at the proposed EU-LCI value.

Substance profile and proposed EU-LCI-value for n- and isopropyl acetate

The two isomer aliphatic esters, n-propyl acetate (nPA) and isopropyl acetate (iPA), are colourless, only slightly water-soluble liquids with a fruity odour. Both compounds are large-scale industrial products which, like similar alkyl acetates, are used as solvents in a variety of applications, e.g. for coatings and in printing, but also as synthetic flavour and adjuvant in food.

Data on the occurrence of n- and isopropyl acetate in indoor air from studies carried out in Germany showed that nPA could be detected in about 3 % of 1250 measurements and iPA in about 8 % of 1501 measurements, with concentrations mostly around 1 – 2 µg/m^3 with maximum values of 50 or 100 µg/m^3, respectively.

Toxicokinetic data regarding the hydrolysis of the esters are available from respiratory bioavailability studies in rats. Inhalation exposure of rats demonstrated the rapid hydrolysis of the esters, similar to other alkyl acetates, with the formation of the corresponding alcohol. Following enzymatic hydrolysis of nPA, the n-propanol formed is oxidised to propanal and

further to propanoic acid. Propanoic acid is further metabolised via the methylmalonyl pathway and may enter the citric acid cycle. In case of iPA, the hydrolysis product isopropanol is oxidised in a first step to acetone by the alcohol dehydrogenase of the liver. Acetone is either exhaled or eliminated unchanged in the urine or further metabolised via hydroxypropanone (hydroxyacetone) in further metabolic reactions involving microsomal monooxygenases and other enzymes. Minor amounts of isopropanol are conjugated and excreted as glucuronide in the urine. Acetic acid formed during the hydrolysis of these esters is largely utilised via the citric acid cycle or for the synthesis of fatty acids.

The acute toxicity of nPA and iPA in animals is low.

A 4-h LC50 for rats of about 7620 ppm (32000 mg/m^3) is reported for nPA and an 8-hour LC50 for rats of 12114 ppm (about 50900 mg/m^3) for iPA. Sensory irritation was observed at high concentrations of nPA and iPA in Alarie tests with mice: An RD50 (concentration leading to a decrease in breathing rate by 50 % as sign of respiratory irritation) of 3311 mg/m^3 (about 788 ppm) is reported for nPA and of 17783 mg/m^3 (about 4234 ppm) for iPA.

Limited data available from studies with humans indicate irritation of the skin, eyes and mucous membranes after exposure with propyl acetates. Furthermore, effects on the central nervous systems (CNS) and even narcosis are to be expected at higher concentrations, but no data for the effect thresholds are available. Some information can be gathered from earlier studies with volunteers: Exposure for 5 min in a room in which 3 min before nPA had been sprayed and distributed evenly, led to mild irritation of the airways, the eyes, nose and throat at the low concentration of 1000 mg/m^3. At 15000 mg/m^3 all these symptoms were still described as weak. The volunteers felt cold and reported dryness in the throat and airways and slight lacrimation. In another study, during exposure for 15 minutes to iPA, most of the volunteers found 200 ppm to be irritative for the eyes and concentrations above 200 ppm also for nose and throat. The odour nuisance of 200 ppm was reported to be slight. 100 ppm was regarded by the test persons as acceptable for an 8-hour exposure.

Liquid nPA or iPA is markedly irritating to the eyes but only slightly irritating to the skin. No skin sensitisation was observed in a maximisation test in humans. No data are available for iPA. It was noted that other analogue alcohol esters of acetic acid, for example ethyl acetate and butyl acetates, have been studied and are not dermal sensitisers.

Repeated dose toxicity studies with n- or isopropyl acetate in humans are not available.

In a subchronic inhalation toxicity study (OECD guideline 413) with n-propyl acetate, rats exposed “whole body” to 0, 150, 500, or 1500 ppm of vapour (0, 630, 2100, 6300 mg/m^3) 6 h/d, 5 d/week for 13 weeks, showed transiently reduced attention, probably due to a narcotic effect of the test substance, during exposure to 1500 ppm, but not afterwards. Effects on body weight or weight gain and food consumption were noted at 1500 ppm. The lowered mean body weight or mean body weight gains were consistent with the reduced food consumption. The target organ was the nasal cavity where concentration-dependent effects were observed in the olfactory epithelium. Focal or multifocal degeneration and/or regeneration in the olfactory epithelium were observed ≥ 500 ppm. No effects were observed at 150 ppm (630 mg/m^3) (NOAEC).

The only identified study with repeated exposure to iPA must be considered unreliable. In this study, mice were exposed to a single concentration of 200000 mg/m^3 for 4 h/d, 5 d/week for 4 weeks and maintained for 2 weeks after exposure. No effects were seen in general appearance, and there were no significant effects on body weight. No further details are available. The

authors conclude that isopropyl acetate is faintly narcotic. It must be noted that the reported exposure level exceeds the saturated vapour concentration.

Regarding genotoxicity, nPA and iPA were not mutagenic *in vitro* in the presence or absence of exogenous metabolic activation system (S9-mix) in several tests with bacteria and mammalian cells. *In vivo* data are not available for both compounds. Isopropanol did not induce micronuclei in the bone marrow of mice. No valid study could be identified for n-propanol. Overall, data for C_2 – C_4 alkyl acetate esters reveal that the chemicals of this group have no mutagenic or genotoxic potential.

Carcinogenicity studies with nPA or iPA are not available. The available genotoxicity data do not raise concern for a genotoxic non-threshold carcinogenic effect of both compounds. Inhalation carcinogenicity studies conducted with isopropyl alcohol in rats and mice have shown that isopropyl alcohol does not exhibit carcinogenic potential relevant to humans.

An extended one-generation reproductive toxicity (EOGRT) study on rats according to OECD guideline 443 was conducted with oral administration of nPA. With the exception of salivation, no treatment-related effects were observed on any of the parameters examined. 1000 mg/(kg bw x d), the highest dose tested, was considered the NOAEL for systemic toxicity, reproductive toxicity and pup development. In a developmental toxicity study on rats following OECD guideline 414, no test substance-related adverse effects on dams, gestational parameters or foetuses were observed at any dose level of n-propyl acetate (NOAEL: 1000 mg/(kg bw x d), the highest dose tested). In the corresponding study with rabbits, maternal toxicity (decreased body weight gain) was noted at 300 mg/(kg bw x d) but no embryo/foetal toxicity or teratogenicity at any dose level. The reported NOAEL for maternal toxicity was 300 mg/(kg bw x d) and for developmental toxicity 1000 mg/(kg bw x d), the highest dose tested.

No reproductive toxicity studies are available for iPA. A 2-generation study (according to OECD guideline 416) on rats with oral exposure to isopropanol, body weight was reduced and mortality increased in the early postnatal period in the F1-generation at 1000 mg/(kg bw x d). At this dose, the mating index of the males of the F1 generation was statistically significantly reduced. Benchmark calculations provided a BMDL5 of 407 mg/(kg bw x d) for this endpoint. Details on the calculation were not provided.

The developmental toxicity of isopropanol via inhalation exposure was studied in pregnant rats. The NOAEC for both developmental and maternal effects was determined to be 3500 ppm (equivalent to about 875 mg/(kg bw x d)). In a developmental toxicity study with oral exposure of rabbits, a NOAEL for maternal toxicity of 240 mg isopropanol/(kg bw x d) was obtained, with no evidence of teratogenicity up to the maximum tested dose of 480 mg/(kg bw x d).

The subchronic inhalation toxicity study with n-propyl acetate on rats is taken as the basis for the derivation of the EU-LCI. This study provided a NOAEC of 150 ppm (630 mg/m^3). The following assessment factors are used:

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

Total assessment factor: 280 leading to a value of 150 ppm: 280 = 0.536 ppm (2250 µg/m^3, rounded to 2300 µg/m^3).

An EU-LCI value of 2300 µg/m³ is proposed for n-propyl acetate.

An odour threshold of 0.24 ppm (1008 µg/m³) is reported for nPA. It is expected that the odour will be perceivable at the proposed EU-LCI value.

The EU-LCI derivation for isopropyl acetate (iPA) was conducted via read-across with n-propyl acetate (nPA). N-propyl acetate (nPA) is the closest homologue compound with an adequate data base. The only difference between the two substances is the branched propyl group, i. e. a 2-methylethyl group in iPA instead of the straight-chain propyl group in nPA.

- Toxicological critical endpoint for nPA: degeneration and/or regeneration of the olfactory nasal epithelium.
- The key assumption underlying the read-across of the EU-LCI value from nPA to iPA is that both compounds have the same critical endpoint and this is caused by their common chemical structure as an alkyl acetate. The effect is associated with the local formation of acetic acid by hydrolysis of the acetate ester, which, after exceeding the specific buffer capacity of the cells, leads to acidification and consequently cytotoxic damage.
- No cut-off rule in place: no difference in chain length between the two homologue compounds nPA and iPA.
- The derived EU-LCI value for nPA of 2300 µg/m³ may be applied to iPA without modification.

For the derivation of an EU-LCI value for isopropyl acetate, it is proposed to perform the read-across from n-propyl acetate.

An EU-LCI value of 2300 µg/m³ is proposed for isopropyl acetate.

An odour threshold of 0.16 ppm (672 µg/m³) is reported for iPA (Nagata, 2003). It is expected that the odour of isopropyl acetate will be perceivable at the proposed EU-LCI value.

Substance profile and proposed EU-LCI-value for isobutyl acetate

Isobutyl acetate (iBA), an aliphatic ester, is a colourless liquid with a moderate vapour pressure (20 hPa) at room temperature. The hardly water-soluble substance has a distinct fruity or floral odour and occurs naturally in many fruits. Isobutyl acetate is a large-scale industrial product which is primarily used as a solvent in a variety of ways, e.g. for coatings, adhesives, printing inks, sealants and cleaning agents, but also in cosmetics and as a flavouring agent in food and beverages.

Data on the occurrence of isobutyl acetate in indoor air indicate that the substance is detected quite often (in about 25 % of performed measurements), with concentrations mostly below 10 µg/m³ but reaching 1660 µg/m³ in extreme cases.

Isobutyl acetate is rapidly absorbed after inhalation exposure; quantitative data are, however, not available. For the isomeric n-butyl acetate, it is stated that about 50 % of the inhaled compound is found in the exhaled air after inhalation exposure. Following contact with the mucous membranes or absorption into the organism, iBA is hydrolysed to isobutanol (2-methyl-propan-1-ol) and acetic acid.

No relevant mammalian species differences are known regarding the metabolism of iBA. Following enzymatic hydrolysis of iBA by esterases, isobutanol is largely oxidised to isobutanal and further to isobutyric acid (2-methylpropanoic acid). The latter is metabolised via

methylmalonic acid to succinic acid which is utilised in the citric acid cycle. Acetic acid formed during the hydrolysis of iBA is also largely utilised via the citric acid cycle or for the synthesis of fatty acids.

The data base regarding the toxicity of iBA is limited.

The acute toxicity of iBA in animals is low. A 4-h LC50 of 6200 ppm (about 30200 mg/m^3) was reported for iBA. Liquid iBA is at most minimally irritating to the eyes and on the skin and is not skin sensitising.

Sensory irritation was observed at high concentrations of iBA in an Alarie test with mice: An RD50 of 818 ppm (about 3910 mg/m^3) was determined, very similar to the RD50 of 730 ppm (about 3490 mg/m^3) determined for n-butyl acetate, indicating a comparable sensory irritation potency of both isomers.

No acute inhalation studies with iBA are available in humans. A clinical study on irritation effects of n-butyl acetate in human volunteers without previous occupational exposure indicated throat irritation and breathing difficulties, and eye redness at 145 ppm (700 mg/m^3) after 4 hours of exposure.

Repeated dose toxicity studies with iBA in humans or animals are not available.

In a subchronic inhalation toxicity study, rats exposed “whole body” to 0, 500, 1500, or 3000 ppm of n-butyl acetate (nBA) vapour (0, 2390, 7170, 14340 mg/m^3) 6 h/d, 5 d/week for 13 weeks showed transient sedation at ≥ 1500 ppm. Also, body weight gain and food consumption were lower at these concentrations, and several changes of organ weights were noted. Histopathology revealed no systemic organ-specific toxicity. Local effects in the nasal epithelia included degeneration of the olfactory epithelium. The severity was mild to moderate at 3000 ppm group and minimal to mild at the 1500 ppm group. No effect was observed at 500 ppm (NOAEC). This NOAEC was confirmed in subchronic inhalation neurotoxicity study on rats.

Isobutyl acetate and its metabolites isobutanol and acetic acid are not mutagenic *in vitro*. No substance-specific data are available regarding genotoxicity of iBA *in vivo*. Carcinogenicity studies with iBA are not available. The available genotoxicity data for iBA and its metabolites do not raise concern for a genotoxic non-threshold carcinogenic effect of iBA.

No studies with iBA are available regarding reproductive and developmental toxicity. Studies with isobutanol do not provide evidence for reproductive or developmental toxicity.

The EU-LCI derivation for isobutyl acetate (iBA) is conducted via read-across with n-butyl acetate (nBA). The key assumption is that nBA is the closest homologue with sufficient existing toxicological data and an already published EU-LCI value. The key assumption underlying the read-across of the EU-LCI value from nBA to iBA is that both compounds have the same critical endpoint (irritation) and this is caused by their common chemical structure as an alkyl acetate. The effect is associated with the local formation of acetic acid by hydrolysis of the acetate ester, which, after exceeding the specific buffer capacity of the cells, leads to acidification and consequently cytotoxic damage.

- No cut-off rule in place: no difference in chain length between the two homologue compounds nBA and iBA.
- The derived EU-LCI value for nBA of 8500 µg/m^3 may be applied to iBA without modification.

An EU-LCI value of 8500 µg/m^3 is proposed for isobutyl acetate.

Isobutyl acetate has an odour threshold of 38 µg/m^3. It is expected that the odour of isobutyl acetate will be perceivable at the proposed EU-LCI value.

Zusammenfassung

Stoffprofil und EU-LCI-Wert-Vorschlag für 4-Hydroxy-4-methylpentan-2-on (Diacetonalkohol)

4-Hydroxy-4-methylpentan-2-on (Diacetonalkohol) ist eine farblose Flüssigkeit mit süßlichem Geruch und gehört zur Gruppe der Beta-Hydroxyketone. Die Substanz kommt in der Natur in einigen Pflanzen vor (z. B. *Camellia sinensis, Angelica gigas*). Das technische Diacetonalkohol kann bis zu 15 % Aceton enthalten. Diacetonalkohol wird hauptsächlich als Lösungsmittel in einer Vielzahl von Produkten verwendet, z. B. in Beschichtungen, Bioziden, Füllstoffen, Pflastern, Kleb- und Dichtstoffen, Spachtelmassen und Modelliermassen. In der Europäischen Union ist der Stoff als Duftstoff in Kosmetika und als Aromastoff in Lebensmitteln zugelassen.

Diacetonalkohol kann aus Konsumgütern (z. B. Lufterfrischern, Duftstoffen, Reinigungsmitteln oder anderen Haushaltsprodukten) und langlebigen Haushaltsgegenständen (z. B. Bodenbelägen, Möbeln, Baumaterialien) in die Raumluft freigesetzt werden. Die in der Raumluft gemessenen Konzentrationen waren niedrig, da sie unter der Nachweisgrenze lagen.

Die verfügbaren toxikokinetischen Daten bei Ratten nach Inhalation von Diaceton-Dämpfen deuten darauf hin, dass die Substanz schnell und umfassend über die Atemwege aufgenommen wird. Eine Anreicherung von Diacetonalkohol im Körper kann nicht ausgeschlossen werden, da die Ausscheidungsrate von der anfänglichen Expositionskonzentration abhängig ist. In einer Studie an Mäusen wurde beobachtet, dass Diacetonalkohol die Blut-Hirn-Schranke überwinden kann. Diacetonalkohol wird hauptsächlich als Sulfat- und Glucuronidkonjugate über die Nieren und in geringerem Maße als Kohlendioxid über die Atemwege ausgeschieden.

Beim Menschen verursachte die akute Inhalation von 457 mg/m^3 (100 ppm) Diacetonalkohol in einem Kammerversuch Symptome wie Kopfschmerzen, Übelkeit und Erbrechen. Bei 100 ppm reizte Diacetonalkohol Augen, Nase und Rachen, nicht jedoch die Haut, nachdem eine münzgroße Menge der Substanz auf den Handrücken aufgetragen wurde. Bei Tieren war die akute Toxizität von Diacetonalkohol relativ gering. In einer älteren Studie an Ratten, die einer Konzentration von 1500 ppm ausgesetzt waren, traten leichte Reizungen der Nase und der Augen auf. Bei Kaninchen verursachte unverdünnter Diacetonalkohol Augenreizungen und war bei abgeschürfter Haut leicht reizend, bei intakter Haut jedoch nicht reizend, wenn es wiederholt angewendet wurde. In Maximierungstests an Meerschweinchen gemäß OECD TG 406 zeigte die Substanz keine hautsensibilisierende Wirkung.

In Bezug auf die Toxizität bei wiederholter Verabreichung gibt es einen Fallbericht, in dem ein 59-jähriger Mann beschrieben wird, der 40 Tage nach einer dreitägigen Exposition gegenüber Diacetonalkohol und einem unbekannten ethanolischen Lösungsmittel eine subakute proliferative Glomerulonephritis entwickelte.

In einer subakuten Inhalationsstudie, die der OECD TG 412 entspricht, wurden Ratten 6 Wochen lang 6 Stunden pro Tag, 5 Tage pro Woche, 0, 233, 1041 oder 4685 mg/m^3 (50, 225 oder 1000 ppm) unverdünnten Diacetonalkohol-Dämpfen ausgesetzt. Es trat keine Mortalität auf, aber es wurden leichte Lethargie, Veränderungen des Körpergewichts (KG) und Veränderungen des Organgewichts, insbesondere in der Leber und den Nieren, festgestellt. Bei männlichen Ratten wurden artspezifische Nierenschäden (eosinophile hyaline Tröpfchen) festgestellt, die für den Menschen irrelevant sind. Aufgrund der Effekte auf Leber und Nieren wurden von der MAK-Kommission und im Registrierungsdossier unterschiedliche NOEL/LOEL- und NOEC/NOAEC-Werte abgeleitet, was auf unterschiedliche Auslegungen der Veränderungen des Lebergewichts zurückzuführen ist. Die Autoren dieser Bewertung betrachten die Gruppe mit der höchsten Konzentration aufgrund einer Erhöhung des Lebergewichts um +23 % als LOAEC. In einer subchronischen oralen Studie gemäß OECD TG 408 wurden Ratten 13 Wochen lang bis zu 600

mg/(kg KG x d) Diacetonalkohol per Magensonde verabreicht. Ein NOAEL von 600 mg/(kg KG x d) wurde auf der Grundlage des verringerten KGs, der hämatologischen Befunde und der biochemischen Veränderungen, die in der höchsten Dosisgruppe beobachtet wurden, abgeleitet.

In-vitro-Studien haben keine Hinweise auf genotoxische Wirkungen von Diacetonalkohol in Bakterien, Hefe und Säugetierzellen ergeben. *In-vivo*-Studien mit Diacetonalkohol liegen nicht vor.

Kanzerogenitätsstudien mit Diacetonalkohol liegen nicht vor. Die verfügbaren Daten aus *In-vitro*-Genotoxizitätsstudien und Studien zur Toxizität bei wiederholter Verabreichung geben keinen Anlass zur Besorgnis hinsichtlich kanzerogener Wirkungen des Stoffes.

Die Reproduktionstoxizität von Diacetonalkohol wurde in mehreren Studien untersucht. In einer erweiterten Ein-Generationen-Studie zur Reproduktionstoxizität mit oraler Exposition von Ratten (OECD TG 443) für die F0- und F1-Generation wurde für männliche Ratten ein NOAEL von 200 mg/(kg KG x d) abgeleitet, basierend auf der erhöhten Schwere der Ansammlung hyaliner Tröpfchen im Zusammenhang mit Nephropathie, während weibliche Ratten bis zur höchsten getesteten Dosis von 600 mg/(kg KG x d) keine nachteiligen Auswirkungen zeigten. Aufgrund des bei beiden Elterngenerationen beobachteten Anstiegs des postnatalen Verlusts bei 600 mg/(kg KG x d) wurde für die F2-Generation ein NOAEL von 200 mg/(kg KG x d) für beide Geschlechter abgeleitet. Studien zur Entwicklungstoxizität gemäß OECD TG 414 wurden an Ratten und Kaninchen durchgeführt. Bei Ratten wurden bis zur höchsten getesteten Dosis von 1000 mg/(kg KG x d) (=NOAEL) keine nachteiligen Auswirkungen auf die Gesundheit der Muttertiere oder die Entwicklung der Föten beobachtet. Bei Kaninchen führten höhere Dosen (800 mg/(kg KG x d)) zu einer verringerten Nahrungsaufnahme, vorübergehendem Gewichtsverlust und der vorzeitigen Euthanasie eines weiblichen Tieres aufgrund schlechter Gesundheit. Zudem zeigten einige Föten äußere, viszerale und/oder skelettale Fehlbildungen, was zu einem abgeleiteten NOAEL für die maternale Toxizität von 300 mg/(kg KG x d) und einem NOAEL für die Entwicklungstoxizität von 100 mg/(kg KG x d) führte.

Die kritischsten Auswirkungen einer Diacetonalkohol-Exposition sind die negativen Auswirkungen auf die Entwicklung, wie z. B. postnatale Letalität und Fehlbildungen, die in mehreren Studien zur Entwicklungstoxizität beobachtet wurden. Daher wird die Studie zur pränatalen Entwicklungstoxizität (OECD TG 414) an Kaninchen als gültig und geeignet für die Ableitung eines EU-LCI-Wertes angesehen. Der NOAEL von 100 mg/(kg KG x d) wird durch eine Pfad-zu-Pfad-Extrapolation auf einen NOAEC von 145,83 mg/m^3 (100 mg/(kg KG x d)/ 2,4 x 70 kg KG/ 20 m^3/Person) korrigiert. Angesichts der Schwere der Effekte wurde ein Extrapolationsfaktor von drei berücksichtigt.

Anpassungen für kontinuierliche Exposition und Studiendauer werden nicht vorgenommen, da die trächtigen Tiere während des kritischen Zeitfensters der Trächtigkeit täglich exponiert wurden.

Die folgenden Extrapolationsfaktoren werden herangezogen:

- Faktor für die Studiendauer: 1
- Allometrische Skalierung: bereits in der Pfad-zu-Pfad-Extrapolation berücksichtigt
- Interspezies-Extrapolation (verbleibende Unterschiede): 2,5
- Intraspezies-Extrapolation (interindividuelle Variabilität, allgemeine Bevölkerung): 10
- Andere (Schwere der Effekte): 3

Gesamtfaktor: 75. Daraus ergibt sich ein Wert von 145,83 mg/m³: 75 = 1,94 mg/m³ (gerundet auf 1900 µg/m³).

Für Diacetonalkohol wird ein EU-LCI-Wert von (gerundet) 1900 µg/m³ vorgeschlagen.

In der Literatur wird ein Geruchsschwellenwert zwischen 0,28 ppm und 100 ppm (1338 µg/m³ und 478000 µg/m³) angegeben. Während der untere Schwellenwert (0,28 ppm) unter dem vorgeschlagenen EU-LCI-Wert liegt, ist der obere Schwellenwert (100 ppm) deutlich höher als der vorgeschlagene EU-LCI-Wert für Diacetonalkohol, was darauf hindeutet, dass der Geruch bei dem vorgeschlagenen EU-LCI-Wert nicht wahrgenommen werden sollte.

Stoffprofil und EU-LCI-Wert-Vorschlag für 1,4-Butandiol (1,4-BD)

Der primäre Alkohol 1,4-Butandiol (1,4-BD) ist bei Raumtemperatur eine farb- und geruchlose Flüssigkeit. Die Substanz kommt in der Natur nicht vor. Sie wird hauptsächlich bei der Herstellung von Polyurethanen und Poly(butylenterephthalat) verwendet, aber auch als Rohstoff für Kunststoffe, Harze und andere Industriechemikalien, als kosmetischer Inhaltsstoff (z. B. als Zusatz in Deodorants) und in Reinigungs- und Haushaltspflegeprodukten (z. B. Glasreiniger). Aus den wenigen verfügbaren Daten über gemessene Konzentrationen in der Raumluft geht hervor, dass 1,4-BD in geringen Konzentrationen nachgewiesen wird, mit einem Medianwert von < 0,001 mg/m³.

Es liegen keine quantitativen Daten zur Aufnahme von 1,4-BD über die Atemwege vor. Eine Studie an Ratten zeigte, dass die Substanz schnell resorbiert wird und innerhalb von 2 Stunden ca. 50 % der verabreichten Dosis als Kohlendioxid in der ausgeatmeten Luft und nur eine geringe Menge im Urin (4 %) und in den Kot (0,6 %) ausgeschieden wurden. 1,4-BD kann die Blut-Hirn-Schranke und die Plazentaschranke überwinden. Die Substanz wird zu γ-Hydroxybutyrat (GHB) umgesetzt, das über Bernsteinsemialdehyd weiter zu γ-Aminobuttersäure (GABA) metabolisiert wird. Bernsteinsemialdehyd wird zu Bernsteinsäure und schließlich über den Tricarbonsäurezyklus zu Kohlendioxid metabolisiert.

Die akute Toxizität von 1,4-BD bei Ratten wurde in Untersuchungen als mäßig eingestuft (4 h-LC50: > 5100 µg/m³). Beim Menschen wird die tödliche orale Dosis mit 60 mg/kg KG angegeben. Bei Patch-Tests am Menschen wurden keine reizenden oder sensibilisierenden Wirkungen von 1,4-BD festgestellt. Bei Kaninchen wirkte unverdünntes 1,4-BD nicht hautreizend, verursachte jedoch leichte und reversible Effekte (innerhalb von 48 Stunden) an den Augen. An Meerschweinchen wurde kein hautsensibilisierendes Potenzial von 1,4-BD beobachtet (GPMT-Tests).

Die meisten Vergiftungsfälle beim Menschen beschreiben eine akute, versehentliche, orale Aufnahme von 1,4-BD. Die Hauptsymptome sind Auswirkungen auf das zentrale Nervensystem, einschließlich Sedierung bis hin zum Koma, die meist innerhalb von Stunden reversibel sind.

In einer subakuten Inhalationsstudie, die ähnlich der OECD TG 412 durchgeführt wurde (einschließlich einer Recovery-Gruppe), wurden Ratten 6 Stunden täglich, 5 Tage pro Woche über einen Zeitraum von zwei Wochen nur über die Nase einem 1,4-BD-Aerosol von 0,20, 1,1 oder 5,2 mg/L (200, 1100 oder 5200 mg/m³) ausgesetzt. Es gab keine klinischen Symptome, aber die Körpergewichtszunahme in der höchsten Konzentrationsgruppe war während des Expositionszeitraums bis zu 4 Tage nach der Exposition im Vergleich zu den Kontrollen signifikant geringer (28 %). In den Lungen der Ratten der höchsten Konzentrationsgruppe wurden keine pathologischen Veränderungen beobachtet. Zu den weiteren beobachteten Auswirkungen in der höchsten Konzentrationsgruppe gehörten Veränderungen in der klinischen Chemie, der hämatologische Parameter und histopathologische Befunde (Atrophie

des Thymusgewebes), die entweder biologische Schwankungen darstellten, reversibel waren oder in der Recovery-Gruppe nicht auftraten. Der NOAEC wurde auf 1100 mg/m^3 festgelegt. In einer kurz berichteten subchronischen Inhalationsstudie wurden Ratten 4 Monate lang täglich 2 Stunden lang 1500–2000 mg 1,4-BD/m^3 ausgesetzt. Es wurden lokale Reizungen (z. B. ausgedehntes Lungenemphysem, leichtes Lungenödem) und klinische Anzeichen wie Inaktivität und Schläfrigkeit beobachtet, die innerhalb von 10 bis 20 Minuten nach Ende der Exposition reversibel waren. Ein LOAEC von 1500–2000 mg/m^3 wurde für Wirkungen auf das zentrale Nervensystem (ZNS) abgeleitet. In einer nicht richtlinienkonformen Studie an männlichen Ratten wurden bis zur höchsten getesteten Konzentration von 500 mg 1,4-BD/m^3 für 2 Stunden/Tag, 6 Tage/Woche über 4 Monate keine Effekte beobachtet.

Es liegen keine Studien zur Toxizität bei wiederholter oraler oder inhalativer Gabe mit subchronischer/chronischer Expositionsdauer für 1,4-BD vor.

1,4-BD war *in vitro* in Tests mit Bakterien (Ames-Test) und Säugetierzellen (Genmutationstest) nicht gentoxisch und induzierte keine Chromosomenaberrationen in Säugetierzellen (Chromosomenaberrationstest). Es liegen keine *in vivo* Untersuchungen noch Studien zur Kanzerogenität für 1,4-BD vor.

In einer kombinierten Studie zur Toxizität bei wiederholter Verabreichung mit einem Screening auf Reproduktions-/Entwicklungsstörungen (gemäß OECD TG 422) bei Ratten, denen 200, 400 und 800 mg 1,4-BD/(kg KG x d) verabreicht wurden, wurde bei den Elterntieren (F0) keine Beeinträchtigung der Fortpflanzungsfähigkeit beobachtet. Zu den systemischen Auswirkungen auf die Elterntiere gehörten eine verringerte Körpergewichtszunahme, pathologische Veränderungen der Harnblase in den mittleren und hohen Dosisgruppen und eine dosisabhängige leichte Abnahme des Blutzuckerspiegels ab 200 mg/(kg KG x d). Ein NOAEL für Auswirkungen auf die Elterntiere wurde bei 200 mg/(kg KG x d) abgeleitet. Bei den Jungtieren wurden bis zur höchsten getesteten Dosis keine Verringerung der Lebensfähigkeit oder Anzeichen von morphologischen Anomalien beobachtet. Ein verringertes KG der Nachkommen wurde als sekundärer Effekt der maternalen Toxizität bewertet. Der NOAEL für Fruchtbarkeit, Reproduktionsleistung und Entwicklungstoxizität betrug 800 mg/(kg KG x d).

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

Die folgenden Extrapolationsfaktoren werden herangezogen:

- Anpassung für die kontinuierliche Exposition (6 h/d, 5 d/w): 5,6
- Faktor für die Studiendauer: 6
- Interspezies-Extrapolation: 2,5
- Intraspezies-Extrapolation: 10

Gesamtextrapolationsfaktor: 840. Daraus ergibt sich ein Wert von 1100 mg/m^3: 840 = 1,31 mg/m^3 für 1,4-Butandiol (gerundet auf 1300 µg/m^3).

Für 1,4-Butandiol wird ein EU-LCI-Wert von 1300 µg/m^3 vorgeschlagen.

Es kann keine Aussage über die Geruchswahrnehmung der Substanz beim vorgeschlagenen EU-LCI-Wert getroffen werden, da für 1,4-BD keine Geruchsschwelle vorliegt.

Stoffprofil und EU-LCI-Wert-Vorschlag für Acetophenon

Acetophenon (Phenylethanon, Methylphenylketon) ist ein farbloser, schwerflüchtiger, bei Raumtemperatur bereits schmelzender Feststoff. Der Geruch wird als süßlich und stechend beschrieben, aber auch als mandelartig, nach Orange und Jasmin duftend oder an Flusswasser erinnernd.

Acetophenon ist ein großtechnisches Industrieprodukt, das unter anderem in Beschichtungen, Zementen und Füllstoffen, Modelliermassen, Schmiermitteln und Fetten, Wasch- und Reinigungsmitteln, Lufterfrischern und Fingerfarben verwendet wird. Der Stoff kommt auch natürlich als Bestandteil pflanzlicher ätherischer Öle und in Lebensmitteln vor, z. B. in Honig, Haselnüssen, Nektarinen oder Käse.

Daten zum Vorkommen von Acetophenon in der Innenraumluft aus in Deutschland durchgeführten Studien zeigten, dass der Stoff in etwa 33 % der Proben nachgewiesen werden konnte, normalerweise in geringen Konzentrationen um 2 µg/m^3, in Extremfällen jedoch bis zu 2300 µg/m^3. Eine mögliche Quelle für Acetophenon in der Innenraumluft sind Dämmstoffe auf Polystyrolbasis, die zu Acetophenon-Emissionen führen können.

Systemische Wirkungen nach oraler und dermaler Exposition sowie die Ausscheidung von Metaboliten nach oraler Verabreichung belegen die Bioverfügbarkeit nach Exposition gegenüber Acetophenon über diese Wege. Eine Bioverfügbarkeit nach inhalativer Exposition ist anzunehmen. Genauere quantitative Daten zur Resorptionsverfügbarkeit liegen jedoch nicht vor.

Acetophenon wurde um die Wende zum 20. Jahrhundert aufgrund seiner ihm zugeschriebenen sedativ-hypnotischen Wirkung als Hypnotikum (Markenname „Hypnon“) vermarktet; diese Wirkung wurde jedoch auch als fragwürdig bezeichnet.

Für die Bewertung einer wiederholten inhalativen Exposition gegenüber Acetophenon liegen keine verwertbaren Humandaten vor.

Auch aus Tierversuchen liegen nur wenige Informationen zur Inhalationstoxizität von Acetophenon vor. Studien an Mäusen zur reizenden Wirkung von Acetophenon auf die Atemwege ergaben einen RD50-Wert (Konzentration, die zu einer Abnahme der Atemfrequenz um 50 % als Zeichen einer Atemwegsreizung führt) im Bereich von 500 mg/m^3 (100 ppm).

In einer subakuten Inhalationsstudie an Mäusen führte die zweiwöchige Inhalation der einzigen getesteten Konzentration von 1500 mg/m^3 zu keinen histologisch nachweisbaren Schäden im Nasenepithel oder in tieferen Abschnitten der Atemwege; andere Gewebe und Organe wurden nicht untersucht. Eine weitere Inhalationsstudie an Ratten berichtete, dass nach kontinuierlicher subakuter Exposition gegenüber 8,9 mg/m^3 Acetophenon histologische Veränderungen der Mitralzellen im Riechkolben auftreten. Die Adversität dieser Veränderungen kann jedoch anhand der in der Studie bereitgestellten Informationen nicht geklärt werden.

Die orale Exposition von Ratten war mit Auswirkungen auf das zentrale Nervensystem verbunden, die sich unmittelbar nach einer Verabreichung per Schlundsonde, d. h. als Bolusverabreichung, in Form von Bewegungsstörungen manifestierten. Die wirksamen oralen Dosen lagen im Bereich von 500–700 mg/kg KG und damit im gleichen Dosisbereich wie die intraperitoneal verabreichten Dosen (400–500 mg/kg KG), die bei Mäusen entsprechende Auswirkungen auf das zentrale Nervensystem hervorriefen.

Bei fortgesetzter oraler Exposition traten unspezifische Auswirkungen wie eine verminderte Gewichtszunahme und Veränderungen der hämatologischen oder klinisch-chemischen Parameter auf. Diese waren leicht und lagen teilweise im Bereich historischer Kontrollen. Es wurde auch ein erhöhtes Lebergewicht beobachtet, ohne dass histologisch nachweisbare

zytologische Schäden vorlagen. Aus einer subchronischen Toxizitätsstudie lässt sich ein NOAEL von 250 mg/(kg KG x d) ableiten. Wird der dosisabhängige Anstiegs des relativen Lebergewichts bei dieser Konzentration als advers angesehen, könnte der NOAEL jedoch auf 125 mg/(kg KG x d) festgelegt werden.

Die verfügbaren Ergebnisse von Genotoxizitätsstudien *in vitro* und *in vivo* geben keinen Anlass zu Bedenken hinsichtlich solcher Wirkungen, mit Ausnahme eines schwach positiven Befundes hinsichtlich der Induktion von Chromosomenaberrationen in Gegenwart eines exogenen Metabolisierungssystems. Es liegen keine Studien zur karzinogenen Wirkung von Acetophenon vor. Eine im Rahmen des NTP durchgeführte Studie mit 1-Phenylethan-1-ol, das zu Acetophenon metabolisiert wird, zeigte eine erhöhte Nephropathie und Hyperplasie der Nierentubuluszellen bei männlichen Ratten sowie eine erhöhte Inzidenz von Tumoren der Nierentubuli. Acetophenon verursachte in einer subchronischen Fütterungsstudie hyaline Einschlüsse in der Niere männlicher Ratten, wobei α2u-Mikroglobulin nachgewiesen wurde. Diese Form der α2u-Nephropathie und die damit verbundene Bildung von Nierentumoren wird als eine artspezifische und geschlechtsspezifische Reaktion angesehen, die für die Risikobewertung beim Menschen nicht relevant ist.

In einer erweiterten Eingenerationen-Reproduktionstoxizitätsstudie (EOGRTS, OECD-Leitlinie 443) erhielten Ratten 0, 75, 225 oder 500 mg Acetophenon/(kg KG x Tag) per Magensonde. Zu Beginn der Paarungsperiode waren die Elterntiere bereits seit zehn Wochen exponiert. Die Exposition wurde während der zweiwöchigen Paarungsperiode fortgesetzt (Weibchen nur bis zur erfolgreichen Paarung) und anschließend wurden beide Geschlechter für weitere 6 Wochen bis zum Ende der Laktationsperiode exponiert. Die Nachkommenkohorten 1A, 1B und 2A wurden ab dem 22. Tag nach der Geburt direkt exponiert. Die Kohorte 2B wurde nicht direkt exponiert. Klinische Anzeichen für Auswirkungen auf das ZNS wurden bei allen Dosen bei den Elterntieren und in den nachfolgenden Generationen beobachtet. Veränderungen der Organgewichte beinhalteten ein erhöhtes relatives und absolutes Lebergewicht bei der mittleren und hohen Dosis. Bei allen Dosen zeigte die Histopathologie eine dosisabhängige hepatozelluläre Hypertrophie. Bei der höchsten Dosis wurden unter anderem eine Follikelzellhypertrophie in der Schilddrüse und eine erhöhte Inzidenz von Vaginalvergrößerungen festgestellt. Drei Weibchen bei der niedrigen Dosis, eines bei der mittleren und drei bei der hohen Dosis mussten zwischen dem Trächtigkeitstag 23 und 26 getötet werden, da sie Schwierigkeiten bei der Geburt hatten (Dystokie). In diesen potenziellen Würfen waren 1 von 11 und 6 von 15 Föten tot. Es gab drei Weibchen in der mittleren und elf in der Gruppe mit der höchsten Dosis mit toten Föten. Es wurde hervorgehoben, dass Acetophenon keine ausgeprägte systemische Toxizität verursachte und nur die Dystokie der Grund für die Tötung der Weibchen bei der Geburt war. Die niedrigste Dosis von 75 mg/(kg KG x Tag) wird aufgrund der eindeutigen Hinweise auf Dystokie (Geburtsbeschwerden) als LOAEL (P0-Weibchen, Sexualfunktion und Fruchtbarkeit) angesehen.

Dieser LOAEL wird als Schlüsselstudie für die Ableitung eines EU-LCI-Wertes für Acetophenon verwendet.

Toxikokinetische Daten zeigen, dass bei oraler und intraperitonealer Verabreichung qualitativ und quantitativ vergleichbare Metabolitenmuster auftreten. Es wird geschlossen, dass der Metabolismus von Acetophenon keinem ausgeprägten First-Pass-Effekt in der Leber unterliegt. Hinweise, die gegen eine Extrapolation von einer Verabreichungsform auf eine andere sprechen, liegen nicht vor.

Die Schlüsselstudie lieferte einen LOAEL, jedoch keinen NOAEL. Daher wurde eine Extrapolation von einem LOAEL auf einen NOAEL vorgenommen. Insgesamt werden folgende Extrapolationsfaktoren verwendet:

- Pfad-zu-Pfad-Extrapolation: 1,15 m^3/kg KG x d
- Standardfaktor für Unterschiede zwischen Inhalation und oraler Absorption: 2
- LOAEL zu NOAEL: 3
- Schwere der Wirkung: 3 (da die kritische Wirkung ein schwerwiegender Effekt ist: fötale Letalität)
- Zeitextrapolation: 2
- Allometrische Skalierung: bereits in der Pfad-zu-Pfad-Extrapolation berücksichtigt
- Interspeziesextrapolation (verbleibende Unterschiede): 2,5
- Intraspezies-Extrapolation (interindividuelle Variabilität, allgemeine Bevölkerung): 10

Extrapolation des LOAEL von oraler auf inhalative Exposition:
75 mg/(kg KG x Tag) : 1,15 m^3/(kg KG x Tag) : 2 = 32,6 mg/m^3

Gesamtextrapolationsfaktor: 450, was zu einem Wert von 0,072 mg/m^3 (gerundet auf 70 µg/m^3) führt.

Für Acetophenon wird ein EU-LCI-Wert von 70 µg/m^3 vorgeschlagen.

Für Acetophenon wird eine Geruchsschwelle von 2,9 µg/m^3 angegeben. Daher ist zu erwarten, dass der Geruch bei dem vorgeschlagenen EU-LCI-Wert wahrnehmbar sein wird.

Stoffprofil und EU-LCI-Wert-Vorschlag für n-Propylacetat und Isopropylacetat

Die beiden isomeren aliphatischen Ester n-Propylacetat (nPA) und Isopropylacetat (iPA) sind farblose, nur geringfügig wasserlösliche Flüssigkeiten mit einem fruchtigen Geruch. Beide Verbindungen sind großtechnisch hergestellte Industrieprodukte, die wie andere Alkylacetate in einer Vielzahl von Anwendungen als Lösungsmittel eingesetzt werden, z. B. für Beschichtungen und im Druckwesen, aber auch als synthetische Aromastoffe und Zusatzstoffe in Lebensmitteln.

Daten zum Vorkommen von n- und Isopropylacetat in der Innenraumluft aus in Deutschland durchgeführten Studien zeigten, dass nPA in etwa 3 % von 1250 Messungen und iPA in etwa 8 % von 1501 Messungen nachgewiesen werden konnte, wobei die Konzentrationen meist bei 1– 2 µg/m^3 lagen, mit Höchstwerten von 50 bzw. 100 µg/m^3.

Toxikokinetische Daten zur Hydrolyse der Ester liegen aus Studien zur Bioverfügbarkeit in der Atemluft von Ratten vor. Dabei zeigte sich eine schnelle Hydrolyse der Ester, ähnlich wie bei anderen Alkylacetaten, unter Bildung des entsprechenden Alkohols. Nach der enzymatischen Hydrolyse von nPA wird das gebildete n-Propanol zu Propanal und weiter zu Propansäure oxidiert. Propansäure wird über den Methylmalonylweg weiter metabolisiert und im Citratzyklus verwertet. Im Falle von iPA wird das Hydrolyseprodukt Isopropanol in einem ersten Schritt durch die Alkoholdehydrogenase der Leber zu Aceton oxidiert. Aceton wird entweder ausgeatmet oder unverändert im Urin ausgeschieden oder über Hydroxypropanon (Hydroxyaceton) in weiteren Stoffwechselreaktionen unter Beteiligung von mikrosomalen Monooxygenasen und anderen Enzymen weiter metabolisiert. Geringe Mengen an Isopropanol werden konjugiert und als Glucuronid im Urin ausgeschieden. Die bei der Hydrolyse dieser Ester entstehende Essigsäure wird größtenteils über den Citratzyklus oder für die Synthese von Fettsäuren verwertet.

Die akute Toxizität von nPA und iPA bei Versuchstieren ist gering.

Für nPA wird eine 4-Stunden-LC50 für Ratten von etwa 7620 ppm (32000 mg/m^3) und für iPA eine 8-Stunden-LC50 für Ratten von 12114 ppm (etwa 50900 mg/m^3) angegeben. Bei hohen Konzentrationen von nPA und iPA wurden in Alarie-Tests mit Mäusen sensorische Reizungen beobachtet: Für nPA wird ein RD50-Wert (Konzentration, die zu einer Abnahme der Atemfrequenz um 50 % als Zeichen einer Atemwegsreizung führt) von 3311 mg/m^3 (etwa 788 ppm) und für iPA von 17783 mg/m^3 (etwa 4234 ppm) angegeben.

Aus Humanstudien liegen nur begrenzte Daten vor, die auf eine Reizung der Haut, der Augen und der Schleimhäute nach Exposition gegenüber Propylacetaten hinweisen. Darüber hinaus sind bei höheren Konzentrationen Auswirkungen auf das zentrale Nervensystem (ZNS) bis hin zu narkoseartigen Wirkungen zu erwarten, jedoch liegen keine Daten zu Wirkungsschwellen vor. Einige Informationen lassen sich aus früheren Probanden gewinnen: Eine 5-minütige Exposition in einem Raum, in dem 3 Minuten zuvor nPA versprüht und gleichmäßig verteilt worden war, führte bei einer Konzentration von 1000 mg/m^3 zu leichten Reizungen der Atemwege, der Augen, der Nase und des Rachens. Bei 15000 mg/m^3 wurden alle diese Symptome noch als schwach beschrieben. Die Probanden empfanden Kälte und berichteten von Trockenheit im Hals und in den Atemwegen sowie leichtem Tränenfluss. In einer anderen Studie empfanden die meisten Probanden bei einer 15-minütigen Exposition gegenüber iPA eine Konzentration von 200 ppm als reizend für die Augen und Konzentrationen über 200 ppm auch für Nase und Rachen. Die Geruchsbelästigung bei 200 ppm wurde als gering empfunden. 100 ppm wurden von den Testpersonen als akzeptabel für eine 8-stündige Exposition angesehen.

Flüssiges nPA oder iPA ist deutlich reizend für die Augen, aber nur leicht reizend für die Haut. In einem Maximierungstest am Menschen wurde keine Hautsensibilisierung beobachtet. Für iPA liegen keine Daten vor. Andere analoge Alkoholester der Essigsäure, beispielsweise Ethylacetat und Butylacetate, zeigen keine hautsensibilisierende Wirkung.

Studien zur Toxizität bei wiederholter Verabreichung von n- oder Isopropylacetat beim Menschen liegen nicht vor.

In einer subchronischen Inhalationstoxizitätsstudie (OECD-Leitlinie 413) mit n-Propylacetat zeigten Ratten, die 6 Stunden pro Tag, 5 Tage pro Woche über einen Zeitraum von 13 Wochen 0, 150, 500 oder 1500 ppm Dampf (0, 630, 2100, 6300 mg/m^3) 5 Tage/Woche über 13 Wochen hinweg ganzkörperexponiert wurden, während der Exposition gegenüber 1500 ppm, jedoch nicht danach, eine vorübergehende Verringerung der Aufmerksamkeit, wahrscheinlich aufgrund einer narkotischen Wirkung der Testsubstanz. Bei 1500 ppm wurden Auswirkungen auf das KG oder die Gewichtszunahme und die Nahrungsaufnahme festgestellt. Das verringerte durchschnittliche KG oder die verringerte durchschnittliche Gewichtszunahme standen im Einklang mit der verringerten Nahrungsaufnahme. Das Zielorgan war die Nasenhöhle, wo konzentrationsabhängige Wirkungen im Riechepithel beobachtet wurden. Bei ≥ 500 ppm wurde eine fokale oder multifokale Degeneration und/oder Regeneration im Riechepithel beobachtet. Bei 150 ppm (630 mg/m^3) (NOAEC) wurden keine Auswirkungen beobachtet.

Die einzige vorliegende Studie mit wiederholter Exposition gegenüber iPA muss als unzuverlässig angesehen werden. In dieser Studie wurden Mäuse 4 Wochen lang 4 Stunden pro Tag, 5 Tage pro Woche einer Konzentration von 200000 mg/m^3 ausgesetzt und nach der Exposition 2 Wochen lang weiter beobachtet. Es wurden keine Auswirkungen auf das allgemeine Erscheinungsbild festgestellt, und es gab keine signifikanten Auswirkungen auf das KG. Weitere Details sind nicht verfügbar. Die Autoren kommen zu dem Schluss, dass iPA schwach narkotisch wirkt. Es ist zu beachten, dass die angegebene Expositionskonzentration die gesättigte Dampfkonzentration überschreitet.

In Bezug auf die Genotoxizität waren nPA und iPA in mehreren Tests mit Bakterien und Säugetierzellen *in vitro* in Anwesenheit oder Abwesenheit eines exogenen metabolischen Aktivierungssystems (S9-Mix) nicht mutagen. Für beide Verbindungen liegen keine I*n-vivo*-Daten vor. Isopropanol induzierte keine Mikronuklei im Knochenmark von Mäusen. Für n-Propanol konnte keine valide Studie identifiziert werden. Insgesamt zeigen Daten für C2-C4-Alkylacetatester, dass die Chemikalien dieser Gruppe kein mutagenes oder genotoxisches Potenzial aufweisen.

Karzinogenitätsstudien mit nPA oder iPA liegen nicht vor. Die verfügbaren Gentoxizitätsdaten geben keinen Anlass zu Bedenken hinsichtlich einer genotoxischen, nicht schwellenwertabhängigen karzinogenen Wirkung beider Verbindungen. Inhalationsstudien mit Isopropylalkohol an Ratten und Mäusen haben gezeigt, dass Isopropylalkohol kein für den Menschen relevantes karzinogenes Potenzial aufweist.

Eine erweiterte Studie zur Reproduktionstoxizität über eine Generation (EOGRT) gemäß OECD-Leitlinie 443 wurde mit oraler Verabreichung von nPA an Ratten durchgeführt. Mit Ausnahme von Speichelfluss wurde bei keinem der untersuchten Parameter behandlungsbedingte Auswirkungen festgestellt. 1000 mg/(kg KG x Tag), die höchste getestete Dosis, wurde als NOAEL für systemische Toxizität, Reproduktionstoxizität und Entwicklung der Jungtiere angesehen. In einer Studie zur Entwicklungstoxizität an Ratten gemäß OECD-Richtlinie 414 wurden bei keiner Dosierung von nPA substanzbedingte adverse Auswirkungen auf die Muttertiere, Schwangerschaftsparameter oder Föten beobachtet (NOAEL: 1000 mg/(kg KG x Tag), die höchste getestete Dosis). In der entsprechenden Studie mit Kaninchen wurde bei 300 mg/(kg KG x Tag) maternale Toxizität (verringerte Körpergewichtszunahme) festgestellt, jedoch bei keiner Dosis Embryo-/Fötotoxizität oder Teratogenität. Der berichtete NOAEL für mütterliche Toxizität betrug 300 mg/(kg KG x Tag) und für Entwicklungstoxizität 1000 mg/(kg KG x Tag), die höchste getestete Dosis.

Für iPA liegen keine Studien zur Reproduktionstoxizität vor. In einer 2-Generationen-Studie (gemäß OECD-Leitlinie 416) an Ratten mit oraler Exposition gegenüber Isopropanol war bei 1000 mg/(kg KG x Tag) in der frühen postnatalen Phase der F1-Generation eine Verringerung des KGs und eine Erhöhung der Mortalität zu beobachten. Bei dieser Dosis war der Paarungsindex der Männchen der F1-Generation statistisch signifikant verringert. Benchmark-Berechnungen ergaben einen BMDL5-Wert von 407 mg/(kg KG x Tag) für diesen Endpunkt. Details zur Berechnung wurden nicht berichtet.

Die Entwicklungstoxizität von Isopropanol bei inhalativer Exposition wurde an trächtigen Ratten untersucht. Der NOAEC-Wert für sowohl entwicklungsbezogene als auch mütterliche Auswirkungen wurde mit 3500 ppm (entspricht etwa 875 mg/(kg KG x Tag)) angegeben. In einer Studie zur Entwicklungstoxizität bei oraler Exposition von Kaninchen wurde ein NOAEL für die mütterliche Toxizität von 240 mg Isopropanol/(kg KG x Tag) ermittelt, wobei bis zur höchsten getesteten Dosis von 480 mg/(kg KG x Tag) keine Anzeichen für Teratogenität festgestellt wurden.

Die subchronische Inhalationstoxizitätsstudie mit nPA an Ratten dient als Grundlage für die Ableitung des EU-LCI. Diese Studie ergab einen NOAEC-Wert von 150 ppm nPA (630 mg/m^3). Die folgenden Extrapolationsfaktoren werden verwendet:

- Adjustierung auf kontinuierliche Exposition (6 h/Tag, 5 Tage/Woche): 5,6
- Zeitextrapolation: 2
- Interspeziesextrapolation: 2,5

- Intraspezies-Extrapolation (interindividuelle Variabilität, allgemeine Bevölkerung): 10

Gesamtextrapolationsfaktor: 280, was zu einem Wert von 150 ppm führt: 280 = 0,536 ppm (2250 µg/m³, gerundet auf 2300 µg/m³).

Für n-Propylacetat wird ein EU-LCI-Wert von 2300 µg/m³ vorgeschlagen.

Als Geruchsschwelle wurden für nPA 0,24 ppm (1008 µg/m³) angegeben. Es ist zu erwarten, dass der Geruch bei dem vorgeschlagenen EU-LCI-Wert wahrnehmbar sein wird.

Die EU-LCI-Ableitung für Isopropylacetat (iPA) erfolgte durch Read-Across mit n-Propylacetat (nPA). nPA ist die nächstverwandte homologe Verbindung mit einer ausreichenden Datenbasis. Der einzige Unterschied zwischen den beiden Substanzen ist die verzweigte Propylgruppe, d. h. eine 2-Methylethylgruppe in iPA anstelle der geradkettigen Propylgruppe in nPA.

- Toxikologischer kritischer Endpunkt für nPA: Degeneration und/oder Regeneration des olfaktorischen Nasenepithels.
- Die wichtigste Annahme, die dem Read-Across des EU-LCI-Wertes von nPA auf iPA zugrunde liegt, ist, dass beide Verbindungen denselben kritischen Endpunkt haben, was auf ihre gemeinsame chemische Struktur als Alkylacetat zurückzuführen ist. Der Effekt steht im Zusammenhang mit der lokalen Bildung von Essigsäure durch Hydrolyse des Acetatesters, die nach Überschreiten der spezifischen Pufferkapazität der Zellen zu einer Ansäuerung und damit zu zytotoxischen Schäden führt.
- Keine Cut-off-Regel: kein Unterschied in der Kettenlänge zwischen den beiden homologen Verbindungen nPA und iPA.
- Der abgeleitete EU-LCI-Wert für nPA von 2300 µg/m³ kann ohne Änderung auf iPA angewendet werden.

Für die Ableitung eines EU-LCI-Wertes für Isopropylacetat wird vorgeschlagen, den Read-Across von n-Propylacetat durchzuführen.

Für Isopropylacetat wird ein EU-LCI-Wert von 2300 µg/m³ vorgeschlagen.

Für iPA wird eine Geruchsschwelle von 0,16 ppm (672 µg/m³) angegeben. Es ist zu erwarten, dass der Geruch von Isopropylacetat bei dem vorgeschlagenen EU-LCI-Wert wahrnehmbar sein wird.

Stoffprofil und EU-LCI-Wert-Vorschlag für Isobutylacetat

Isobutylacetat (iBA), ein aliphatischer Ester, ist eine farblose Flüssigkeit mit einem bei Raumtemperatur mäßigen Dampfdruck (20 hPa). Die kaum wasserlösliche Substanz hat einen ausgeprägten fruchtigen oder blumigen Geruch und kommt in vielen Früchten natürlich vor. Isobutylacetat ist ein großtechnisches Industrieprodukt, das vor allem als Lösungsmittel in vielfältiger Weise verwendet wird, z. B. für Beschichtungen, Klebstoffe, Druckfarben, Dichtungsmittel und Reinigungsmittel, aber auch in Kosmetika und als Aromastoff in Lebensmitteln und Getränken.

Daten zum Vorkommen von Isobutylacetat in der Innenraumluft zeigen, dass die Substanz recht häufig nachgewiesen werden konnte (in etwa 25 % der durchgeführten Messungen), wobei die Konzentrationen meist unter 10 µg/m³ lagen, in Extremfällen jedoch 1660 µg/m³ erreichten.

Isobutylacetat wird nach inhalativer Exposition schnell absorbiert; quantitative Daten liegen jedoch nicht vor. Für das isomere n-Butylacetat wird angegeben, dass etwa 50 % der inhalierten Verbindung nach der Inhalation in der ausgeatmeten Luft zu finden sind. Nach Kontakt mit den Schleimhäuten oder Aufnahme in den Organismus wird iBA zu Isobutanol (2-Methyl-propan-1-ol) und Essigsäure hydrolysiert.

Es sind keine relevanten Unterschiede zwischen Säugetierarten hinsichtlich des Metabolismus von iBA bekannt. Nach der enzymatischen Hydrolyse von iBA durch Esterasen wird iBA weitgehend zu Isobutanol und weiter zu Isobutansäure (2-Methylpropansäure) oxidiert. Letztere wird über Methylmalonsäure zu Bernsteinsäure metabolisiert, die im Zitronensäurezyklus verwertet wird. Die bei der Hydrolyse von iBA entstehende Essigsäure wird ebenfalls weitgehend über den Zitronensäurezyklus oder für die Synthese von Fettsäuren verwertet.

Die Datenlage zur Toxizität von Isobutylacetat (iBA) ist begrenzt.

Die akute Toxizität von iBA im Tierversuch ist gering. Für iBA wurde eine 4-Stunden-LC50 von 6200 ppm (etwa 30200 mg/m^3) angegeben. Flüssiges iBA ist höchstens minimal reizend für die Augen und die Haut und nicht hautsensibilisierend.

In einem Alarie-Test mit Mäusen wurde bei hohen iBA-Konzentrationen eine sensorische Reizung beobachtet: Es wurde ein RD50-Wert von 818 ppm (etwa 3910 mg/m^3) ermittelt, der dem für n-Butylacetat ermittelten RD50-Wert von 730 ppm (etwa 3490 mg/m^3) sehr ähnlich ist, was auf eine vergleichbare sensorische Reizwirkung beider Isomere hindeutet.

Es liegen keine Studien zur akuten Inhalation von iBA beim Menschen vor. Eine klinische Studie zu den Reizwirkungen von n-Butylacetat bei freiwilligen Probanden ohne vorherige berufliche Exposition ergab nach 4-stündiger Exposition bei 145 ppm (700 mg/m^3) Reizungen im Rachenraum und Atembeschwerden sowie gerötete Augen.

Es liegen keine Studien zur Toxizität bei wiederholter Verabreichung von iBA bei Menschen oder Versuchstieren vor.

In einer subchronischen Inhalationstoxizitätsstudie zeigten Ratten, die mit 0, 500, 1500 oder 3000 ppm n-Butylacetat (nBA)-Dampf (0, 2390, 7170, 14340 mg/m^3) 6 Stunden/Tag, 5 Tage/Woche über 13 Wochen „ganzkörperexponiert“ wurden, bei ≥ 1500 ppm eine vorübergehende Sedierung. Außerdem waren die Körpergewichtszunahme und die Nahrungsaufnahme bei diesen Konzentrationen geringer, und es wurden Veränderungen des Gewichts mehrerer Organe festgestellt. Die Histopathologie ergab keine systemische organspezifische Toxizität. Zu den lokalen Auswirkungen auf das Nasenepithel gehörte eine Degeneration des Riechepithels. Deren Schweregrad war in der 3000-ppm-Gruppe leicht bis mäßig und in der 1500-ppm-Gruppe minimal bis leicht. Bei 500 ppm (NOAEC) wurde keine Wirkung beobachtet. Dieser NOAEC wurde in einer subchronischen Inhalationsneurotoxizitätsstudie an Ratten bestätigt.

Isobutylacetat und seine Metaboliten Isobutanol und Essigsäure sind *in vitro* nicht mutagen, *in vivo* liegen keine substanzspezifischen Daten zur Genotoxizität von iBA vor und ebenso auch keine Studien zur Karzinogenität. Die verfügbaren Daten zur Genotoxizität von iBA und seinen Metaboliten geben keinen Anlass zu Bedenken hinsichtlich einer genotoxischen, nicht schwellenwertabhängigen karzinogenen Wirkung von iBA.

Es liegen keine Studien zu iBA hinsichtlich Reproduktions- und Entwicklungstoxizität vor. Studien mit Isobutanol liefern keine Hinweise auf Reproduktions- oder Entwicklungstoxizität.

Die EU-LCI-Ableitung für iBA erfolgt durch Read-Across mit nBA. Innerhalb der chemischen Gruppe der „Butylacetate" ist nBA die nächstverwandte homologe Verbindung mit einer ausreichenden Datenbasis. Der einzige Unterschied zwischen den beiden Stoffen ist die verzweigte Butylgruppe, d. h. eine 2-Methylpropylgruppe in iBA anstelle der geradkettigen Butylgruppe in nBA.

- Toxikologisch kritischer Endpunkt für nBA: lokale Reizung der oberen Atemwege und der Augen.
- Die wichtigste Annahme, die dem Read-Across des EU-LCI-Wertes von nBA auf iBA zugrunde liegt, ist, dass beide Verbindungen denselben kritischen Endpunkt (Reizung) haben, der durch ihre gemeinsame chemische Struktur als Alkylacetat verursacht wird. Der Effekt steht im Zusammenhang mit der lokalen Bildung von Essigsäure durch Hydrolyse des Acetatesters, die nach Überschreiten der spezifischen Pufferkapazität der Zellen zu einer Ansäuerung und damit zu zytotoxischen Schäden führt.
- Keine Cut-off-Regel: kein Unterschied in der Kettenlänge zwischen den beiden homologen Verbindungen nBA und iBA.
- Der abgeleitete EU-LCI-Wert für nBA von 8500 µg/m³ kann ohne Änderung auf iBA übertragen werden.

Für Isobutylacetat (iBA) wird ein EU-LCI-Wert von 8500 µg/m³ vorgeschlagen.

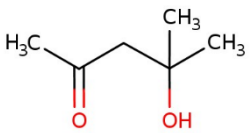
Isobutylacetat hat eine Geruchsschwelle von 38 µg/m³. Es ist zu erwarten, dass der Geruch von Isobutylacetat bei dem vorgeschlagenen EU-LCI-Wert wahrnehmbar sein wird.

1 Toxicological evaluation of 4-hydroxy-4-methylpentan-2-one (diacetone alcohol) as basis for the derivation of an EU-LCI value

1.1 Substance identification

4-Hydroxy-4-methylpentan-2-one (better known as diacetone alcohol) belongs to the group of beta-hydroxy ketones. Substance identification data of diacetone alcohol are shown in Table 1.

Table 1: Substance identification of 4-hydroxy-4-methylpentan-2-one (diacetone alcohol) (ECHA, 2024b)

CAS-No. EC-No. CLP-Index-No.	Systematic name, common name	Sum formula	Structural formula
123-42-2 204-626-7 603-016-00-1	4-Hydroxy-4-methyl-pentan-2-one, diacetone alcohol, DA	$C_6H_{12}O_2$	

1.2 Substance properties and uses

The physiochemical properties of diacetone alcohol are shown in Table 2. At room temperature, diacetone alcohol is a colourless liquid with a sweet odour (Silverman et al. 1946; cited in Greim and MAK Commission, 2001; NLM, 2024). The substance is quite volatile and soluble in water, alcohol and other solvents. It occurs naturally in some plants (e.g. *Camellia sinensis, Angelica gigas*) where it plays a role as a plant metabolite (NLM, 2024).

Table 2: Physicochemical properties of 4-hydroxy-4-methylpentan-2-one (diacetone alcohol) (ECHA, 2024b; OECD, 2000)

Molar mass (g/mol)	Melting point. (°C)	Boiling point (°C)	Vapour pressure (hPa) (at 20 °C)	Conversion 1 ppm = x mg/m³ (23 °C)	log pow	Solubility in water (g/L)
116.16	-44	167.9	129	4.78	-0.14	400 at 20°C

According to REACH, diacetone alcohol is registered in a total tonnage band ≥ 10000 to < 100000 tonnes/a and is used as a solvent in a wide variety of products such as coating and antifreeze products, hydraulic fluids, lubricant and greasers, biocides, fillers, plasters, adhesives and sealants, putties, modelling clay, and finger paints (OECD, 2000). Furthermore, in the EU diacetone alcohol is approved as a fragrance in cosmetics and a flavouring substance for food (Nikitakis and Kowcz 2019; cited in CIR, 2022; NLM, 2024). The technical grade of diacetone alcohol can contain up to 15 % acetone (NLM, 2024).

1.3 Exposure

1.3.1 Indoor air

Indoor releases into the air may occur from consumer products such as air fresheners, fragrances, detergents or other inhouse-products. Furthermore, some furnishing such as flooring, furniture, and construction materials, leather products etc. could also release the substance into the air over time (ECHA, 2024b). Few data are available on measured diacetone alcohol concentration in indoor air (see Table 3). The substance was not detected in any of the 128 samples tabulated in the "Database on the occurrence of volatile organic compounds in indoor air" (Datenbank zum Vorkommen von flüchtigen organischen Verbindungen in der Raumluft) (Hofmann and Plieninger, 2008). In 632 samples, diacetone alcohol concentration was also below the detection limit (LoD) of 1 µg/m^3 (AGÖF, 2013). At two production sites, concentrations of diacetone alcohol were measured with an average concentration of 0.95 and 13.89 mg/m^3 respectively (OECD, 2000).

Table 3: Data on the occurrence of diacetone alcohol in indoor air

Indoor	N	LoD (µg/m³)	N > LoD	Median (µg/m³)	P95 (µg/m³)	Maximum (µg/m³)	Source
Indoor air (not further specified), Germany, 2006-2012	632	not reported		< 1.0	< 1.0		(AGÖF, 2013)
Offices, homes, (pre)-schools, Germany	128	1.0	0 (0 %)	< 1.0	< 1.0		(Hofmann and Plieninger, 2008)
Occurrence at workplace							
Production site 1 (not further specified), Japan	30	Not reported		950	Not reported	Not reported	(OECD, 2000)
Production site 2 (not further specified), Japan	2	Not reported		13890	Not reported	Not reported	(OECD, 2000)

1.3.2 Other sources

Other potential sources of diacetone alcohol are for example constructions of different material (metal, wood, plastic) and building materials paints (OECD, 2000) with a low release rate of diacetone alcohol. Furthermore, diacetone alcohol naturally occurs in food and has been found in honey, passion fruit, roasted chicken, annatto and truffles, among other things (EFSA, 2014; Fortier et al., 2022). The EFSA Panel on Food Contact Materials, Enzymes, Flavourings and

Processing Aids (CEF) evaluated 11 flavouring substances, including diacetone alcohol, and estimated the intake from current uses. The average *per capita* intake based on the Maximised Survey-derived Daily Intake (MSDI) of diacetone alcohol as flavouring agent is estimated to be 0.085 µg/*capita*/day. The intake estimated on the basis of the modified Theoretical Added Maximum Daily Intake (mTAMDI) is reported to be 1600 µg/person/day (EFSA, 2014).

1.4 Toxicokinetics

The toxicokinetics following inhalation of diacetone alcohol were studied in male Sprague-Dawley rats (9 animals per concentration group). The substance was administered as a vapour at concentrations of 500 and 1000 ppm (analytical concentrations: 3.43 mg/L and 7.42 mg/L (3430 and 7420 mg/m^3)) by a nose-only exposure system for a single 6-h exposure and plasma samples were taken at nine time-points (0.5 – 24 h) after the end of exposure. Plasma samples taken from the rats after the end of the exposure showed that diacetone was rapidly and extensively absorbed through the respiratory tract. Maximum plasma concentrations (C_{max}) of 389 and 848 µg diacetone alcohol/ml were measured 30 minutes after the end of exposure for both concentration levels respectively. The half-life of diacetone alcohol was determined to range between 2.92 and 4.91 hours. The elimination rate was dependent on the initial exposure concentration, with a lower elimination rate and higher half-life at 1000 ppm, indicating a saturation of the excretion pathway and a potential for the substance to accumulate in the body if exposure persists (ECHA, 2024b).

A dermal penetration study using human abdominal skin is available. 25 mg/cm^2 (313 µl/cm^2 of an 80 mg/ml solution) of diacetone alcohol in water (vehicle) was applied to the skin for either 10 or 60 minutes. No dermal irritation was observed after the 10- and 60-minutes exposure period and the total recovery was between 89.6 – 91.7 %. A permeability coefficient (K_P) of 5.77 *10^{-4} and a short-term penetration rate of 56.6 µg/cm^2/h (10-minute exposure) or 37.3 µg/cm^2/h (60-min exposure) was established, based on a skin penetration of 0.04 (10 min), 0.15 (60 min) and 5.17 % (24 h). A skin penetration of 1 % over 8 hours was calculated (ECHA, 2024b).

Furthermore, two different mathematical models estimated an intake of approximately 530 mg and 2900 mg of diacetone alcohol, assuming a 1-hour exposure to a saturated aqueous solution with a skin surface area of 2000 cm^2 (hands and forearms) (Fiserova-Bergerova et al. 1990 as well as Guy and Potts 1993; both cited in Greim and MAK Commission, 2001).

The oral uptake of diacetone alcohol was investigated in an older study following OECD TG 417 in male Sprague-Dawley rats administered 5.81 g diacetone alcohol (vehicle: 18.25 g of corn oil) by gavage, and plasma samples were collected at nine timepoints (0.25 to 24 h) after the administration. Although there was an initial rise in concentration after 1 hour (4.40 mmol/L in plasma), C_{max} was not reached until 6 hours after administration end (4.82 mmol/L), indicating that diacetone alcohol is absorbed more slowly over time, leading to a gradual increase in concentration (prolonged absorption phase). The half-life was 2.3 hours (CIR, 2022; ECHA, 2024b).

In CD-1 mice, in addition to blood plasma, diacetone alcohol was also detected in the brain, 15-90 minutes after i.p. application of 2.5 mmol/kg bw, suggesting that diacetone alcohol can cross the blood-brain-barrier (Granvil et al. 1994; cited in Greim and MAK Commission, 2001). Furthermore, *in vitro* studies with isolated rat liver microsomes have demonstrated that, while not affecting the microsomal enzyme concentration, diacetone alcohol stimulates NADPH oxidation by binding to cytochrome P-450, similar to cytochrome P-450 substrates (Ivanetich et

al. 1978; cited in Heimbürger and Nordic Council of Ministers Nordic Expert Group for Documentation of Occupational Exposure, 1989).

There are conflicting reports in literature regarding the metabolism of diacetone alcohol. Some sources suggest that methyl isobutyl carbinol (MIBC) and methyl isobutyl ketone (MIBK) are precursors of diacetone alcohol, with diacetone alcohol acting as a potential metabolite of both compounds (NLM, 2024). Other studies indicate that MIBC and MIBK are themselves metabolites of diacetone alcohol. In the inhalation and oral studies with Sprague-Dawley rats described earlier, plasma levels of MIBC and MIBK were also assessed. However, in both studies, the concentrations of MIBC and MIBK in plasma remained below the limit of quantification (LOQ)(ECHA, 2024b).

The primary routes of excretion for diacetone alcohol include the formation of sulphate and glucuronide conjugates which are eliminated via renal pathway. Additionally, diacetone alcohol can also be excreted through the respiratory system as carbon dioxide after being introduced into intermediary metabolism (DiVicenzo et al. 1976; cited in Greim and MAK Commission, 2001).

1.5 Health effects

1.5.1 Acute toxicity, sensory irritation, and local effects

Acute toxicity

In humans, exposure to 475 mg/m^3 (100 ppm) diacetone alcohol through a chamber test led to headache, nausea or vomiting and had unspecified effects on the sense organs (Silverman et al. 1946; cited in OECD, 2000). This test is discussed in more detail under “Irritation”.

No mortality was observed in an inhalation study according to OECD TG 403 in which rats were exposed to 7.6 mg/L air (7600 mg/m^3/approx. 1590 ppm) (range 7.2 to 8.1 mg/L air) of diacetone alcohol vapour for 4 hours. No toxic signs were observed during exposure or 14-day observation period (CIR, 2022; ECHA, 2024b).

In an older study from 1946, exposure to an atmosphere saturated with vapour of diacetone alcohol (1500 ppm) for 8 h led to signs of slight nasal and eye irritation in rats but no lethality was observed (Smyth and Carpenter 1948 & Union Carbide 1946a; both cited in Greim and MAK Commission, 2001).

An acute dermal LD50 value of >13630 mg/kg bw was obtained for rabbits which showed skin erythema. No further information is provided (Smyth and Carpenter 1948 & Union Carbide 1946a; both cited in Greim and MAK Commission, 2001).

In another study the LD50 was reported to be 14.5 ml/kg bw (13593.75 mg/kg bw) in rabbits after application of diacetone alcohol via occlusive patch (24 h) led to no skin injury beyond erythema followed by shallow scaling. Amount or concentration of diacetone alcohol was not stated (CIR, 2022; ECHA, 2024b).

In rats, a study that was conducted similar to OECD TG 402 is reported. The test substance, applied in the largest volume possible to the skin, was administered at an undiluted concentration of 2 ml/kg bw (1875 mg/kg bw) and left on the shaved dorsal skin for 24 hours under occlusive conditions. No mortalities or clinical signs were observed during the observation period of 14 or 21 days and the reported LD50 was > 1875 mg/kg bw (CIR, 2022; ECHA, 2024b).

Oral toxicity studies in rats report LD50 values ranging from 2520 to 4000 mg/kg bw (CIR, 2022; ECHA, 2024b; Greim and MAK Commission, 2001).

Two studies report effects on the liver (e.g. increased number and activity of lymphocytes and Kupfer cells, vacuolization in the periportal fields in the liver, reversible cloudy swelling of the liver cells, liver damage), mention narcotic effects such as drowsiness, anaesthesia or respiratory depression and an effect on erythrocytes (Keith 1932; cited in Greim and MAK Commission, 2001). Another study reported a LD50 value of 3002 mg/kg bw in a detailed study conducted similar to OECD TG 401. Concentrations of 1880, 2369, 3002, 3760, or 5969 mg/kg bw were administered orally by gavage. In all animals, lethargy, piloerection and ataxy were observed. At higher concentrations, the rats were comatose and starting at 3002 mg/kg bw, all animals died (CIR, 2022; ECHA, 2024b). In mice and rabbits, the oral LD50 values were 3950 and 4653 mg/kg bw, respectively (CIR, 2022).

Irritation

In the above-mentioned chamber test with 24 volunteers (12 male and 12 female test persons), a 15-minute exposure to 100 ppm of diacetone alcohol caused irritation of the eyes, nose, and throat for most participants. The majority found the odour unpleasant. Based on the symptoms and the assessment of the subjects, a limit of 50 ppm was derived as safe for an 8-hour exposure (Silverman et al. 1946; cited in ACGIH, 2001; ECHA, 2024b; Greim and MAK Commission, 2001; OECD, 2000).

In another study, diacetone alcohol was tested on human volunteers. A coin-sized amount of the substance was applied to the back of their hands and allowed to evaporate. The volunteers did not report any uncomfortable sensation, such as itching or irritation and the skin remained unchanged. No further details were reported (CIR, 2022).

Reversible irritation effects were reported in an older study from 1978 (similar to OECD TG 405), where 0.2 ml (200 mg) of undiluted diacetone alcohol was instilled into the eyes of white rabbits in a single exposure experiment. Symptoms such as conjunctival redness, chemosis, corneal opacity, and iris irritation appeared within hours and resolved completely within 2-7 days. In a similar study according to OECD TG 405 with half the amount of diacetone alcohol (0.1 ml, undiluted, single exposure), it took up to 21 days for the same symptoms to disappear (ECHA, 2024b).

In another study albino rabbits eye lids were retracted and treated with 0.005 ml (5 g) of undiluted diacetone alcohol for approximately 1 minute. It was reported that diacetone alcohol caused grade 5 injury (scale 1-10) (Carpenter and Smyth 1946; cited in CIR, 2022). Overall, diacetone alcohol was determined to be irritating to the eye of rabbits.

On skin, the substance has been reported to be only slightly irritating. In a study conducted according to OECD TG 404, rabbits were exposed to an occlusive application of 0.5 ml undiluted diacetone alcohol for 24 hours. No irritation was observed in animals with intact skin, while reversible slight erythema was noted in some of those with abraded skin (CIR, 2022; ECHA, 2024b).

No skin irritation was reported in studies with rabbits and guinea pigs after brushing diacetone alcohol on either the inside of the right ear (rabbit) or the back (guinea pigs) once per day for 10 consecutive days. No further information on test guideline or dosing was reported (BASF Corporation 1995; cited in CIR, 2022).

Sensitisation

A guinea pig maximisation test, conducted in accordance with OECD TG 406 and EU Method B.6, demonstrated no sensitisation potential for diacetone alcohol. In the induction phase, on day 1, six intradermal injections were administered on the dorsal region between the shoulders of the guinea pigs (three injections on each side of the shoulder region). Each of the injections consisted of 0.1 ml of either 50% (v/v) dilution of Freund's complete adjuvant in sterile isotonic saline (0.9 % NaCl), the test substance at 25 % (w/w) in 0.9 % NaCl or a mixture of the adjuvant and the test substance at a 50/50 (w/v) ratio. The control group received the same procedure without the test substance. On day 7, local irritation was induced by treating them with 0.5 ml of sodium lauryl sulphate (10 % w/w) in vaseline. On day 8, a topical application with 0.5 ml of undiluted diacetone alcohol was performed and secured in place for 48 hours. In the challenge phase, on day 22, the treatment and control animals both received a challenge application of 0.5 ml of the undiluted test substance for 24 hours through an occlusive dressing. Afterwards no signs of skin reactions, such as erythema or oedema, were observed in any of the animals (ELF Atochem North America Inc , 1998; cited in CIR, 2022; ECHA, 2024b).

In an older guinea pig maximisation test (OECD TG 406) from 1978, the animals received two rows of three intradermal injections in the shoulder. These injections consisted of 0.1 ml of Freund's complete adjuvant (FCA), 0.1 ml of the test substance in solvent and 0.1 ml of the test substance in a 50:50 mixture of FCA and solvent The concentrations used were 0.5 % w/v of diacetone alcohol in corn oil. The topical application followed a week after, where a paper soaked with 0.3 ml undiluted test substance was applied to the injection site and held in place for 48 hours. The challenge phase occurred two weeks after the topical induction. A paper soaked with 0.15 ml of undiluted test substance was applied to the shaved flank and covered for 24 hours. No cutaneous reactions were observed afterwards. It was concluded that diacetone alcohol was not a skin sensitiser (ECHA, 2024b).

1.5.2 Repeated dose toxicity

Human data

In a case report, a 59-year-old man was exposed to diacetone alcohol and an unknown ethanolic solvent for three days. Forty days after this exposure, the man exhibited an inflammation of the kidneys, which were diagnosed as subacute proliferative glomerulonephritis (NLM, 2024). No further human data are available.

Animal data

No studies with repeated dermal exposure to diacetone alcohol are available.

In a short-term repeated dose inhalation study equivalent to OECD TG 412, 12 rats per sex were exposed whole-body to 0, 233, 1041 and 4685 mg/m^3 (50, 225 and 1000 ppm, analytical concentration) of undiluted diacetone alcohol (purity: 99.44 %) for 6 h/d, 5 d/w for 6 weeks. In the process, 0.6, 0.6 and 4.1 % acetone were produced by decomposition at the evaporator. No mortality was observed. Starting week 4 of exposure, slight lethargy was observed in several animals of the 1041 and 4685 mg/m^3 concentration group, which subsided after a few hours. Additionally, the female animals of the highest exposure group had significantly reduced body weights, the haematological findings showed higher haemoglobin levels, and the clinical chemistry revealed significantly higher lactase dehydrogenase levels. In males of the high concentration group, higher plasma protein levels and reduced plasma chloride levels were observed. The latter was also noted in the males of the medium concentration group. Furthermore, all male animals showed reduced plasma sodium levels. The pathological observations showed effects on the organ weights of liver and kidney. Both organ weights were

significantly higher in the high concentration groups (+23 % for liver, +17 % for kidney) and the liver weights were also higher in the medium concentration group (+13 %). At the histologic level, diacetone alcohol exposure led to eosinophilic hyaline droplets in the proximal tubular cells of the kidneys in males of the highest concentration group. Those effects are species- and sex-specific and generally of little or no relevance to humans. A thickening of the alveolar wall in the lungs and a local irritation of the respiratory tract was also observed, however none of the changes appeared to be treatment-related. The MAK commission reported a NOEL of 233 mg/m^3 and a marginal LOEL of 1041 mg/m^3, while in the registration dossier a NOAEC of 4685 mg/m^3 and a NOEC of 1041 mg/m^3 were derived. This discrepancy can be attributed to the different evaluation of the liver weight changes, with the authors of the registration dossier entry considering the changes to be secondary to metabolic overload (Shell Pol Company 1980, cited in CIR, 2022; ECHA, 2024b; Greim and MAK Commission, 2001; OECD, 2000).

Several repeated dose studies for oral exposure of diacetone alcohol are available:

In a subchronic study, according to OECD TG 408, male and female Sprague-Dawley rats were treated with 0, 25, 150 and 600 mg/(kg bw x d) diacetone alcohol in corn oil via gavage for 13 weeks (10 animals per sex at dose levels 25 and 150 mg/(kg bw x d) and 15 animals/sex at dose levels of 0 and 600 mg/(kg bw x d)). At the end of the treatment, 10 animals/group were sacrificed, and the 5 additional animals from the control and the highest concentration group were kept for a 6-week recovery period. No mortalities from exposure to diacetone alcohol were observed. Significantly lower body weights were noted in male animals at 600 mg/(kg bw x d). In the same group (male) a significantly increased neutrophil count was observed in the haematological findings. At dose levels 150 and 600 mg/(kg bw x d) in female rats, the red blood cell count was significantly reduced, which was associated with a packed cell volume and lower haemoglobin at 600 mg/(kg bw x d). Furthermore, in females at the highest concentration group, a lower white blood cell count was also observed as well as a slightly lower lymphocytes count. Regarding blood biochemistry examinations, a higher cholesterol concentration was reported in male and female animals of the highest concentration group. A lower inorganic phosphorus concentration was also reported in male rats from the two highest concentration groups. These blood biochemistry findings were not considered adverse, and the effects were no longer observed at the end of the 6-week recovery period. Likewise, previously observed urinary findings were also no longer noted. In the liver, non-adverse centrilobular hepatocellular hypertrophy, as well as increases in liver weights and incidences of accentuated lobular pattern were found, however there was a complete recovery of the latter at the end of the recovery period. In the kidneys, male rats of all diacetone alcohol exposure groups showed increased kidney weights, which correlated with microscopic alterations such as increased incidences of tubular hyaline droplets, tubular basophilia and granular casts. Like in the study described above, the effects on the kidney are species- and sex-specific and irrelevant for humans. Therefore, a NOAEL of 600 mg/(kg bw x d) was derived (CIR, 2022; ECHA, 2024b).

In another study, 10 Sprague Dawley rats per sex and concentration group were exposed to 0, 30, 100, 300 or 1000 mg/(kg bw x d) via gavage in a combined repeated dose and reproductive/development toxicity screening test according to OECD TG 422. Male rats were exposed for 44 days, while female rats were exposed from 14 days before mating to day three of lactation. Except for one female that had to be euthanised after delivery, no mortality was observed. Both sexes of the 300 and 1000 mg/(kg bw x d) group displayed pre-narcotic effects such as decreased locomotor activity and stimulation response to knocking sounds or palpation. Female rats in the highest concentration group showed a significantly reduced body weight during the premating period, while male rats in the highest concentration group showed an increase in the number of platelets. Clinical chemistry examinations were performed in male

rats only and showed a significant increase in total protein, total cholesterol, total bilirubin, blood urea nitrogen, creatinine, and calcium, and a significant decrease in glucose in the 1000 mg/(kg bw x d) group. Alterations in the kidney were observed mainly in male rats of the 300 and 1000 mg/(kg bw x d) groups such as increased depositions of hyaline droplets in the proximal tubular epithelium (excluded in evaluation due to species-specific effect), dilation of distal tubules, and an overall increase in kidney weight. In female rats, only slight increases of dilated distal tubules and fatty degeneration of the proximal tubular epithelium were observed. Both sexes displayed hepatocellular hypertrophy in the 1000 mg/(kg bw x d) group. A NOAEL of 100 mg/(kg bw x d) was derived for both sexes (Ministry of Health and Welfare 1997; cited in CIR, 2022; ECHA, 2024b; Greim and MAK Commission, 2001; OECD, 2000).

Less detailed 30-day repeated dose studies in rats reported swelling and degeneration in tubules cells after doses of 0.04 mg/(kg bw x d) diacetone alcohol in drinking water and unspecified micropathological alterations after doses of 40 mg/(kg bw x d) diacetone alcohol (Union Carbide 1946 b; cited in Greim and MAK Commission, 2001) (Smyth and Carpenter 1948; cited in OECD, 2000). Another study established a maximum tolerated dose (MTD) of >1000 mg/(kg bw x d) in rabbits, after oral exposure of 100, 300 or 1000 mg/(kg bw x d) diacetone alcohol, administered via gavage. In this study, a significant decrease in food consumption was seen in the highest concentration group (ECHA, 2024b).

1.5.3 Genotoxicity and carcinogenicity

Genotoxicity

Diacetone alcohol was not considered as genotoxic based on the results of several *in vitro* studies in bacteria and mammalian cells.

Ames tests were negative for diacetone alcohol in *Salmonella typhimurium* TA1538 up to 4000 µg/plate, in TA1537 and *Escherichia coli* WP2 uvrA up to 5000 µg/plate, and in TA97, TA98, TA100 and TA1535 up to 10000 µg/plate. All tests were done in the presence or absence of exogenous metabolising system (Brooks et al. 1988 & Ministry of Health and Welfare 1997;both cited in AICIS, 2013; Greim and MAK Commission, 2001; NTP, 2024). The results were negative in mitotic recombination tests in yeast (*Saccharomyces cerevisiae* JD1) with up to 5 mg/ml diacetone alcohol with and without metabolic activation. Diacetone alcohol was also not clastogenic in chromosome aberration tests in Chinese hamster lung cells (according to OECD TG 473) at up to 1.2 mg/ml (ECHA, 2024b). Furthermore, the substance did not show any mutagenic activity in mouse lymphoma L5178Y cells (test according to OECD TG 476 and EU Method B.17), either in the presence or absence of exogenous rodent liver microsomes. Ambiguous results were obtained with RL4 cells (rat epithelial-type liver cell), were diacetone alcohol induced a slightly increased chromatic damage within concentrations of 2000 – 4000 µg/ml. However, this effect was not quantitatively dose-related and was attributed to the detergent-like properties and osmolar changes in the culture media caused by solvents. Ultimately, the results were judged as negative by the Scientific Panel on food additives, flavourings, processing aids and materials in contact with food (AFC) (Brooks et al. 1998; cited in ECHA, 2024b; Greim and MAK Commission, 2001).

In vivo mutagenicity data are not available.

Carcinogenicity

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

1.5.4 Toxicity to reproduction

Fertility

The reproductive toxicity of diacetone alcohol was examined in a combined repeated dose and reproductive/development toxicity screening test according to OECD TG 422. Study details can be found in section 1.5.2. Non-significant effects on fertility were observed in the 1000 mg/(kg bw x d) group: decrease in fertilisation rate, implantation numbers and implantation rate. There were no macroscopic effects in the offspring. However, lower overall birth rate, a lower number of live pups, lower birth weight and decreased pup survival at day 4 of lactation at 1000 mg/(kg bw x d) were observed, although not significant. The observed effects were attributed to the maternal toxicity and thus a NOAEL of 300 mg/(kg bw x d) for toxicity to reproduction as well as for developmental toxicity was derived (Ministry of Health and Welfare 1997; cited in CIR, 2022; ECHA, 2024b; Greim and MAK Commission, 2001).

In a reproduction/development toxicity screening test according to guideline 421, a total of 105 Sprague Dawley rats (45 males/60 females) were exposed to 0, 50, 250 or 750 mg/(kg bw x d) via gavage. The NOAEL of >750 mg/(kg bw x d) was derived for male and female rats, due to significant decrease in food consumption in females and adverse effects on the kidney in males. A NOAEL of 250 mg/(kg bw x d) was considered for the developmental toxicity, since there was a progressive decrease in the pups survival during the lactation period, as well as effects on body weights in the highest dose group (ECHA, 2024b).

In an extended one-generation reproductive toxicity study with F2 generation (EOGRTS, OECD TG 443) parental Sprague-Dawley rats (at least 25/sex/group) received daily oral doses of 50, 200 and 600 mg diacetone alcohol/(kg bw x d) by gavage. The control group were given corn oil. Males were exposed for at least two weeks before pairing up until sacrifice, for a minimum of ten weeks. Females were exposed starting two weeks before pairing until sacrifice on postpartum day 21. At weaning, for each group, one or two male and female pups were randomly selected from each litter (40 F1 pups/sex/group) to form cohort 1A and cohort 1B (each cohort 20/sex/group). Cohort 1A received diacetone alcohol for 13/14 weeks before sacrifice. The animals from cohort 1B were treated for at least 10 weeks before mating and exposure continued for males up to the day before sacrifice (after the weaning of the majority F2 litters) and for females until day 21 after giving birth. In the first parental generation (P0), no treatment-related mortality was reported. Treatment-related, reversible reduced body weight gain was observed in females at 600 mg/(kg bw x d) on day 7 and at all dose levels on day 14 post coitum. Changes in haematology parameters and clinical biochemistry.were often reported as either not adverse or not-treatment related. Urinalysis findings showed increased ketonuria in males at 200 and males and females at 600 mg/(kg bw x d). No effect on the number of oestrous cycles were observed. A slight decrease regarding the fertility index in males and females at dose levels of 200 and 600 mg/(kg bw x d) and an increase in post-natal loss in females exposed to 600 mg/(kg bw x d) were considered unlikely to be treatment related. Due to increased severity of hyaline droplets accumulation associated with nephropathy in males of the highest dose group a NOAEL of 200 mg/(kg bw x d) was derived for male rats, while for female rats a NOAEL of 600 mg/(kg bw x d) was derived for the P0 generation. In the second parental generation (P1), no treatment-related mortality was observed. Treatment-related side effects were observed in cohort 1B as follows: In males an increase in cholesterol, triglycerides and creatinine was noted, while in females, an increase in cholesterol, triglycerides, alanine aminotransferase, and bilirubin was observed at 600 mg/(kg bw x d). At 200 mg/(kg bw x d), male rats showed a general increase in triglycerides and glucose. Cohort 1A showed similar effects in the highest dose group for some parameters, but in both cohorts these were considered as the result of adaptive changes and not tissue/organ injury. Due to diacetone

alcohol catabolism, a dose related trend of increased urinary ketones was observed at 200 and 600 mg/(kg bw x d) in males and females in both, cohort 1A and 1B. The males in the 600 mg/(kg bw x d) group showed increases in liver (relative) and kidney weights (relative and absolute). An increase in post-natal loss was observed in lactating females treated with 600 mg/(kg bw x d), both at birth and on day 4 postpartum, the latter being statistically significant. The persistence of this effect in cohort 1B suggests a possible relationship with the test substance at the higher dose. At 200 mg/(kg bw x d), an increase in post-natal loss was also noted on Day 4 postpartum compared to the control group, but the effect was not clearly confirmed since the magnitude remained consistent between parental and cohort 1B females, indicating no definite dose-related effect at this concentration. For cohort 1B and cohort 1A, based on adverse kidney effects, a NOAEL of 200 mg/(kg bw x d) was derived for male rats and a NOAEL of 600 mg/(kg bw x d) was derived for female rats who did not show effects even at the highest dose tested. In the F2 generation, observed mortality was considered not treatment-related. No effects were observed regarding body weight changes, sexual maturation (anogenital distance), organ weights and gross pathological findings. Other findings (haematological, clinical biochemistry, urinalysis) were not examined. Based on the increase in post-natal loss seen in lactating parental females (P0 and Cohort 1B) at 600 mg/(kg bw x d), a NOAEL of 200 mg/(kg bw x d) for both sexes was reported for the F2 generation (ECHA, 2024b).

In the study conducted according to OECD TG 408, which is already described above (see section 1.5.2), reproduction parameters were investigated. The number of cycles measured in female animals were reported to be slightly lower in the high-dose group than in the control group, which was considered treatment-related but non-adverse. No treatment-related effects were seen on mean epididymal sperm motility and morphology, mean testicular sperm head and the daily sperm production rate. A trend towards lower mean epididymal sperm count was noted in the 600 mg/(kg bw x d) group but considered unlikely to be treatment related due to various factors (low magnitude, large standard derivation, no microscopic findings and comparable individual results). Overall, the study found no significant reproductive effects of diacetone alcohol on the rats and a NOAEL of 600 mg/(kg bw x d) was derived (ECHA, 2024b).

Developmental toxicity

In a prenatal developmental toxicity study according to OECD TG 414, pregnant Sprague-Dawley rats (24/dose group) were exposed to 0, 100, 300 or 1000 mg/(kg bw x d) via gavage daily from Day 6 to day 20 post-coitum inclusive. No maternal deaths were observed. Excessive salvation was noted in the 1000 mg/(kg bw x d) group, as well as tremors in one female. No treatment-related findings were observed in the females. A NOAEL of 1000 mg/(kg bw x d) was considered for maternal parameters. All pregnant females had viable foetuses, with no observed deaths, and no effects on mean foetal body weight or sex ratio. All litters in the highest dose group had foetuses with unossified or incomplete ossification of various parts of the skeleton and one foetus had knobby ribs. These findings were not considered adverse as they were attributed to the presence of cartilage. The NOAEL was considered to be 1000 mg/(kg bw x d) for embryo-foetal development (ECHA, 2024b).

Another prenatal development toxicity study according to OECD TG 414 was conducted with rabbits (24/dose group). 100, 300 or 800 mg/(kg bw x d) of diacetone alcohol in water were given to the animals via gavage daily from GD 6 – 28. A control group received the vehicle water. In the highest dose group treatment-related reduced food consumption and a transient body weight change was observed in all females, leading to one female being euthanised prematurely due to bad health. The pathological examination showed a gall bladder dilatation, as well as whitish coloured areas of the stomach mucosa with dry content in that rabbit. In the offspring, five litters from the 800 mg/(kg bw x d) group had one foetus each showing one of the following

malformations: external, visceral and skeletal malformations (omphalocele, meningoencephalocele, fused caudal vertebrae, split frontal in addition to a fused sternebrae, malpositioned kidneys and adrenals, multiple heart great vessel malformations (dilated aorta, pulmonary trunk and retroesophageal aortic arch)). A dilated aorta was noted in two foetuses from two different litters in the 300 mg/(kg bw x d) group. For the maternal toxicity, a NOAEL of 300 mg/(kg bw x d) was derived by the registrant due to the reduction of body weight and food consumption. For embryo-foetal development, a NOAEL of 100 mg/(kg bw x d) was derived by the registrant based on the malformation (ECHA, 2024b).

In a non-GLP preliminary study with only five rabbits per dose group and doses of 0, 100, 300 and 1000 mg/(kg bw x d), reduced food and water consumption as well as body weight loss in the dams were observed and one female had to be euthanised prematurely due to body weight reduction (19 %) and almost no intake of food or water. There were no clinical signs, necropsy findings, or foetal malformations related to the test item. Based on the observed maternal toxicity, it was considered in the registration dossier that the highest tested dose of 1000 mg/(kg bw x d) may have exceeded the Maximum Tolerated Dose (MTD) in pregnant rabbits based on the mortality at this dose. The NOAEL for developmental toxicity was considered to be 1000 mg/(kg bw x d) (ECHA, 2024b).

1.5.5 Odour perception

The odour of diacetone alcohol is described as sweetish and pleasant (Hellman and Small 1974; cited in Greim and MAK Commission, 2001; Heimbürger and Nordic Council of Ministers Nordic Expert Group for Documentation of Occupational Exposure, 1989). However, the majority of the volunteers in the 15-minute chamber test (see section 1.5.1) described the odour as unpleasant (Silverman et al. 1946; cited in ECHA, 2024b; Greim and MAK Commission, 2001). Following a single exposure to diacetone alcohol, 50 % of the selected collective identified 0.28 ppm as the odour threshold (Greim and MAK Commission, 2001). In the literature, an odour threshold between 0.28 and 100 ppm has been reported for diacetone alcohol (Hellman and Small 1974, as well as Ruth 1986; both cited in Greim and MAK Commission, 2001).

1.6 Evaluation

1.6.1 Existing regulations and classifications

In its harmonised classification according to Annex VI of Regulation (EC) No. 1272/2008 diacetone alcohol is classified for Eye Irritation 2 (H319) (ECHA, 2024a).

Existing guide values for diacetone alcohol in air are summarised in Table 4.

A DNEL of 5.8 mg/m^3 is derived in the registration dossier for the protection of the general population via inhalation route. The DNEL is based on the NOAEL of 100 mg/(kg bw x d) for developmental toxicity/teratogenicity effects obtained in a prenatal developmental toxicity study (OECD TG 414) in rabbits. The NOAEL was converted to a modified NOAEC of 145 mg/m^3 and the DNEL calculated by applying a total extrapolation factor of 25, which is composed of an interspecies factor of 2.5 and an intraspecies factor of 10.

For chronic inhalation exposure of workers, the same study with the NOAEL of 100 mg(kg bw x d) was used. A modified NOAEC of 408 mg/m^3 was derived (see Table 4). Assessment factors of 2.5 and 5 accounted for differences in interspecies and intraspecies, respectively (total of 12.5). While the NOAEL is listed as being derived from a study with rats, a closer look at the reference and the values used for the NOAEC calculation strongly indicates that the species is rabbit.

Additionally, a harmonised classification and labelling proposal for diacetone alcohol was published on the ECHA website on 19.09.2024 and is open for consultation, in which ANSES proposes a classification for reproductive toxicity category 1B (H360D) for diacetone alcohol. The proposal is based on the developmental adverse effects (post-natal lethality and malformations) seen in rats or rabbits in different studies.

The MAK commission based the derivation of a MAK value on a chamber test with volunteers (see section 1.5.1). Due to the statement that "most" effects occurred at 100 ppm, the authors of the MAK evaluation could not rule out the possibility that effects also occurred at the next-lower concentration of 50 ppm. Although the majority of subjects described 50 ppm as tolerable for an 8-hour exposure, a MAK value of 20 ppm (=96 mg/m^3) was therefore derived (Greim and MAK Commission, 2001).

A NIK value of 0.96 mg/m^3 is reported by AgBB (2024)[1].

Even though diacetone alcohol is frequently used in the cosmetic industry, the Cosmetic Ingredient Database (CosIng) does not specify any restrictions or maximum concentration for diacetone alcohol (EC, 2024).

Diacetone alcohol used as a food flavouring agent was assigned a threshold of concern of 1800 µg/person/day, which is not exceeded by the estimated intake based on the mTAMDI approach (1600 µg/person/day) (EFSA, 2014).

1.6.2 Derivation of an EU-LCI value

Inhalation exposure of undiluted diacetone alcohol was tested in rats according to OECD TG 412. The animals were exposed to 0, 233, 1041 and 4685 mg/m^3 (50, 225 and 1000 ppm) of the substance for 6h/d, 5 d/w for 6 weeks. It was reported that 0.6, 0.6 and 4.1 % acetone were produced by decomposition at the evaporator. In this study, liver weight increases of +13% and +23% were observed in the medium and high concentration groups respectively, without any accompanying microscopic liver changes. Clinical chemistry data that could help interpret these changes were not observed. The interpretation of liver weight changes remains a topic of significant debate within the scientific community. Currently, there is no established consensus on what degree of liver weight increase should be considered harmful or adverse. In 2018, the Working Group – Human Health of the Biocidal Products Committee (ECHA) worked on the interpretation of liver effects in toxicological studies in rodents, resulting in the publication of an annex which provides guidance on the subsequent principles to be undertaken. In the annex, the authors state that for mice and rats, *"[…] an increase of relative (to body weight) liver weight up to 15 % is part of normal biological variation […]"*(Anon, 2018). A weight of evidence approach and expert ruling is recommended. Based on the annex data and the absence of any histopathological changes in the liver, the observed +13 % liver weight increase is considered to fall within normal variability. Furthermore, the potential role of acetone production in contributing to the liver weight changes cannot be excluded. With the +23 % liver weight increase, the possibility of an adverse effect cannot be ruled out, particularly due to the lack of sufficient clinical chemistry data to clarify the cause. Therefore, a revised LOAEC of 4685 mg/m^3 was established by the authors of this evaluation. If this LOAEC were to be used as POD for the derivation of an EU-LCI value with a total assessment factor of 2520 (adjustment for continuous exposure: 5.6,

[1] AgBB (Ausschuss zur gesundheitlichen Bewertung von Bauprodukten) Requirements for the Indoor Air Quality in Buildings: Health-related Evaluation Procedure for Emissions of Volatile Organic Compounds (VVOC, VOC and SVOC) from Building Products. Updated list of LCI-values 2020 in the annex. Committee for Health-related Evaluation of Building Products. Online: https://www.umweltbundesamt.de/sites/default/files/medien/4031/dokumente/agbb_evaluation_scheme_2024.pdf. Accessed on 24.09.2024

adjustment study length factor: 6, interspecies extrapolation: 2.5, intraspecies extrapolation: 10, LOAEC to NOAEC: 3), it would result in an EU-LCI value of 1900 µg/m³ (rounded).

However, the most critical effects of diacetone alcohol exposure are the developmental adverse effects such as post-natal lethality and malformations observed in several developmental toxicity studies, which led to a proposal for a Repro 1B classification. Therefore, for the derivation of an EU-LCI value, a NOAEL of 100 mg/(kg bw x d) obtained in a prenatal development toxicity study according to OECD TG 414 with oral exposure of rabbits with diacetone alcohol in water is used as POD. This NOAEL is based on embryotoxic/teratogenic effects (external, skeletal and visceral malformation in several foetuses and litters).

The oral NOAEL of 100 mg/(kg bw x d) for the rabbit is transferred to humans with a factor of 2.4 for allometric scaling and then translated into air concentration with standard human body weight (70 kg) und a default breathing volume of 20 m³ for general population in 24 hours, resulting in an adjusted NOAEC of 145.83 mg/m³ (100 mg/(kg bw x d)/ 2.4 x 70 kg bw/ 20 m³/person = 145.83 mg/m³).

Adjustments for continuous exposure and study length are not applied as the pregnant animals were exposed daily throughout the critical time window of pregnancy.

The following assessment factors are used:

- Adjustment study length factor: 1
- Allometric scaling: already included in route-to-route extrapolation
- Interspecies extrapolation: 2.5
- Intraspecies extrapolation (interindividual variability, general population): 10
- Other (severity of effects): 3

Total assessment factor: 75 leading to a value of 145.83 mg/m³ : 75 = 1.94 mg/m³ (rounded to 1900 µg/m³).

An EU-LCI value of (rounded) 1900 µg/m³ is proposed for diacetone alcohol.

An odour threshold value between 0.28 ppm and 100 ppm (1338 µg/m³ and 478000 µg/m³) has been reported in the literature (Hellman and Small 1974, as well as Ruth 1986; both cited in Greim & MAK Commission, 2001). While the lower threshold (0.28 ppm) falls below the the proposed EU-LCI value, the upper threshold (100 ppm) significantly exceeds the proposed EU-LCI value for diacetone alcohol, suggesting that it should not be expected that the odour will be percieved at the proposed EU-LCI value.

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A Appendix

A.1 Data collection and fact sheet for 4-hydroxy-4-methylpentan-2-one

Table 4: Data collection sheet for 4-hydroxy-4-methylpentan-2-one (diacetone alcohol)

Compound	**4-hydroxy-4-methylpentan-2-one**			
Nº CAS: 123-42-2 1 ppm = 4.78 mg/m³ at 23 °C	**EU-Classification:** **CLP, harmonised classification:** Eye Irritation 2 (H319)			
Organisation name	**REACH registrant**	**REACH registrant**	**AgBB**	**MAK Commission**
Risk value name	DNEL	DNEL	NIK ('Lowest Concentration of Interest')	MAK value
Risk value (mg/m³)	5.8	32.6	0.96	96
Reference period	Chronic (general population)	Chronic (workers)		-
Risk value (mg/m³) Short term (15 min)	Not derived	Not derived		192
Year	2019	2019	2024	2001
Key study	Not explicitly reported	Not explicitly reported	Not reported	Silverman et al. 1946; cited in ACGIH (2001); ECHA (2024); Greim and MAK Commission (2001); OECD (2000)
Study type	OECD 414	OECD 414		Chamber test
Species	Rabbit, New Zealand White (n = 24 F/dose)	Rabbit, New Zealand White (n = 24 F/dose)		Human
Duration of exposure in key study	Day 6 – 28 post coitum (p.c.) inclusive	Day 6 – 28 post coitum (p.c.) inclusive		15 minutes
Critical effect	Developmental toxicity/teratogenicity	Developmental toxicity/teratogenicity		Acute toxicity/irritation
Critical dose value	NOAEL: 100 mg/(kg bw x d)	NOAEL: 100 mg/(kg bw x d)		

Compound	**4-hydroxy-4-methylpentan-2-one**			
Adjusted critical dose	100 x 1.45 = 145 mg/m³	NOAEL/0.23 [(1)] m³/kg x 7d/5d x 6.7 m³/10 m³ = 408 mg/m³		
Single assessment factors	UF_A 2.5, UF_H 10; total = 25	UF_A 2.5, UF_H 5; total = 12.5		
Other effects				
Remarks			Ascribed EU-LCI-value	

[(1)] The DNEL was calculated based on a developmental study with rabbits, however the registrant based the calculations on the species rat. The value of 0.23 cannot be verified by the authors of this evaluation.

Table 5: Fact sheet for 4-hydroxy-4-methylpentan-2-one (diacetone alcohol)

Compound	**4-Hydroxy-4-methylpentan-2-one C6H12O2**		**Fact sheet**
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	1900
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2025
General information			
CLP-Index No.	4	INDEX	603-016-00-1
EC-No.	5	EINECS	204-626-7
CAS-No.	6	Chemical Abstract Service number	123-42-2
Harmonised CLP classification	7	Human health risk related classification	Eye Irritation 2
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	116.16 g/mol 1 ppm = 4.78 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	Bentz 2019 as cited in ECHA (2024) Prenatal Developmental Toxicity Study (OECD 414)
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	Rabbit, New Zealand White
Route / type of study	12	Inhalation, oral feed, etc.	Oral
Study length	13	Days, subchronic, chronic, etc.	Days 6 to 28 post coitum (p.c.) inclusive
Exposure duration	14	h/d, d/w	Daily
Critical endpoint	15	Effect (s), site of	Embryotoxicity/teratogenicity
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEL
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	100 mg/(kg bw x d)
Assessment factors (AF)			
Adjustment for exposure duration	19	Study exposure h/d, d/w	1
Study length	20	sa→sc→c	1
Route-to-route extrapolation factor	21	-	0.6857 m³/(kg bw x d)[(1)]

Compound	4-Hydroxy-4-methylpentan-2-one C6H12O2		Fact sheet
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	1
	22b	Severity of effect (R8 6d)	3
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	1
	23b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		1
Other adjustment factors Quality of database	26	Quality of database	1
Results			
Summary of assessment factors	27	Total Assessment Factor	75 x 0.6857
POD/TAF	28	Calculated value [µg/m³ and ppb]	1944 µg/m³ and 406.7 ppb
Molar adjustment factor	29	Used in read-across	-
Rounded value	30	[µg/m³]	1900
Additional comments	31		
Rationale selection	32		

(1): Value based on the allometric scaling calculation (rabbits – general population): 2.4 x 70 kg bw/ 20 m^3/person.

Rationale for critical effects

Diacetone alcohol shows relatively low acute toxicity. In humans, a chamber test with exposure to 457 mg/m^3 (100 ppm) diacetone alcohol caused symptoms such as headaches, nausea and vomiting (Silverman et al. 1946; cited in OECD, 2000). Studies in rat following inhalation of 7.6 mg/L air (1590 ppm) for 4 hours revealed no toxic signs or mortality (CIR, 2022; ECHA, 2024). Slight nasal and eye irritation occurred in an older study in rats with exposure to 1500 ppm (Smyth and Carpenter 1948 & Union Carbide 1946a; both cited in Greim and MAK Commission, 2001). Acute toxicity studies in rabbits report acute dermal LD50 values of approx. 13600 mg/kg bw with only mild skin irritation (CIR, 2022; ECHA, 2024). Oral toxicity studies in rats determined LD50 values between 2520 and 4000 mg/kg, with effects like lethargy, liver damage, and respiratory depression in high doses (CIR, 2022; ECHA, 2024; Greim and MAK Commission, 2001). Diacetone alcohol has been shown to cause eye, nose, and throat irritation in humans at 100 ppm (Silverman et al. 1946; cited in ACGIH, 2001; ECHA, 2024; Greim and MAK Commission, 2001; OECD, 2000), while no skin irritation has been reported in humans after applying a coin-sized amount of the substance to the back of the hands (CIR, 2022). In rabbits, undiluted diacetone alcohol caused significant eye irritation, with symptoms like conjunctival redness and corneal opacity that resolved in 2-21 days (ECHA, 2024). Skin irritation

was minimal, with only slight and reversible erythema noted in abraded skin, while repeated applications on intact skin did not cause irritation (CIR, 2022; ECHA, 2024). Two guinea pig maximisation tests according to OECD TG 406 examined diacetone alcohol for its skin sensitisation potential. The substance showed no sensitising effects (ECHA, 2024). No data is available concerning sensitising effects of diacetone alcohol on the respiratory tract.

Regarding repeated dose toxicity in humans, a case report is available, describing a 59-year old man developing subacute proliferative glomerulonephritis 40 days after being exposed to diacetone alcohol and an unknown ethanolic solvent for three days (NLM, 2024). No further human data is available.

In a 28-day repeated dose inhalation study equivalent to OECD TG 412, rats exposed to 0, 233, 1041 or 4685 mg/m^3 (50, 225 or 1000 ppm) undiluted diacetone alcohol vapours for 6 h/d, 5 d/w for 6 weeks showed no mortality. However, effects such as slight lethargy, changes in body weight, and organ weight alterations, particularly in the liver and kidneys, were noted. Male rats exhibited species-specific kidney effects (eosinophilic hyaline droplets) irrelevant to humans. Based on liver and kidney effects, different NOEL and NOAEC values were reported due to variations in the interpretation of liver weight changes. The MAK commission reported, a NOEL of 233 mg/m^3 and a marginal LOEL of 1041 mg/m^3, while in the registration dossier a NOAEC of 4685 mg/m^3 and a NOEC of 1041 mg/m^3 were derived (Shell Pol Company 1980, cited in CIR, 2022; ECHA, 2024; Greim and MAK Commission, 2001; OECD, 2000). In a subchronic oral study following OECD TG 408, rats received 0, 25, 150 or 600 mg/(kg bw x d) diacetone alcohol via gavage for 13 weeks. At the highest dose (600 mg/(kg bw x d)) male rats exhibited reduced body weights and higher neutrophil counts, while females showed reductions in red and white blood cell counts. Biochemical changes included increased cholesterol and reduced inorganic phosphorus levels. Non-adverse liver changes such as centrilobular hypertrophy were noted. A NOAEL of 600 mg/(kg bw x d) was derived (CIR, 2022; ECHA, 2024). In an OECD TG 422 study, rats were exposed to 0, 30, 100, 300 or 1000 mg/(kg bw x d) diacetone alcohol via gavage. Both sexes exhibited pre-narcotic effects from 300 mg/(kg bw x d) onwards, and female rats had reduced body weights. Kidney and liver changes were noted from 300 mg/(kg bw x d) onwards, but kidney effects were determined to be sex- and species-specific. A NOAEL of 100 mg/(kg bw x d) was set (Ministry of Health and Welfare 1997; cited in CIR, 2022; ECHA, 2024; Greim and MAK Commission, 2001; OECD, 2000).

Diacetone alcohol was found to be non-genotoxic based on several *in vitro* studies. Ames tests in bacteria showed no mutagenic effects, even at concentrations up to 10000 µg/plate, with or without metabolic activation (Brooks et al. 1988 & Ministry of Health and Welfare 1997;both cited in AICIS, 2013; Greim and MAK Commission, 2001; NTP, 2024). Additional tests, such as mitotic recombination in yeast and chromosome aberration in Chinese hamster lung cells, also produced negative results (ECHA, 2024). Although slight chromatic damage was noted in rat liver cells at high concentrations, it was attributed to the detergent-like properties and osmolar changes in the culture media caused by solvents (Brooks et al. 1998; cited in ECHA, 2024; Greim and MAK Commission, 2001). No *in vivo* genotoxicity data are available. Similarly, no carcinogenicity studies exist, but current genotoxicity and toxicity data do not indicate carcinogenic potential.

The reproductive toxicity of diacetone alcohol was assessed in several studies. In an OECD TG 422 combined repeated dose and reproductive toxicity screening test in rats, slight non-significant effects on fertility were observed at the highest dose (1000 mg/(kg bw x d), including decreased fertilisation, implantation numbers and implantation rates. Lower overall birth rate, lower number of live pups, lower birth weight and decreased pup survival at day 4 of lactation was also observed at 1000 mg/(kg bw x d), although not significant. The effects were attributed

to maternal toxicity, and a NOAEL of 300 mg/(kg bw x d) was established for both toxicity on reproduction and developmental toxicity (Ministry of Health and Welfare 1997; cited in CIR, 2022; ECHA, 2024; Greim and MAK Commission, 2001). In another study conducted according to OECD TG 421, a NOAEL of 750 mg/(kg bw x d) was derived for male and female rats, with adverse effects on the offspring's development noted at 250 mg/(kg bw x d) (= NOAEL for developmental toxicity) due to decreased pup survival and body weights (ECHA, 2024). In an extended one-generation study (OECD TG 443), for the F0 and the F1 generation, a NOAEL of 200 mg/(kg bw x d) was derived for male rats based on increased severity of hyaline droplets accumulation associated with nephropathy, while female rats showed no adverse effects up to the highest tested dose of 600 mg/(kg bw x d). Based on the increase in post-natal loss observed in both parental generations at 600 mg/(kg bw x d) a NOAEL of 200 mg/(kg bw x d) for both sexes was derived for the F2 generation (ECHA, 2024). A study conducted according to OECD TG 408 found no significant reproductive effects of diacetone alcohol in rats. Observed effects, such as slightly lower number of cycles or a trend towards lower epididymal sperm count at 600 mg/(kg bw x d) were considered either not-treatment related or not adverse (ECHA, 2024).

Developmental toxicity studies according to OECD TG 414 have been performed in rats and rabbits. In rats, daily gavage doses of up to 1000 mg/(kg bw x d) showed no adverse effects on maternal health or foetal development, except for excessive salivation at the highest dose. No significant effects on foetal weight, viability, or sex ratio were observed, and skeletal findings were attributed to normal variations. The NOAEL was determined to be 1000 mg/(kg bw x d) for both maternal and developmental toxicity (ECHA, 2024). In rabbits, higher doses (800 mg/(kg bw x d)) resulted in reduced food intake, transient weight loss, and one prematurely euthanised female due to poor health, with some foetuses exhibiting external, visceral and/or skeletal malformations (omphalocele, meningoencephalocele, fused vertebrae, split frontal, malpositioned kidneys and adrenals, multiple heart great vessel malformations (dilated aorta, pulmonary trunk and retroesophageal aortic arch)). The NOAEL for maternal toxicity was set at 300 mg/(kg bw x d) due to these effects, and the NOAEL for developmental toxicity was set at 100 mg/(kg bw x d) based on foetal abnormalities (ECHA, 2024).

Rationale for starting point

Inhalation exposure of undiluted diacetone alcohol was tested in rats according to OECD TG 412. The animals were exposed to 0, 233, 1041 and 4685 mg/m^3 (50, 225 and 1000 ppm) of the substance for 6h/d, 5 d/w for 6 weeks. It was reported that 0.6, 0.6 and 4.1 % acetone were produced by decomposition at the evaporator. In this study, liver weight increases of +13 % and +23 % were observed in the medium and high concentration groups respectively, without any accompanying microscopic liver changes. Clinical chemistry data that could help interpret these changes were not observed. The interpretation of liver weight changes remains a topic of significant debate within the scientific community. Currently, there is no established consensus on what degree of liver weight increase should be considered harmful or adverse. In 2018, the Working Group – Human Health of the Biocidal Products Committee (ECHA) worked on the interpretation of liver effects in toxicological studies in rodents, resulting in the publication of an annex which provides guidance on the subsequent principles to be undertaken. In the annex, the authors state that for mice and rats, *"[…] an increase of relative (to body weight) liver weight up to 15 % is part of normal biological variation […]"* (Anon, 2018). A weight of evidence approach and expert ruling is recommended. Based on the annex data and the absence of any histopathological changes in the liver, the observed +13 % liver weight increase is considered to fall within normal variability. Furthermore, the potential role of acetone production in contributing to the liver weight changes cannot be excluded. With the +23 % liver weight increase, the possibility of an adverse effect cannot be ruled out, particularly due to the lack of clarifying clinical chemistry

data. Therefore, a revised LOAEC of 4685 mg/m³ was established by the authors of this evaluation. If this LOAEC were to be used as POD for the derivation of an EU-LCI value with a total assessment factor of 2520 (adjustment for continuous exposure: 5.6, adjustment study length factor: 6, interspecies extrapolation: 2.5, intraspecies extrapolation: 10, LOAEC to NOAEC: 3), it would result in an EU-LCI value of 1900 µg/m³ (rounded).

However, the most critical effects of diacetone alcohol exposure are the developmental adverse effects such as post-natal lethality and malformations observed in several developmental toxicity studies, which led to a proposal for a Repro 1B classification. Therefore, the prenatal development toxicity study (OECD TG 414) in rabbits is regarded as valid and suitable for the derivation of an EU-LCI value. This study provided a NOAEL of 100 mg/(kg bw x d) based on embryotoxic/teratogenic effects observed (external, skeletal and visceral malformation in several foetuses and litters). Route-to-route extrapolation is performed, and the corrected NOAEC is 145.83 mg/m³ (100 mg/(kg bw x d)/ 2.4 x 70 kg bw/ 20 m³/person). In light of the severity of the effects, an assessment factor of three was taken into account.

Rationale for assessment factors

The following assessment factors are used:

- Adjustment study length factor: 1
- Allometric scaling: already included in route-to-route extrapolation
- Interspecies extrapolation: 2.5
- Intraspecies extrapolation (interindividual variability, general population): 10
- Other (severity of effects): 3

Total assessment factor: 75 leading to a value of 145.83 mg/m³ : 75 = 1.94 mg/m³ (rounded to 1900 µg/m³).

An EU-LCI value of (rounded) 1900 µg/m³ is proposed for diacetone alcohol.

An odour threshold value between 0.28 ppm and 100 ppm (1338 µg/m³ and 478000 µg/m³) has been reported in the literature (Hellman and Small 1974, as well as Ruth 1986; both cited in Greim & MAK Commission, 2001). While the lower threshold (0.28 ppm) falls below the proposed EU-LCI value, the upper threshold (100 ppm) significantly exceeds the proposed EU-LCI value for diacetone alcohol, suggesting that it should not be expected that the odour will be percieved at the proposed EU-LCI value.

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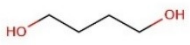
2 Toxicological evaluation of 1,4-butanediol (1,4-BD) as basis for the derivation of an EU-LCI value

2.1 Substance identification

1,4-Butanediol (also known as butane-1,4-diol, 1,4-BD) is a primary alcohol. Substance identification data of 1,4-BD is shown in Table 6.

The toxicological data basis for 1,4-BD has been repeatedly compiled and evaluated by Australian authorities (NICNAS, 2009; NICNAS, 2014), the Organization for economic cooperation and development (OECD) as part of the High Production Volume (HPV) chemicals programme (OECD, 2000), the European Food Safety Authority (EFSA) (EFSA, 2004; EFSA, 2011) and in an assessment by the German Institution for Statutory Accident Insurance and Prevention in the Chemical Industry (BG Chemie) (BG Chemie, 1992). Furthermore, the substance is registered under REACH (ECHA, 2024).

Table 6: Substance identification of 1,4-butanediol (ECHA, 2024)

Cas-No. EC-No. CLP-Index-No.	Systematic Name, common name	Sum formula	Structural formula
110-63-4 203-786-5 -	butane-1,4-diol, 1,4-Butylene glycol, 1,4-Dihydroxybutane, 1,4-BD	C4H10O2	

2.2 Substance properties and uses

The physicochemical properties of 1,4-BD are shown in Table 7. At room temperature, 1,4-BD is an odourless, colourless liquid and does not occur naturally (ECHA, 2024). The substance is highly soluble in water (ECHA, 2024).

1,4-BD is described as raw material for plastics, resins and other industrial chemicals and is used as additive, binder, solvent and plasticiser (NLM, 2024; OECD, 2000). Its most relevant application is the production of polyurethanes and poly(butylene terephthalate) (NLM, 2024). 1,4-BD is additionally used as cosmetic ingredient (e.g. as a supplement in deodorants) (NLM, 2024; OECD, 2000). In addition, it is also used in cleaning and household care products (e.g. glass cleaner), electronics/small appliances such as printer ink, and as a solvent in paints (NLM, 2024). In the USA, 1,4-BD is used as a dietary supplement (OECD, 2000).

NLM (2024) also refers to two studies, in which 1,4-BD is used as sedative drug. However, no further sources or drug trade names were identified.

Table 7: Physicochemical properties of 1,4-BD (ECHA, 2024)

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa) (at 25 °C)	Conversion 1 ppm = x mg/m³ (23 °C)*	log pow	Solubility in water (g/L)
90.12	20.4	230.0	0.014 to 0.019	3.71	-0.88	100 at 20°C

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

2.3 Exposure

2.3.1 Indoor air

Only a few data are available on measured concentrations of 1,4-BD in indoor air (Table 8).

In its publication (AGÖF, 2013) stated that 1,4-BD was detectable in low concentrations in 618 indoor air samples.

For the estimation of occupational exposure, OECD (2000) used the EASE (estimation and assessment of substance exposure) model and calculated a maximum of 184 mg/m³ for workers involved in sampling and lorry filling (no further details provided).

Measurements at workplaces reported air concentrations between 0 to 10 ppm (0 – 37.1 mg/m³). During production and use of 1,4-BD, time-weighted shift averages of < 1 ppm (< 3.71 mg/m³) were obtained for more than 50 samples (AGS, 2006).

Table 8: Data on the occurrence of 1,4-BD in indoor air

Indoor	N	LoD (mg/m³)	N > LoD	Median (mg/m³)	P95 (mg/m³)	Maximum (mg/m³)	Source
Indoor air (not further specified), Germany, 2006-2012	618	Not reported	-	< 0.001[a]	< 0.001[b]	-	(AGÖF, 2013)
Indoor air at workplaces (not further specified), Germany	>50	Not reported	-	< 3.71[c]	-	37.1[d]	(AGS, 2006)

a: 50th percentile

b: 90th percentile

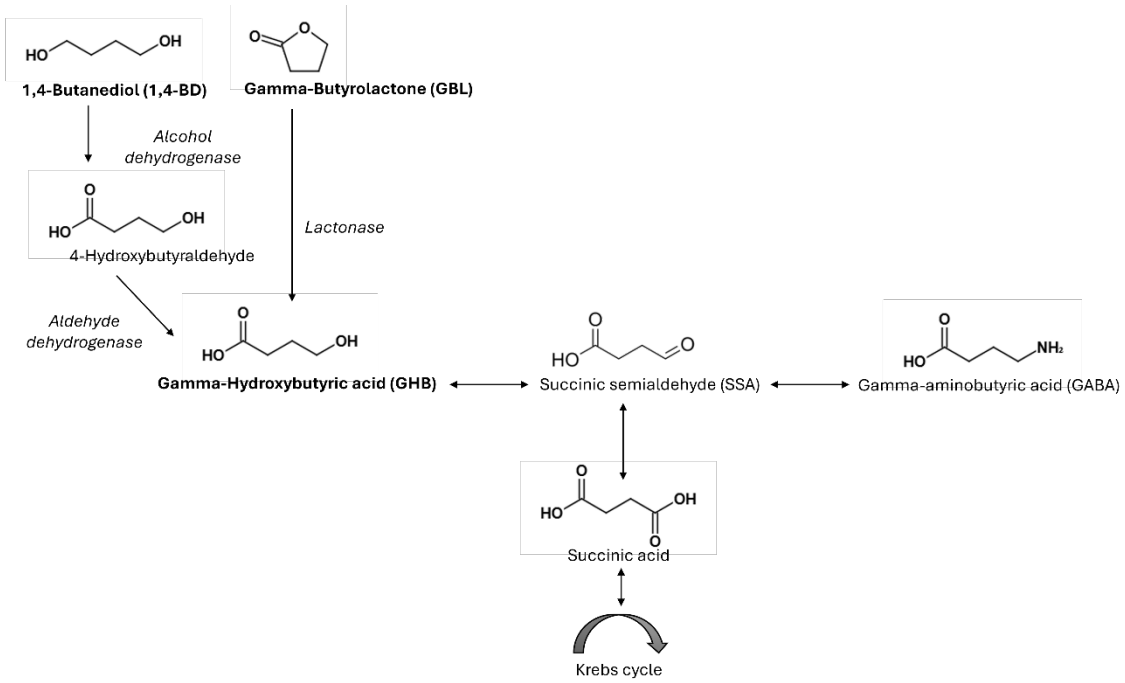
c: shift average (< 1 ppm)

d: maximum concentrations of 10 ppm after short-term measurement (max. 2 h) during sampling, filling and emptying processes.

2.4 Toxicokinetics

A recently published review article from Dufayet et al. (2023) summarises the toxicokinetic knowledge of 1,4-BD, γ-butyrolactone (GBL, CAS: 96-48-0) and γ-hydroxybutyrate (GHB) mainly after oral uptake or i.v. application obtained in experimental animal studies and humans. 1,4-BD and GBL are structural analogous of the common metabolite GHB (Figure 1). 1,4-BD and GBL are industrially used substances, whereas GHB is endogenously formed at concentrations of 1 – 4 µM γ-aminobutyric acid (GABA) (Dufayet et al., 2023). There is no toxicokinetic information available for 1,4-BD after inhalation and dermal application in animals.

Figure 1: Metabolic pathway of GHB, GBL, and 1,4-BD, modified from Dufayet et al. (2023)



However, for 1,4-BD the dermal absorption rate is estimated to be 0.14 mg/cm² hr (no further information) (ECHA, 2024).

C^{14} radiolabelled 1,4-BD was rapidly absorbed by four male rats given 4, 40, 120, or 400 mg/kg bw by oral gavage. Approximately 50 % of the orally administered dose was excreted within 2 h of dosing (ECHA, 2024; NTP, 1996). In humans, 25 healthy volunteers receiving 25 mg 1,4-BD/kg orally had measurable GHB levels after 5 minutes of ingestion, with maximum 1,4-BD plasma concentrations reached within 24 ± 12 minutes and maximum GHB levels reached within 39.4 ± 11.2 minutes (Ortmann et al., 2009). Compared to GHB, GBL and 1,4-BD are faster absorbed with a non-saturable absorption kinetic and have a higher bioavailability (Dufayet et al., 2023). Following i.v. administration of 1,4-BD, the plasma concentration-time profile of the GHB metabolite is observed to occur rapidly and resembles that of an i.v. injection of GHB. It is noteworthy that 1,4-BD is rapidly metabolised to GHB (NICNAS, 2009; NICNAS, 2014). After percutaneous administration, approximately 10 % of the administered dose is estimated to be absorbed by the rat (ECHA, 2024).

1,4-BD is distributed rapidly and metabolised in brain, liver, kidney, intestinal tract and heart after oral or i.v. administration in humans and animals (not further specified) (Dufayet et al., 2023; NICNAS, 2009; NICNAS, 2014) and crosses the haemato-encephalic and placental barriers with greater ease than GHB (Dufayet et al., 2023).

No evidence of bioaccumulation in any tissue was found (Dufayet et al., 2023; ECHA, 2024; NICNAS, 2009; NICNAS, 2014). 1,4-BD is metabolised via oxidation by alcohol dehydrogenase and aldehyde dehydrogenase to GHB, which is metabolised via succinic semialdehyde to γ-aminobutyric acid (GABA). Succinic semialdehyde can be metabolised to succinic acid and finally to carbon dioxide (CO_2) via the tricarboxylic acid cycle (Krebs cycle) (Dufayet et al., 2023). In humans an extensive conversion of 1,4-BD to GHB after oral ingestion was detected, almost equivalent to GHB intake itself (NICNAS, 2009; NICNAS, 2014). There is a competitive inhibition of metabolism by ethanol, so that the corresponding tissue concentrations of 1,4-BD are considerably higher when ethanol is administered at the same time.

After oral administration in rats, 1,4-BD is excreted as $^{14}CO_2$ in exhaled breath with approximately 50 % of the administered dose within the first 2 h and 85 % within 72 h. The kidney and gastrointestinal tract were minor routes of excretion with 4 % $^{14}CO_2$ in the urine and 0.6 % in the faeces, respectively, and the amount remaining in the carcass after 72 h was 2.28 %, with the largest amounts present in liver, muscle, and skin (ECHA, 2024; NICNAS, 2009; NICNAS, 2014). After 72 h post-treatment, a total of 2.3 % of the applied/administered dose was detected in the carcass (main concentration was detected in skin and liver) (NICNAS, 2009; NICNAS, 2014). In humans, the mean elimination half-life of 1,4-BD was 39.3 ± 11 minutes (Ortmann et al., 2009).

2.5 Health effects

2.5.1 Acute toxicity, sensory irritation, and local effects

Acute Toxicity

Human data

The database for the assessment of acute human exposure to 1,4-BD includes mainly case reports of poisoning. However, reports of confirmed exposure are limited (Stefani and Roberts, 2020). Recently published literature includes cases of 1,4-BD being taken intentionally as a 'party drug' to supplement GHB (Lora-Tamayo et al., 2003), as a dietary supplement (Zvosec et al., 2001) or accidental oral exposure by children through plastic toys (Ortmann et al., 2009). Ingestion of 1,4-BD as substitute of GHB together with other illegal drugs, namely 3,4-methylenedioxymethamphetamine (MDMA) and cocaine, resulted in hospitalisation and coma (Glasgow Coma Scale of 7) of a young man (Lora-Tamayo et al., 2003). In addition, seven case reports of acute intoxication after ingestion of 1 to 20 g 1,4-BD resulted in two deaths and five cases with symptoms including vomiting, urinary and faecal incontinence, confusion, ataxia, agitation, combativeness, extremely unstable level of consciousness, and respiratory depression (Zvosec et al., 2001). Accidental ingestion of a plastic toy (aqua dots containing 10.8 ± 1.9 mg 1,4-BD per beat) by a 20-month-old child was reported in the United States. The child was diagnosed with coma (Glasgow Coma Scale of 8) due to 1,4-BD (used as solvent), which was reversible within 5 h (Ortmann et al., 2009). Three additional cases related to the same toy were reported in Australia (two case reports) and one case in the United Kingdom (Ortmann et al., 2009). An older study investigated the effect of an oral administration of 25 mg 1,4-BD/kg bw in eight healthy volunteers and reported that within 90 minutes the following symptoms were observed: feeling of reduced alertness and vigilance, reduced concentration and a feeling of increased dizziness, mild respiratory depression and transient increases in blood pressure were also observed, but overall, the changes were considered unlikely to have serious clinical consequences (NICNAS, 2009; NICNAS, 2014). The lethal dose after acute ingestion in humans is reported to be 60 mg/kg bw (Dufayet et al., 2023). Furthermore, rectal administration of 15 or 30 g 1,4-BD induced a deep comatose state with miosis and complete absence of reflexes

(areflexia) for 1 to 16 h after administration. Two patients (a man using 30 g and a woman using 15 g) died within 72 h. For the woman postmortem examination showed swelling of the brain, colon, spleen as well as lung damage, vascular damage, and heart muscle changes. Furthermore, unspecified renal dysfunction was reported as cause of death, whereas five patients fully recovered from the adverse effects (screaming, vomiting, and coma) (Kinney et al., 1991; NICNAS, 2009; NICNAS, 2014). Intravenous administration of 30 mg 1,4-BD/kg bw or by infusion of 15-22 mg/kg bw/h for 38-68 h produced symptoms of restlessness and limb muscle spasms (NICNAS, 2009; NICNAS, 2014). Intravenous administration of 30 mg 1,4-BD/kg bw or by infusion of 15-22 mg/kg bw/h for 38-68 h produced symptoms of restlessness and limb muscle spasms (NICNAS, 2009; NICNAS, 2014). No cases of human poisoning resulting from inhalation have been identified.

Animal data

In an acute inhalation toxicity study (fixed concentration method; OECD TG 433), rats were exposed 'nose only' to 4.6, 9.4 or 15 mg 1,4-BD/m^3 (aerosol; highest dose level tested, as higher atmospheric concentrations could not be generated) for 4 h. At 4.6 and 9.4 g/m^3, rats were lethargic with laboured breathing. At 9.4 and 15 mg/m^3, clinical signs were observed: lethargy, immobility, and laboured breathing. At 15 mg/m^3, all rats exhibited slight to severe weight loss one day after exposure in a dose-dependent manner, followed by resumption of normal weight gain. At the high concentration group 1/10 animal died one day post exposure. The NOAEC was set at 4.6 mg/m^3 and the 4 h LC50 was set at > 15 mg/m^3 (ECHA, 2024; NICNAS, 2009; NICNAS, 2014). In addition, an OECD TG 403 study in rats exposed 'nose/head only' to 5.1 mg 1,4-BD/m^3 for 4 h showed an LC50 value > 5.1 mg/m^3 with slight changes in respiratory function during and immediately after treatment, which was reversible after one day. No deaths occurred and no gross pathological abnormalities were observed (BG Chemie, 1992; ECHA, 2024; NICNAS, 2009; NICNAS, 2014; OECD, 2000).

Dermal toxicity of 1,4-BD has been investigated in male/female rats under occlusive conditions with 24 h of exposure resulting in a LD50 value of > 2000 mg/kg bw. Observed clinical signs were dyspnoea, restlessness and a poor general condition during the first 2 h of exposure. At the site of application a slight erythema was seen when the patch was removed (ECHA, 2024). An additional study tested 5000 mg/kg bw in female rats under occlusive conditions. During the histopathological examination, changes that were limited to the liver and skin (at site of application) with no further details were reported (ECHA, 2024; NICNAS, 2009; NICNAS, 2014; OECD, 2000).

The oral LD50 value for 1,4-BD administered to male and female rats is 1500 mg/kg bw. Administration of the substance produced systemic toxicity in a dose-dependent manner with clinical signs of dyspnoea, apathy, abnormal position, staggering, atony, unusual pain reflex, unusual cornea reflex, narcotic-like state, tremor, scrubby fur, exsiccosis, exophthalmos, poor general state in males and dyspnoea, apathy, abnormal position in females (ECHA, 2024). In a second acute toxicity study testing 1500 to 2500 mg/kg bw, the oral LD50 values were 1830 mg/kg and 2000 mg/kg for male and female rats, respectively. A single oral dose of 1,4-BD (no further information available) resulted in histopathological alterations in the liver and kidney. The effects on the liver and kidney were reversible, and the changes were observable after 14 days (ECHA, 2024; NICNAS, 2009; NICNAS, 2014; NTP, 1996).

Further acute toxicity studies in animals (mainly rodents) with different administration routes namely i.v. and i.p. are reported in the literature, but these administration routes are not relevant for the consideration of the present assessment.

Irritation

Human data

In humans 1,4-BD was not found to be a skin irritant in patch test (no further information) (NICNAS, 2009; OECD, 2000).

Animal data

According to the studies on skin irritation in rabbits, the substance is not irritating to the skin (ECHA, 2024; NICNAS, 2009; NICNAS, 2014; OECD, 2000).

Two eye irritation studies in rabbits showed slight conjunctival irritation which was reversible within 48 h (ECHA, 2024; NICNAS, 2009; NICNAS, 2014; OECD, 2000).

1,4-BD was described as slightly irritating to the respiratory tract based on the findings of the acute inhalation toxicity studies presented in section 2.5.1 'Animal data: Acute toxicity' (NICNAS, 2009; NICNAS, 2014; OECD, 2000).

Sensitisation

Human data

In patch tests on more than 200 volunteers, no sensitising potential of 1,4-BD on the skin was observed (no further information) (NICNAS, 2009; NICNAS, 2014).

Animal data

Based on the results of a Guinea Pig Maximisation Test (GPMT) in which 1,4-BD was applied at a concentration of 10 % (intradermal injections) and 30 % (topical application) at induction, the challenge was performed with 10 % and 30 % 1,4-BD. According to the results, 1,4-BD is not considered to be a skin sensitiser. Furthermore, 1,4-BD is not a respiratory sensitiser (ECHA, 2024; NICNAS, 2009; NICNAS, 2014; OECD, 2000).

2.5.2 Repeated dose toxicity

Human data

No relevant human data was identified on chronic intoxication with 1,4-BD in humans (Dufayet et al., 2023). A recent review article summarises the chronic intoxication effects of GHB/GBL, including the withdrawal syndrome for GHB and its analogues GBL and 1,4-BD, which is similar to that known for ethanol and/or benzodiazepines, with symptoms including delirium, but also other non-specific symptoms (Dufayet et al., 2023). Substance-related disorders associated with repeated use of GHB and its analogues GBL and 1,4-BD are associated with mental health problems, including anxiety, aggression, irritability, depression, confusion, disorientation and memory problems (Dufayet et al., 2023). Moderate use of GHB/GBL is associated with acute cognitive impairment, whereas regular use at high doses (no further information) can lead to multiple comas and long-term cognitive depression (Dufayet et al., 2023).

Animal data

In an inhalation study equivalent or similar to OECD TG 412 (nasal only), rats (10 males/dose) were exposed to 1,4-BD (purity > 99.7 %) as an aerosol at 0.20, 1.1 or 5.2 mg/L (200, 1100 or 5200 mg/m^3 analytical concentration) for 6 h/d, 5 d/week for two weeks. Five rats per group were sacrificed after the 10th exposure and five rats per group were sacrificed after a recovery period of 14 days post-exposure. No mortality was observed. The high concentration animals had a significantly lower total body weight gain (28 %) compared to the control group during the exposure period. There were also slight changes in the haematological system, namely

increased haematocrit and erythrocyte count. However, these effects are considered to be biological variations by the authors of the study. The clinical chemistry of these animals showed significantly decreased cholesterol levels after ten exposures, without histopathological correlation. There was also a significant reduction in heart weight after ten exposures (not significant on an organ/body weight basis), but no histopathological findings. Thymic tissue atrophy was observed in three out of five rats in the high concentration group. No pathological changes were observed in the lungs of the high-concentration rats. Except for the observed changes in body-weight gain, all effects were reversible and were not present in the recovery group. The NOAEC was 1.1 mg/L (1100 mg/m^3) and the LOEC was 5.2 mg/L (5200 mg/m^3) (Kinney et al., 1991).

In a briefly reported inhalation study (not according to OECD test guideline), 15 male rats were exposed to an aerosol of 1.5 – 2.0 mg/L (1500 – 2000 mg/m^3) 1,4-BD for 2 h/d for 4 months. Clinical signs of toxicity observed included inactivity and drowsiness (occurring after the first 3 to 4 weeks) and were reversible within 10 to 20 min after the end of exposure. Histopathological examination revealed local irritation (extensive pulmonary emphysema, mild pulmonary oedema and, in a few animals, inflammatory changes). A LOAEL of 1.5 mg/L (1500 – 2000 mg/m^3) was established for central nervous system (CNS) effects (BG Chemie, 1992; NICNAS, 2009; NICNAS, 2014). In an additional study, male rats were exposed to a vapour of 0.3 – 0.5 mg 1,4-BD/L (300 – 500 mg 1,4-BD/m^3) for 2 h/d, 6 d/week for 4 months. No clinical signs of toxicity were observed, therefore the NOAEC was determined to be 0.5 mg/L (500 mg/m^3) (BG Chemie, 1992).

In a 28-day, repeated-dose, non-guideline study (no further information; compared to OECD TG 407 several deviations were identified including inadequate high dose selection), eight male and eight female rats per dose were treated at 5, 50 and 500 mg/(kg bw x d) seven times per week by oral gavage. No deaths occurred. In male rats a significant decrease in red blood cell count was observed in all treated groups (no further information). Haemoglobin concentration was increased in males (all treated groups), while haematocrit was decreased in males at the low- and high-dose group. The number of thrombocytes was statistically significant decreased in the high-dose males. In addition, the clinical chemistry parameters alanine aminotransferase and sorbitol dehydrogenase were increased, whereas total protein was decreased in males of the high-dose group. In female rats, a significant decrease in erythrocyte count was observed in the low- and high-dose group (no further information). The number of thrombocytes was statistically significant decreased in the low- and mid-dose females. Erythrocytic parameters (MCV, MCH, and MCHC) and reticulocyte counts (total and differentiated white blood cell count) were also changed (no further information). Furthermore, treatment related differences in platelet counts were detected in males and females (no further information). Liver proliferation of bile ducts and periportal infiltrations of fibroblasts and mononuclear cells were most frequently observed in treated males and females at all dose levels (dose-dependent) and assessed as mild to moderate liver inflammation. Overall, a low level of systemic toxicity was observed. The NOAEL was 50 mg/(kg bw x d) (based on clinical biochemistry, histopathology (non-neoplastic)) and the LOAEL was 500 mg/(kg bw x d) (based on clinical biochemistry, histopathology (non-neoplastic)) (ECHA, 2024; EFSA, 2011; NICNAS, 2009; NICNAS, 2014; NTP, 1996; OECD, 2000). NICNAS (2009) stated, that the relevance of this study is limited by the absence of the described neurological effects observed in other oral studies.

In a combined repeated dose toxicity study with the reproduction/development screening test (OECD TG 422), 13 male and female rats were exposed at 200, 400 and 800 mg/(kg bw x d) by oral gavage. Males were exposed for 42 days, while females were exposed from pre-mating to day three of lactation. There were dose-related acute and transient central nervous system

toxicity effects after exposure to 1,4-BD including hyperactivity and suppression of activity in a dose dependent manner. At 200 mg/(kg bw x d) (not considered an adverse effect) transient hyperactivity was observed, whereas at 400 mg/(kg bw x d) activity was rather suppressed. After the treatment with 800 mg/(kg bw x d), animals became comatose after exhibiting hypoactivity and recumbency (no further information). The animals recovered from these symptoms 5 h after exposure. Suppression of body-weight gain was limited to the early period of administration in the mid- and high-dose groups with an associated decrease in food consumption. A statistically significant and dose-related slight decrease in blood glucose was observed in males at all ages (from 200 mg/(kg bw x d) and onwards). In addition, pathological changes with diffuse transitional epithelial hyperplasia and fibrosis in the lamina propria of the urinary bladder were observed at 400 and 800 mg/(kg bw x d). Based on effects on the body weight and weight gain, food consumption, compound intake and histopathology (non-neoplastic) the NOAEL for systemic toxicity was set at 200 mg/(kg bw x d) for the parental (F0) generation. A NOEL based on the observed hyperactivity at 200 mg/(kg bw x d) was set at < 200 mg/(kg bw x d) (ECHA, 2024; NICNAS, 2009; NICNAS, 2014; OECD, 2000). For details on fertility see section 2.5.4.

Read across

The read across hypothesis is based on the knowledge, that 1,4-BD (target substance) and GBL (source substance) have similar effects after repeated exposure, namely, anaesthetic, CNS-depression, which is presumably caused by the common metabolite GHB. In the presynaptic neurons of the brain, GHB dehydrogenase metabolises GHB to succinic semialdehyde (SSA), which is further metabolised to γ-aminobutyric acid (GABA) (for details on metabolism see chapter 2.4Figure 1:) (Dufayet et al., 2023).

In a study equivalent or similar to the OECD TG 408 reported in the registration dossier, conducted with the structural analogue GBL in Fischer 344 rats, ten males and ten females were given doses of 56, 112, 225, 450 or 900 mg/(kg bw x d) by oral gavage for 13 weeks (5 days per week). Rats started to show signs of sedation at 225 mg/(kg bw x d) and above. The effects were observed during the first 2-3 weeks of the study and decreased with continued dosing time. After three weeks rats showed no longer visible signs of sedation after dosing. Males at 450 mg/(kg bw x d) gained less body weight. Mortality was observed in all high-dose males and one high-dose female. Inflammation/irritation of the nasal mucosa was observed in all dose groups but was considered to be a non-specific effect of gavage treatment with a volatile agent. The registration dossier specifies: '*NTP reports that similar lesions have been observed in other NTP gavage studies with a variety of chemicals and that the lack of any histologically evident degenerative lesions may be attributed in part to the rapid absorption and metabolism of the chemic*al'. The NOAEL for males, based on body-weight effects, was 225 mg/(kg bw x d). The NOAEL for females was 450 mg/(kg bw x d), based on one dead female (ECHA, 2024).

Additionally, in a study similar to OECD TG 408, conducted with GBL in B6C3F1 mice, ten male and female mice were treated for 13-weeks by oral gavage with doses of 65, 131, 262, 525 or 1050 mg/(kg bw x d). Mortality occurred in the high-dose group in males (3/10) and females (1/10). Furthermore, final mean body weight was 11% lower compared to controls in the highest dose. At 525 mg/(kg bw x d) and above males and females became recumbent several minutes after dosing during the first 2-3 weeks but were normal at the next observation. The NOAEL was set at 525 mg/(kg bw x d) (ECHA, 2024).

2.5.3 Genotoxicity and carcinogenicity

Genotoxicity

No mutagenicity of 1,4-BD was observed *in vitro* in the absence or presence of exogenous metabolic activation systems in assays with bacteria (similar to OECD TG 471, Ames test with *Salmonella* typhimurium strains TA98, TA100, TA1535, TA1537 and with *Escherichia coli* WP2 uvrA) (ECHA, 2024; NICNAS, 2009; NICNAS, 2014; OECD, 2000). An *in vitro* mammalian chromosome aberration test with Chinese hamster lung cells with and without metabolic activation of 1,4-BD was negative as well (ECHA, 2024; NICNAS, 2009; NICNAS, 2014; OECD, 2000). Furthermore, an *in vitro* mammalian gene mutation assay in Chinese hamster Ovary (CHO) cells according to OECD TG 476 in the presence and absence of S9 mix was negative (ECHA, 2024; NICNAS, 2009; NICNAS, 2014). In conclusion, 1,4-BD was not genotoxic and no clastogenic effects were observed after 1,4-BD treatment *in vitro* (ECHA, 2024).

In vivo studies with 1,4-BD are not available.

Carcinogenicity

Carcinogenicity studies with 1,4-BD are not available (ECHA, 2024; NTP, 1996).

Read across: No clear evidence of carcinogenicity was observed in two-year carcinogenicity studies in which F344/N rats or B6C3F1 mice (50 M + 50 F/group) (NTP, 1992) were exposed to the structural 1,4-BD analogue GBL by oral gavage. No evidence was found in male and female F344/N rats up to the highest dose tested (males at 225 mg/(kg bw x d) and females at 450 mg/(kg bw x d) and in female B6C3F1 mice at 525 mg/(kg bw x d)) (ECHA, 2024). However, there was equivocal evidence of carcinogenicity at the low dose in male B6C3F1 mice, based on slightly increased incidences of proliferative lesions and primarily hyperplasia of the adrenal medulla. The sensitivity of the study in male mice to detect a carcinogenic effect was reduced by low survival due to fighting in the high-dose group (ECHA, 2024).

2.5.4 Toxicity to reproduction

Fertility

In a combined repeated dose toxicity study with the reproduction/development screening test (OECD TG 422), 13 male and 13 female Sprague-Dawley rats were treated with 200, 400 or 800 mg/(kg bw x d) 1,4-BD by **oral gavage**. Males were treated for a total of 42 days. Females were treated for 14 days prior to mating until day three of lactation. No impairment of reproductive performance was observed in parental (F0) animals. No reduction in pup viability or signs of morphological abnormalities were observed in the pups up to the highest dose of 800 mg/(kg bw x d). However, there was a statistically significant slight decrease in body weight in the pups, which was secondary to maternal toxicity (reduced food consumption and body weight gain). The NOAEL for fertility and reproductive performance (P0) was 800 mg/(kg bw x d). The NOAEL for developmental toxicity (F1) was 800 mg/(kg bw x d) (ECHA, 2024; NICNAS, 2009; NICNAS, 2014). For details on systemic toxicity see section 2.5.2.

Developmental toxicity

One prenatal developmental toxicity study (similar to OECD TG 414) was conducted with 1,4-BD in Swiss albino CD-1 mice. 32 female mice were treated with 1,4-BD from gestation day (GD) 6 to day 15 per dose by **oral gavage**. The study was terminated on GD 17. Three dose groups of 100, 300, or 600 mg/(kg bw x d) were evaluated. In the mid- and high-dose groups, signs of central nervous system toxicity (hypoactivity, immobility, loss of righting reflex and/or recumbency) were observed within 4 h after dosing. Other indications of maternal toxicity included a reduced

body weight and body weight gain at the mid- and high-dose group as well as decreased liver weights and reduced food consumption. For maternal toxicity the NOAEL was determined at 100 mg/(kg bw x d). Developmental toxicity was limited to a reduction in mean foetal body weight at the mid- and high-dose groups (92 % and 83 % compared to control (100%)) and NOAEL for embryonic toxicity in Swiss albino CD-1 mice was set at 100 mg/(kg bw x d) (ECHA, 2024; NICNAS, 2009; NICNAS, 2014; NTP, 1996; OECD, 2000).

Read across: An OECD TG 414 study was conducted with GBL in Himalayan Chbb:HM (outbred strain) rabbits. 15 rabbits (time-mated) were exposed at a concentration of 0.5, 1.4 or 5.0 mg/L (0.5, 1.4 or 5000 mg/m^3) by inhalation (head-nose exposure) from gestation day 7 to 19. Animals were killed on day 29. There was no evidence of either maternal or embryonic toxicity. Therefore, the NOAEC for maternal and embryonic toxicity in the Himalayan Chbb:HM rabbit was set at 5 mg/L air (ECHA, 2024).

These findings are supported by another OECD TG 414 equivalent or similar to guideline in Sprague-Dawley rats treated with GBL by oral gavage using concentrations of 10, 50, 125, 250 and 500 mg/(kg bw x d). Ten animals per dosage group and nine control animals were treated once daily from GD 6 through 15. There was no evidence of either maternal or embryonic toxicity. Therefore, the NOAEL for maternal and embryonic toxicity in Sprague-Dawley rats was set at ≥ 500 mg/(kg bw x d) (ECHA, 2024).

2.5.5 Odour perception

No odour threshold for 1,4-BD is available (ECHA, 2024).

2.5.6 Existing regulations and classifications

There is no harmonised classification for 1,4-BD available yet, but according to the ECHA website (ECHA, 2024), Germany is planning to develop a harmonised classification.

Existing guide values for 1,4-BD in air are summarised in Table 9.

A NIK (Lowest Concentration of Interest) value of 2000 µg/m^3 is reported for 1,4-BD by the Committee for Health-related Evaluation of Building Products (AgBB). Furthermore, an occupational exposure limit (OEL) of 200 mg/m^3 is reported for 1,4-BD in Germany (AGS, 2024; DGUV, 2024).

In the registration dossier for 1,4-BD, a chronic DNEL of 136 mg/m^3 for the protection of workers via inhalation route has been derived by applying a read-across approach. As starting point for the DNEL derivation, the NOAEL of 225 mg/(kg x bw x d) from an oral subchronic toxicity study performed in rats with the source substance GBL was used. This starting point was adjusted for: the molecular weight from the source substance GBL to the target substance 1,4-BD by a factor of 1.05 (1,4-BD/GBL = (90.1 g/mol)/(86.1 g/mol)), absorption from oral to inhalation by a factor of 1, route-to-route extrapolation by a factor of 2.60 (1/0.38 (8 h inhalation)) and adjustment of 0.67 (modification for respiratory volume under light activity for workers) leading to a NOAEC of 410 mg/m^3 (see Table 9 for details) (ECHA, 2024). As assessment factor, the factor of 1 for extrapolation from subchronic to chronic exposure was applied, which is not in accordance with the ECHA Guidance on DNEL derivation. This guidance document recommends a default value of 2 (ECHA, 2019). Furthermore, the following assessment factors were applied: a factor of 1 for dose response relationship, a factor of 3 for intraspecies differences (note: according to ECETOC) and a factor of 1 for interspecies differences was applied according to the ECHA dossier (due to rapid metabolism from 1,4-BD to GHB). The recommended intraspecies factor for workers according to ECHA Guidance on DNEL derivation is 5 (ECHA, 2019). By following the ECHA Guidance for chronic worker DNEL

derivation a total assessment factor of 5 (ECHA, 2019), would lead to a chronic worker DNEL of 82.3 mg/m^3. This is not in line with the reported chronic worker DNEL of 136 mg/m^3 (total assessment factor of 3) presented in the registration dossier of the lead registrant (ECHA, 2024).

Next to the chronic worker DNEL an acute worker DNEL of 958 mg/m^3 was derived from an inhalation acute toxicity study with a LOAEC of 5100 mg/m^3 by the lead registrant (ECHA, 2024). The LOAEL was adjusted for: adjustment of 0.67 (modification for respiratory volume under light activity for worker), transforming the LOAEL to the NOAEC was done by using a correction factor of 3 and a time correction factor of 2.5 (4 h to 15 min) was applied, leading to a NOAEC of 2874 mg/m^3 (see Table 9 for details) (ECHA, 2024). The adjusted starting point was 2847.5 mg/m^3. Furthermore, the following assessment factors were applied: 1 for the dose response relationship, 1 for interspecies differences (due to rapid metabolism from 1,4-BD to GHB) and a factor of 3 for intraspecies differences (note: according to ECETOC). The intraspecies factor for workers according to ECHA Guidance on DNEL deviation is 5 (ECHA, 2019). By following the ECHA Guidance on DNEL derivation (ECHA, 2019) a DNEL of 569 mg/m^3 (applying a total assessment factor of 5) would have been derived. This DNEL is lower compared to the existing DNEL of 958 mg/m^3 (applying a total assessment factor of 3) (ECHA, 2024).

For the general population via inhalation route no hazard was identified and thus no DNEL has been reported in the registration dossier (ECHA, 2024).

2.5.7 Derivation of an EU-LCI value

There are several options for deriving the EU LCI value for 1,4-BD based on the available data. The most appropriate options are presented and discussed below.

The chronic DNELs for workers and general population of the lead registrant presented in the ECHA dossier were derived by using a read-across approach with 1,4-BD as target substance and GBL as source substance. Using this approach the oral subchronic toxicity study with rats and the source substance GBL (see section 2.5.2) is taken as the basis for the derivation of the EU-LCI. This study provides a NOAEL of 225 mg/(kg bw x d) (ECHA, 2024). An adjustment of this starting point for route-to-route extrapolation (oral to inhalation) by a factor of 1.15 leads to a corrected NOAEC of 196 mg/m^3. The NOAEC was adjusted for the molecular weight (target/source substance (90.1 (1,4-BD)/86.1 (GBL) =1.05), continuous exposure (5 d/week) by a factor of 1.4, study length factor (subchronic study) by a factor of 2, interspecies extrapolation by a factor of 2.5 (allometric scaling not performed since route of exposure is inhalation) and an intraspecies extrapolation factor of 10. By applying the total assessment factor of 70 and the molecular weight correction fraction due to the read-across approach by a factor of 1.05 an EU-LCI of ((196 mg/m^3: 70) x (1.05)) = 2.94 mg/m^3 (rounded to 2900 µg/m^3) would be derived.

According to EC (2013), inhalation studies are preferred over oral studies. Therefore, the subacute inhalation study (14 days treatment followed by a recovery period of 14 days without treatment) conducted with 1,4-BD in rats (equivalent or similar to OECD TG 412) was preferred over the subacute oral study (28-day treatment) conducted with 1,4-BD in rats (no guideline study, compared to OECD TG 407 deviations include selection of highest dose inadequate (too low)). Additionally, the subacute inhalation study, is described in sufficient detail and was also used as a basis for deriving the national OEL value for 1,4-BD in Germany (AGS, 2006; AGS, 2024). Therefore, this study is considered a suitable key study for the derivation of an EU-LCI value for 1,4-BD and preferred over the read-across approach (described above) with the subchronic oral repeated dose toxicity study performed with GBL.

The subacute inhalation toxicity study in rats (see section 2.5.2 for details) is taken as basis for the derivation of the EU-LCI value. This study provided a NOAEC of 1100 mg/m^3 (Kinney et al., 1991).

The following assessment factors are used:

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

Total assessment factor: 840 leading to a value of 1100 mg/m^3: 840 = 1.31 mg/m^3 (rounded to 1300 µg/m^3).

An EU-LCI value of (rounded) 1300 µg/m^3 is proposed for 1,4-BD.

Since no odour threshold is available for 1,4-BD (ECHA, 2024), no conclusions can be drawn regarding olfactory perception of the substance at the proposed EU-LCI value.

2.6 List of References

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B Appendix

B.1 Data collection and fact sheet for 1,4-BD

Table 9: Data collection sheet for 1,4-butanediol (1,4-BD)

Compound	**1,4-Butanediol**	**Data collection sheet**	
Nº CAS: 110-63-4 1 ppm = 3.71 mg/m³ at 23 °C	**EU-Classification:** **CLP, harmonised classification:** none		
Organisation name	**REACH registrant**	**AgBB**	**AGS**
Risk value name	DNEL	NIK ('Lowest Concentration of Interest')	AGW value (occupational exposure limit, OEL)
Risk value (mg/m³)	136 (based on subchronic oral toxicity study)	2	200
Reference period	Chronic (workers)		Chronic (workplace)
Risk value (mg/m³) Short term (15 min)	958 (based on acute inhalation study in rats)		
Year	2022	2024	2006
Key study	OECD TG 413 (Subacute Inhalation Toxicity: 28-Day) (ECHA, 2024)	see below	Kinney et al. (1991)
Study type	Long term: Subchronic oral toxicity study Short term: Acute inhalation toxicity study		Subacute inhalation toxicity study
Species	Long term: Rat (Fischer 344) Short term: Rat (SPF-Wistar)		Rat, Crl:CD (n = 10 M /group)
Duration of exposure in key study	Long term: Daily, 5 d/week, 13 weeks Short term: 4 h, single exposure		6 h/d, 5 d/week, 2 weeks
Critical effect	Long term: Less body weight gain (males) Mortality (females) Short term:		Reduction in body weight gain

Compound	1,4-Butanediol	Data collection sheet	
	Slight respiratory symptoms, no pathological findings.		
Critical dose value	Long term: NOAEL♂ = 225 mg/(kg bw x d) (based on less body weight gain) NOAEL♀ = 450 mg/(kg bw x d) (based on mortality) Short term: LOAEL = 5100 mg/m³ (no mortality, slight respiratory symptoms)		NOAEC: 1100 mg/m³
Adjusted critical dose	Long term: 225 mg/(kg bw x d)*1.05(1)*1(2)*2.60(3)*0.67(4) = 410 mg/m³(5) Short term: (5100 mg/m³*0.67(4)*2.5(6))/3(7) = 2874 mg/m³(8)		
Single assessment factors	Long term: UF_A 1.0, UF_H 3.0, ABS_{inh}/ABS_{oral} 1; total = 3(9) Short term: UF_A 1.0, UF_H 3.0; total = 3(9)		
Other effects			
Remarks	Long term: read-across from source substance GBL as supporting substance (structural analogue or surrogate) Short term: study was performed with 1,4-BD	Adopted ascribed EU-LCI-value	

(1): MW adjustment: 1,4-BD/GBL = (90.1 g/mol)/(86.1 g/mol), (2): Absorption: 100 %, (3): Route-to-route extrapolation: 1/0.38 (8 h inhalation), (4): Modification for respiratory volume under light activity for worker: 6.7 m³/10 m³, (5): unrounded, corrected NOAEC = 411.5 mg/m³, (6): time correction factor: 2.5 (4 h → 15 min), (7): factor to correct from LOAEC → NOAEC, (8): unrounded value = 2847.5 mg/m³, (9): The lead registrant referred to ECETOC and applied an assessment factor of 3. However, according to ECHA Guidance (ECHA, 2019) an assessment factor of 5 is recommended.
AgBB: Committee for Health-related Evaluation of Building Products, UF_L: Used LOAEL, UF_H: Intraspecies variability, UF_A: interspecies variability, UF_S: Used subchronic study, UF_{SA}: Used subacute study, UF_D: data deficiencies

Table 10: Fact sheet for 1,4-butanediol

Compound	1,4-Butanediol C4H10O2		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	1300
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2025
General information			
CLP-Index No.	4	INDEX	-
EC-No.	5	EINECS	203-786-5
CAS-No.	6	Chemical Abstract Service number	110-63-4
Harmonised CLP classification	7	Human health risk related classification	no
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	90.12 1 ppm = 3.71 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	OECD TG 412 (Subacute Inhalation Toxicity: 28-Day), Kinney et al. (1991)
Read across compound	10	Where applicable	-
Species	11	Rat, human, etc.	Rat, CD:Crl
Route / type of study	12	Inhalation, oral feed, etc.	Inhalation
Study length	13	Days, subchronic, chronic, etc.	Subacute (28 d)
Exposure duration	14	h/d, d/w	6 h/d, 5 d/week
Critical endpoint	15	Effect (s), site of	Decrease in body weight
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEC
POD value	17	[mg/m³] or ppm or [mg/kg bw x d]	1100 mg/m³
Assessment factors (AF)			
Adjustment for exposure duration	19	Study exposure h/d, d/w	5.6
Study length	20	sa→sc→c	6
Route-to-route extrapolation factor	21	-	1

Compound	1,4-Butanediol C4H10O2		Fact sheet
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	1
	22b	Severity of effect (R8 6d)	1
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	1
	23b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		1
Other adjustment factors Quality of database	26	Quality of database	1
Results			
Summary of assessment factors	27	Total Assessment Factor	840
POD/TAF	28	Calculated value [µg/m³ and ppb]	1310 µg/m³ and 353 ppb
Molar adjustment factor	29		
Rounded value	30	[µg/m³]	1300
Additional comments	31		
Rationale selection	32		

Rationale for critical effects

The data basis for 1,4-BD is limited. No reliable inhalation study with 1,4-BD after subchronic or chronic exposure is available.

The acute toxicity of 1,4-BD in rats is determined as moderate in acute toxicity studies. In an acute inhalation toxicity study (OECD TG 403, 'nose/head only', exposure for 4 h) a LC50 > 5100 µg/m^3 was determined. In another acute inhalation toxicity study (fixed concentration method; OECD TG 433), rats were exposed 'nose only' to 4.6, 9.4 or 15 mg 1,4-BD/m^3 (aerosol; highest concentration tested, as higher atmospheric concentrations could not be generated) for 4 h. At 4.6 and 9.4 mg/m^3, rats were lethargic with laboured breathing. At 9.4 and 15 mg/m^3, clinical signs were observed: lethargy, immobility, and laboured breathing. At 15 mg/m^3, all rats exhibited slight to severe weight loss one day after exposure in a concentration-dependent manner, followed by resumption of normal weight gain. At the high-dose group 1/10 animal died one day post exposure. The NOAEC was set at 4.6 mg/m^3 and the 4 h LC50 was set at > 15 mg/m^3 (ECHA, 2024; NICNAS, 2009; NICNAS, 2014).

The lethal dose after acute ingestion in humans is reported to be 60 mg/kg bw (Dufayet et al., 2023).

When applied locally to the skin, undiluted 1,4-BD causes no irritation of the skin in rabbits. Slight and reversible (within 48 h) irritant effects on the eyes of rabbits were detected. Sensitising tests in guinea pigs (Guinea pig maximisation test, GPMT test), showed no sensitising potential of 1,4-BD. Furthermore, in patch tests in humans no irritating or sensitising effects were detected.

There are several repeated dose studies available, investigating the toxicological effects of 1,4-BD after inhalation. In an inhalation study equivalent or similar to OECD TG 412 (nose only), rats (10 males/dose) were exposed to 1,4-BD (purity: > 99.7 %) as an aerosol of 0.20, 1.1 or 5.2 mg/L (200, 1100 or 5200 mg/m^3 actual concentration) for 6 h/d, 5 d/week for two weeks. Five rats per group were sacrificed after the 10th exposure and five rats per group were sacrificed after a recovery period of 14 days post-exposure. There were no clinical symptoms, but the body weight gain of the high-concentration group was significantly lower (28 %) compared to controls during the exposure period. In addition, there was a significant decrease in serum cholesterol (no histopathological correlation) and haematological parameters (increase in erythrocyte count and haematocrit values) which were assessed by the authors of the study as biological variations and not related to 1,4-BD treatment. Both the cholesterol level and the blood values normalised during the follow-up period. The histopathological examinations showed that three out of five rats had slight atrophy of lymphoid cells in the thymus, which also normalised during the follow-up period. No pathological changes were observed in the lungs of the high-concentration rats. The no adverse effect level (NOAEC) was set at 1100 mg 1,4-BD/m^3 (Kinney et al., 1991). In a briefly reported subchronic inhalation study, rats were exposed to 1500 – 2000 mg 1,4-BD/m^3 for 2 h/d for 4 months. Clinical signs of toxicity observed included inactivity and drowsiness (occurring after the first 3 to 4 weeks) and were reversible within 10 to 20 min after the end of exposure. Histopathological examination revealed local irritation (extensive pulmonary emphysema, mild pulmonary oedema and, in a few animals, inflammatory changes). A LOAEC of 1500 – 2000 mg/m^3 was established for CNS effects (BG Chemie, 1992; NICNAS, 2009; NICNAS, 2014). In an additional study (not according to OECD test guideline), male rats were exposed to a vapour of 300 – 500 mg 1,4-BD/m^3 for 2 h/d, 6 d/week for 4 months. No clinical signs of toxicity were observed; therefore, the NOAEC was determined to be 500 mg/m^3 (BG Chemie, 1992).

In a subacute oral toxicity study (no guideline study, compared to OECD TG 407 deviations include selection of highest dose inadequate (too low)) rats (8 M + 8 F/group) were exposed to 1,4-BD by gavage at doses of 5, 50 or 500 mg/(kg bw x d) 7 d/week for 4 weeks. No mortality was observed. Significant changes in haematological and clinical chemistry parameters were observed. In males, a significant decrease in red blood cell counts in all dose groups and an increase in haemoglobin concentrations in the low and high-dose group were observed. Males in the high-dose group had a significant decrease in thrombocytes and haematocrit values and changes in clinical chemistry parameters (decrease in total protein, increase in alanine aminotransferase and sorbitol dehydrogenase). In female rats of low and high-dose groups a significant decrease in erythrocyte count was seen. The number of thrombocytes was statistically significant decreased in the low- and mid-dose females. Mild to moderate liver inflammation (proliferation of bile ducts and periportal infiltrations of fibroblasts and mononuclear cells) occurred in all dose levels of both sexes but was most prominent in the highest dose group. The NOAEL was 50 mg/(kg bw x d) and the LOAEL was 500 mg/(kg bw x d) (ECHA, 2024; EFSA, 2011; NICNAS, 2009; NICNAS, 2014; NTP, 1996; OECD, 2000).

As outlined above, there are no repeated dose oral or inhalation toxicity studies with subchronic/chronic exposure durations available for 1,4-BD.

However, repeated dose studies performed with the structural analogue γ-butyrolactone (GBL, CAS: 96-48-0) are available for subchronic/chronic exposure durations. A read-across from 1,4-BD to GBL is justified as both substances have the same common metabolites, namely γ-hydroxybutyrate (GHB) and γ-aminobutyric acid (GABA), which cause the typical toxicity signs (e.g. narcosis, CNS depression) observed after repeated exposure to 1,4-BD or GBL.

In a study equivalent or similar to OECD TG 408 conducted with GBL, Fischer 344 rats (10 M +10 F) were given doses of 56, 112, 225, 450 or 900 mg/(kg bw x d) by oral gavage 5 d/week for 13 weeks. Rats started to show signs of sedation at 225 mg/(kg bw x d) and above. The effects were observed during the first 2-3 weeks of the study and decreased with continued dosing time. After 3 weeks, rats showed no longer visible signs of sedation after dosing. Males at 450 mg/(kg bw x d) gained less body weight. Mortality was observed in all high-dose males and one high-dose female. Inflammation/irritation of the nasal mucosa was observed in all dose groups but was considered to be a non-specific effect of gavage treatment with a volatile agent. In the registration dossier, the following information is documented: '*NTP reports that similar lesions have been observed in other NTP gavage studies with a variety of chemicals and that the lack of any histologically evident degenerative lesions may be attributed in part to the rapid absorption and metabolism of the chemic*al'. The NOAEL for males, based on body-weight effects, was 225 mg/(kg bw x d). The NOAEL for females was 450 mg/(kg bw x d), based on mortality (ECHA, 2024). A study conducted in a similar manner to the previous one, derived NOAELs of 525 mg/(kg bw x d) for mice of both sexes.

No genotoxicity of 1,4-BD was observed in *in vitro* assays with bacteria and mammalian cells. Neither *in vivo* genetic toxicity data nor carcinogenicity studies are available for 1,4-BD. A two year carcinogenicity study in rats and mice with the analogue GBL provided no evidence of carcinogenicity (NTP, 1992).

A combined repeated dose toxicity study with reproduction/developmental screening (according to OECD TG 422) in rats dosed with 200, 400 and 800 mg 1,4-BD/(kg bw x d) observed no impairment of reproductive performance in parental (F0) animals. Systemic parental effects showed a reduced body weight gain associated with a decrease in food consumption in the mid- and high dose group. Furthermore, a statistically significant and dose-related slight decrease in blood glucose (observed in males at all ages from 200 mg/(kg bw x d) and onwards) and pathological changes with diffuse transitional epithelial hyperplasia and fibrosis in the lamina propria of the urinary bladder at 400 and 800 mg/(kg bw x d) were observed. A NOAEL of 200 mg/(kg bw x d) was determined. Additionally, based on the observed hyperactivity at 200 mg/(kg bw x d) a NOEL was set at < 200 mg/(kg bw x d). In pups, no reduction of viability or signs of morphological abnormalities were observed up to the highest dose tested. Reduced pup body weight was assessed as a secondary maternal toxicity effect. The NOAEL for fertility, reproductive performance and developmental toxicity was 800 mg/(kg bw x d).

A developmental toxicity study (similar to OECD TG 414) in mice showed no adverse effects on the foetal development. The observed reduction in mean foetal body weight in the mid- and high-dose groups were evaluated as secondary maternal toxicity effects.

Most human poisoning cases describe acute accidental ingestion of 1,4-BD by the oral route. The main symptoms are central nervous system effects, including sedation up to coma, which are mostly reversible within hours.

Rationale for starting point

There are several studies that could be used as a basis for deriving an EU-LCI value for 1,4-BD.

Oral and inhalation studies with a subchronic/chronic exposure duration to 1,4-BD are not reported in the literature. For the structural analogue GBL oral subchronic/chronic studies are available (for read-across justification see above). For GBL an adopted EU-LCI is already set (EU-LCI value: 2800 µg/m³). If the subchronic oral toxicity study performed with GBL in rats and its derived NOAEL of 225 mg/(kg.bw x d) are used as a starting point, adjustment for route-to-route extrapolation (oral to inhalation) by a factor of 1.15 has to be performed, resulting in a corrected NOAEC of 196 mg/m³. Applying a total assessment factor of 70 (adjustment for exposure duration: 1.4, adjusted study length: 2, interspecies extrapolation of 2.5, intraspecies extrapolation of 10) and the correction factor for the molecular weight (90.1 (1,4-BD)/86.1 (GBL)) would result in an EU-LCI value of ((196 mg/m³: 70) x (1.05)) = 2.94 mg/m³ (rounded to 2900 µg/m³).

According to EC (2013), inhalation studies are preferred for the derivation of an EU-LCI value. Therefore, the subacute inhalation study (14 days treatment followed by a recovery period of 14 days) conducted with 1,4-BD in rats (equivalent or similar to OECD TG 412) was preferred over the subacute oral study (28-day treatment, non-guideline study) conducted with 1,4-BD in rats. The subacute inhalation study performed according to OECD TG 412 was also used as a basis for deriving the national occupational exposure limit (OEL) for 1,4-BD in Germany (AGS, 2006; AGS, 2024). Therefore, this study is considered a suitable key study for the derivation of an EU-LCI value for 1,4-BD. The NOAEC of 1100 mg/m³ is based on a significantly lower total body weight gain (28 %) compared to the control group during the exposure period in the high-concentration group and is used as POD for the calculation.

Rationale for assessment factors

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

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

Total assessment factor: 840. This leads to a value of 1100 mg/m³: 840 = 1.31 mg/m³ for 1,4-BD (rounded to 1300 µg/m³).

An EU-LCI value of 1300 µg/m³ is proposed for 1,4-BD.

Since no odour threshold is available for 1,4-BD (ECHA, 2024), no conclusions can be drawn regarding olfactory perception of the substance at the proposed EU-LCI value.

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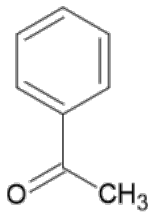
3 Toxicological evaluation of acetophenone as basis for the derivation of an EU-LCI value

(Note: For the compilation of the data, parts of an earlier report are used, which was prepared by the same main author as a basis for deriving guideline values for indoor air, also on behalf of the German Environment Agency, in 2015/2016).

3.1 Substance identification

Acetophenone is a mixed aliphatic aromatic ketone. Substance identification data of acetophenone are shown in Table 11.

Table 11: Substance identification of acetophenone (AIR, 2022; ECHA Chemicals Database, 2022)

CAS-No. EC-No. CLP-Index-No.	Systematic name, common name	Sum formula	Structural formula
98-86-2 202-708-7 606-042-00-1	1-Phenylethanone, acetophenone, methyl phenyl ketone, acetyl benzene	C_8H_8O	

3.2 Substance properties and uses

The physiochemical properties of acetophenone are shown in Table 12. At room temperature, acetophenone is an easily melting, colourless solid of low volatility that forms laminar crystals. The odour of acetophenone is described as characteristically “sweet orange blossom” (ECHA Chemicals Database, 2022), but also as sweet, pungent, almond-like or reminiscent of river water (AIHA, 2013). Acetophenone is slightly soluble in water, but freely soluble in alcohol, chloroform, ether, fatty oils, and glycerol (ECHA Chemicals Database, 2022).

Acetophenone does occur naturally as a flavouring component, e. g., in various fruits, nuts, meats and seafood (Api et al., 2018; WHO, 2001).

Table 12: Physicochemical properties of acetophenone (ECHA Chemicals Database, 2022)

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa) at 25 °C	Conversion 1 ppm = x mg/m³ at 23 °C	log pow at 20 °C	Solubility in water (g/L) at 20 °C
120.15	20.0	202.1	0.45	4.95	1.65	6.2

Acetophenone is produced commercially by the catalytic acetylation of benzene or by the catalysed reaction of acetic and benzoic acid (U.S.EPA, 2011). Acetophenone is a large-scale industrial product registered in the European Union in a total tonnage band ≥ 10000 to < 100000 tonnes/a (ECHA Dissemination, 2023).

Acetophenone is used as a component of coatings, putties and filling materials, modelling compounds, lubricants and greases, as a solvent for plastics and resins, as a fragrance in

cosmetics, in detergents and cleaning agents, as constituent of air fresheners, and in finger paints (ECHA Dissemination, 2023). At the turn of the 20th century, acetophenone was marketed under the name of "hypnon" as a sleeping aid because of the sedative-hypnotic effect attributed to it (Fischer, 1893; Schneider, 1969).

3.3 Exposure

3.3.1 Indoor air

A possible source of acetophenone in indoor air is polystyrene-based insulation materials, which can cause acetophenone emissions (Scherer, 2011). Data on the occurrence of acetophenone presented in Table 13 show that acetophenone could not be detected in indoor air in the majority of the measurements. In cases where acetophenone could be detected, concentrations reported were predominantly of the order of 1 µg/m^3; values of 10 µg/m^3 were only exceeded in individual cases. No data were reported for acetophenone in the German Environmental Survey for Children and Adolescents 2014–2017 (GerES V, Part 2: Indoor Air Quality) (Lahore et al., 2025).

Regarding the analytical determination of acetophenone it should be noted that the sorbents commonly used, especially Tenax, react with ozone in the air samples to form numerous carbonyl compounds, including acetophenone (Lee et al., 2006; Marcillo et al., 2017). This can result in false positive or too high values of acetophenone in air samples.

Table 13: Data on the occurrence of acetophenone in indoor air

Indoor location	N	LoD (µg/m³)	N > LoD	Median (µg/m³)	P95 (µg/m³)	Maximum (µg/m³)	Source
Not further specified, Germany, 2006-2012	1252	2	412	1.6	6.8	230	(Hofmann and Plieninger, 2008)
Schools, kindergartens, Schleswig-Holstein, Germany, 2005-2007	285	1	58	< 1	1.0	18	(Ostendorp et al., 2009)
Classrooms in schools	381	Not reported	69	1	5.0	Not reported	(Neumann et al., 2014)

3.3.2 Other sources

Acetophenone was detected as a component of various foods, such as honey (0.1 – 0.2 mg/kg), as a component of the volatile compounds in hazelnuts, clove oil and nectarines and in sweet canned maize (Pubchem, 2025) and as a flavour component in cheese (Adda et al., 1978). It can therefore be assumed that small amounts of acetophenone are taken up with food; however, quantitative data are not available. Approximate estimates of daily dietary intake, based on production volume data and assumptions on the proportion of the exposed population, amount to about 0.3 µg/(kg bw x d) acetophenone, 0.5 µg/(kg bw x d) α-methylbenzyl alcohol and 3 µg/(kg bw x d) α-methylbenzyl alcohol ethyl ester for the EU. The latter two compounds are metabolically related to acetophenone (WHO, 2001).

3.4 Toxicokinetics

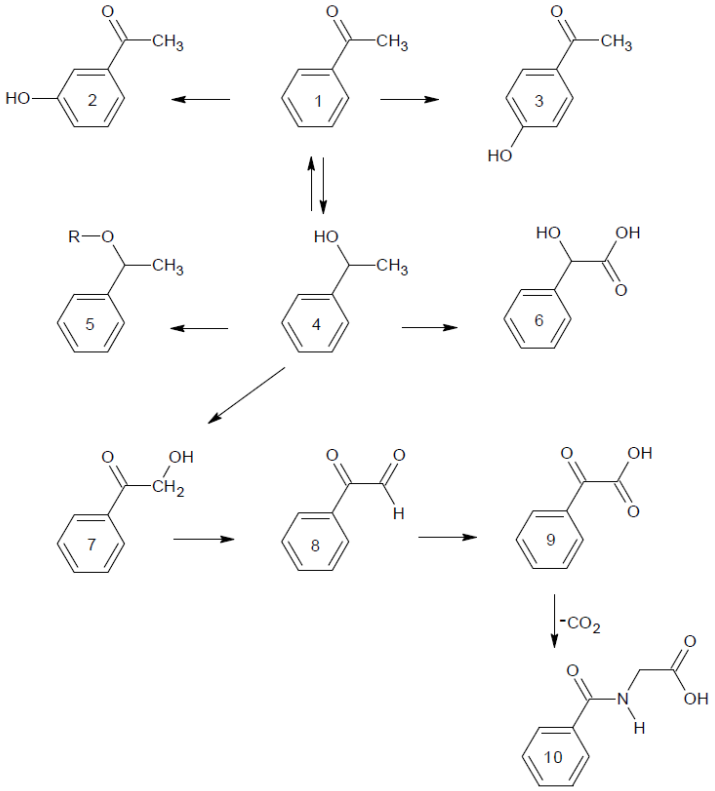
Systemic effects after oral and dermal exposure and excretion of metabolites after oral administration demonstrate the bioavailability of acetophenone after uptake via these pathways. Bioavailability after inhalation exposure is to be assumed. However, more precise quantitative data on absorption availability are not available for all three pathways, nor are data on distribution in organs and tissues.

In vitro studies of cytosolic and microsomal fractions from rat and rabbit liver showed that acetophenone can be reduced to 1-phenylethanol by cytosolic alcohol dehydrogenases as well as aldehyde and keton reductase. Corresponding activity has also been demonstrated in the kidney, heart and lungs, but not in the brain (Leibman, 1971; U.S.EPA, 1987). Conversely, 1-phenyl-ethanol can be oxidised to acetophenone, so both substances are interconvertible and provide similar excretion products (WHO, 2001).

Older sources report that after oral ingestion of acetophenone as a drug in humans, the exhaled air smelled strongly of acetophenone (Lewin, 1899). It can therefore be assumed that part of the substance is exhaled unchanged.

The excretion of acetophenone and its metabolites (Figure 2) takes place largely with urine. The path of application and the species only have little influence on the metabolite spectrum. Several of studies carried out at the beginning and in the middle of the 20th century showed that after oral administration of 480 mg/kg bw of acetophenone or 460 mg/kg bw of α-methylbenzyl alcohol (1-phenylethan-1-ol) to rabbits, about half of the administered dose is excreted in the form of metabolites in urine within 24 h, primarily as (-)1-phenylethanol glucuronide (approx. 47 %) but also as sulfate (3 %). Dogs also excreted about half of a dose of 500 mg/kg bw administered in food within the first 12 h and in subsequent 12 h urine samples (U.S.EPA, 1987; WHO, 2001).

Figure 2: Metabolism* of acetophenone, according to Kiese and Lenk (1974), modified



*1: acetophenone, 2: m-hydroxyacetophenone, 3: p hydroxyacetophenone, 4: 1-phenylethan-1-ol (α-methylbenzyl alcohol), 5: 1 phenylethan-1-ol-R (R = glucoronide or sulphate), 6: mandelic acid, 7: ω-hydroxy acetophenone, 8: phenylglyoxal, 9: phenylglyoxylic acid, 10: hippuric acid (N benzoylglycine).

3.5 Health effects

3.5.1 Acute toxicity, sensory irritation, and local effects

Acute toxicity

In humans, there are no findings relevant for evaluation after inhalation exposure against acetophenone.

At the turn of the 20th century acetophenone was sold as hypnotic human pharmaceutical due to the sedative-hypnotic effects attributed to the substance. Orally administered doses of 0.2-0.5 g were given (Fischer, 1893); however, the effect at this dose is said to have occurred only in individual cases and was not reproducible. No corresponding effect was reported in monkeys either (Lewin, 1899).

No animal toxicity data on acute inhalation exposure are available other than data from an older study. According to that study, exposure of rats for up to 8 hours in an atmosphere saturated with acetophenone at room temperature (about 2130 mg/m^3) did not lead to lethal effects (no further details available). An LC50 value of 1200 mg/m^3 reported in the registration dossier for an unspecified mammal cannot be evaluated because of a lack of any further data (ECHA Chemicals Database, 2022).

After oral administration in rats, LD50 values slightly below 1000 mg/kg bw were reported in older studies, but in more recent studies according to or similar to OECD guidelines, LD50 values were consistently > 2000 mg/kg bw. In one of these studies, 0.71 g/kg bw led to clinical

symptoms within 15 min after oral administration (central nervous effects: unsteady gait, impaired reflexes, ptosis and slowed breathing, as well as watery eyes). In one study on rats comparable to OECD guideline 401, an oral LD50 of 2081 mg/kg bw was determined. Death occurred within 24 hrs after application with unspecific clinical signs. Livers of deceased animals showed hyperaemia (ECHA Chemicals Database, 2022).

Systemic effects also occurred after dermal exposure of rats in a test conducted according to OECD guidelines (at ≥ 1820 mg/kg bw: reduced activity, ptosis, unsteady gait, also lacrimation), the LD50 value was 3300 mg/kg (ECHA Chemicals Database, 2022).

Irritation

The undiluted substance is reported to cause severe irritation of the stomach wall; irritation of the nasal cavity and slight coughing attacks have also been described (Fischer, 1893; Lewin, 1899).

In animal experiments with male Swiss-OF1 mice (at least 4 test concentrations, 6 animals/ concentration each), the sensory irritation effect of acetophenone was examined by means of the decrease in respiration rate (Alarie test). A concentration of 554 ± 56.8 mg/m^3 (111 ± 11.6 ppm) was determined as causing a reduction of the respiratory rate by 50 % (RD50) (Zissu, 1995). Another study reported a very similar RD50 of 102 ppm (509 mg/m^3) (Lehmann et al., 2016).

No signs of eye irritation in rabbits were observed in a study comparable to guideline 405 after applying 0.1 ml of undiluted acetophenone without washout. In other, older studies at most slight transient and rapidly reversible signs of eye irritation were mentioned (ECHA Chemicals Database, 2022).

Acetophenone was slightly irritating to the skin of rabbits after prolonged skin contact for 24 hours under occlusive conditions (primary irritation index 0.5 after 24 h on intact skin). Effects noted included very slight erythema or oedema and were fully reversible within the next 48 hours (ECHA Chemicals Database, 2022).

Sensitisation

In a Human Repeated Insult Patch Test, 2 % acetophenone in petrolatum did not provoke a sensitising response in human volunteers. The test protocol consisted of pretreatment of the skin test site with a mild irritant, five 48-hour closed patches (occlusive) during a 10-day induction period followed by 10 – 14 days without treatment, and a final 48-hour closed patch for challenge (no further data) (ECHA Chemicals Database, 2022).

No evidence of a skin sensitising effect of acetophenone was found in a modified Draize test with 10 Hartley guinea pigs at challenge concentrations of 0.25% for injection and 20% for topical application (no details reported) (ECHA Chemicals Database, 2022).

No data are available on respiratory sensitising effects of acetophenone.

3.5.2 Repeated dose toxicity

Human data

No studies were identified relevant for evaluation.

Animal data

In male Swiss mice (10/group, control: n=5) exposed to a concentration of 1500 mg acetophenone/m^3 (301 ppm) for 2 weeks at 6 h/d, 5 d/week, no changes were detected in the histological examination in the nasal olfactory, in the respiratory epithelium or in deeper sections of the respiratory tract (NOAEC ≥ 1500 mg/m^3) (Zissu, 1995).

In a Russian study available only as an English summary, male rats (15/group) were continuously exposed to 0, 0.007 or 0.076 mg/m^3 acetophenone for 70 d (Imasheva, 1966). At the lower concentration no changes were reported compared to the control. At the higher concentration, several changes were reported during the exposure (chronaxy ratio of muscle antagonists, cholinesterase activity in serum, content and of albumin:globulin ratio in serum) or at the end of exposure (acute hepatic dystrophy, cardiovascular plethora). Due to the lack of essential data, the unclear presentation and the questionable nature of the effects, this study cannot be evaluated.

Effects of inhalation exposure to acetophenone on olfactory mitral cells were studied in male Wistar rats (Pinching and Døving, 1974). Four animals were continuously exposed to 7.4 x 10^{-8}M (8.9 mg/m^3) acetophenone or filtered air (control) for one week and five weeks. At the end of the exposure, light microscopically moderately pronounced changes in the mitral cells were observed like darkening and shrinking of the cell body, which was considered cell degeneration. However, the authors point out that this "degeneration" does not imply cell death at all and mention unpublished findings according to which even highly "degenerated" areas react physiologically "normally". Effects of acetophenone exposure on other tissues or organs were not investigated in this study. In another study by the same group, male Wistar rats were exposed to acetophenone for different periods of time (Dalland and Døving, 1981). Comparable findings on mitral cells as in the first study are mentioned. In addition, responses to conditioning stimuli under different exposure conditions were examined. However, the description of the experimental design, the exposure situation and the results does not allow an evaluation of the study.

In a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test according to OECD Guideline 422, Sprague-Dawley rats (10 M + 10 F/dose each) were treated for at least 46 d with 0, 75, 225 or 750 mg/(kg bw x d) acetophenone in corn oil by gavage. Exposure started at least 14 d before mating and continued throughout the gestation period until day 3 of lactation (ECHA Chemicals Database, 2022; U.S.EPA, 2011). No lethal effects occurred. Starting at the middle dose level, increased salivary flow occurred in most animals immediately after administration of the test substance, which was not evaluated as adverse. In the high-dose group, movement coordination disorders (unsteady gait) and urinary discolouration of the coat were observed following administration. On the 29th day of treatment, the grip strength of the front legs and the average motor activity of the males were reduced. An initially slightly reduced weight gain as well as significant changes in haematological and clinical-chemical parameters, which remained within the range of historical controls, was not considered toxicologically relevant. A dose-dependent increase in total protein, albumin and globulin in serum correlated with a dose-dependent increase in liver weight (significant only at the highest dose, +15 % in males, +40 % in females). Males showed minimal to mild nephropathy with hyaline droplets at all doses. This study resulted in a NOAEL of 225 mg/(kg bw x d). The results of this screening study regarding reproductive toxic effects are described in chapter 3.5.4.

In a study conducted by the US American FDA, Osborne Mendel rats (10 M + 10 F/dosis each) were exposed to acetophenone in their feed for 17 weeks (Hagan et al., 1967). The nominal concentrations were 0, 1000, 2500 and 10 000 mg/kg feed, but losses, probably mainly due to evaporation, resulted in a 31 % loss on day seven of the concentration determination at the end of each week. Taking this information into account, the US EPA concluded that the highest concentration of the administered body dose of 423 mg/(kg bw x d) had a correction factor of 0.845 (U.S.EPA, 1988). In the study, no effects were found for the investigated endpoints body

weight, feed intake, clinical symptoms, haematology, organ weights and histology (including bone marrow and muscle) up to the highest dose (NOAEL ≥ 423 mg/(kg bw x d)).

Furthermore, a subchronic study according to OECD Guideline 408 on Wistar rats is available. In this study, 10 M + 10 F/dose each received 0, 125, 250 or 500 mg/(kg bw x d) acetophenone in corn oil for 90 d. At the highest dose, clinical signs of central nervous effects (reduced spontaneous activity, initially also ataxia) were observed. There were no substance-related lethal effects. In males, weight gain was delayed at the highest dose level (-15%), while weight gain was only initially and slightly reduced at the middle dose level, but not during the further course of the study. In haematology, a dose-dependent increasing proportion of reticulocytes and an increased cell volume were observed. The mean erythrocyte volume (MCV) was slightly but significantly increased from the middle dose on. Among the clinical-chemical parameters, the cholesterol content in serum was significantly increased from the medium dose but remained within the range of historical controls. The same applies to serum glucose. In a FOB, a reduced spontaneous activity was observed from the middle dose onwards. Also, from the middle dose on, the absolute and relative liver weight was increased (absolute increase at middle dose 18 – 20 %, at highest dose 26 –32 %). Histologically, a slight hepatocellular hypertrophy was observed in the liver of some animals, especially in males. In the kidney of male rats, hyaline inclusions with detection of α2u-microglobulin increased in a dose-dependent manner. The registrant concluded that the NOAEL in this study was 250 mg/(kg KG x d), based on reduced body weight gain, reduced spontaneous activity and increased percentage of reticulocytes. However, it was also noted that *"based on the histopathological findings the NOEL of Acetophenone could not be established"* (ECHA Chemicals Database, 2022). Considering the dose-dependent increase in the relative liver weight as adverse, the NOAEL could be set to 125 mg/(kg bw x d).

3.5.3 Genotoxicity and carcinogenicity

Genotoxicity

In vitro, acetophenone was non-mutagenic in an Ames test (according to OECD guideline 471) on all investigated strains (TA98, TA100, TA102, TA1535, TZA1537) of *Salmonella typhimurium* in the presence and absence of exogenous metabolising system (S9). Also in other tests not performed according to guidelines, with and without S9 in bacteria, no evidence was found of DNA damaging effects or induction of DNA repair (*Escherichia coli* PolA+/PolA-, *umu* test with *Salmonella typhimurium* TA1535/ pSK1002), mutagenic effects (*Salmonella typhimurium* TA100, TA1535, TA1537, TA1538) (ECHA Chemicals Database, 2022).

In mammalian cells, acetophenone showed no mutagenic effects in a mutagenicity test with mouse L5178Y lymphoma cells according to OECD guideline 476 and in a test for chromosomal aberrations on Chinese hamster V79 cells according to OECD guideline 473 in the presence and absence of S9. In a study published in Japanese with an English summary, a weak clastogenic effect (induction of chromosomal aberrations) of acetophenone is reported on Chinese hamster lung cells in the presence, but not in the absence of exogenous metabolising system (ECHA Chemicals Database, 2022).

The simultaneous exposure of isolated DNA to UV light and acetophenone has been described to cause the formation of base dimers, primarily thymidine dimers, and DNA strand breaks. In a bacterial strain with defective base excision repair (*Escherichia coli* B/r, WU-11 as well as E. coli WP2) the co-exposure of acetophenone and UV light (313 nm) led to an increased mutation rate (ECHA Chemicals Database, 2022).

In vivo, there are no data available regarding genotoxicity of acetophenone in humans.

In a micronucleus test on NMRI mice performed according to OECD Guideline 474, acetophenone did not lead to an increased formation of micronuclei in peripheral erythrocytes after a single oral administration of up to 515 mg/kg bw (ECHA Chemicals Database, 2022).

Carcinogenicity

Carcinogenicity studies with acetophenone are not available.

Read-across: In a NTP study, F344 rats and B6C3F1 mice (50 M and 50 F/dose each) were treated with 0, 375 or 750 mg/(kg bw x d) α-methylbenzyl alcohol (1-phenylethan-1-ol, as racemate, in corn oil) by gavage for two years (NTP, 1990). No evidence of carcinogenic effects was observed in female rats and both sexes of mice. In male rats, in addition to increased nephropathy and hyperplasia of the renal tubule cells, an increased incidence of adenomas and of the combined incidence of adenomas and carcinomas of the renal tubules ("some evidence of carcinogenicity") was observed. However, the sensitivity of the study was compromised by the high mortality in both exposed groups of male rats and in the female rats of the high-dose group (NTP, 1990).

In an assessment carried out on behalf of EFSA, the relevant committee also concluded that, despite some evidence of positive genotoxic effects *in vitro,* there is no cause for concern for a carcinogenic effect of acetophenone (and 1-phenylethanol) in humans, as the results of the NTP study with 1-phenylethan-1-ol in rats and mice give no cause for concern (EFSA, 2008).

3.5.4 Toxicity to reproduction

There are no available data from studies with humans.

Fertility

In the combined study according to OECD Guideline 422 on toxicity after continued administration/reproductive toxicity in rats described in chapter 3.5.2, adverse effects on the parent animals were found at the highest dose of 750 mg/(kg bw x d). The weight gain of pregnant females was significantly reduced at the highest dose of GD 0-7, the weight development gradually became similar to that of the control group during the further course of gestation. No impairment of fertility (mating and fertility index, gestation duration) occurred up to the highest dose tested; however, oestrus cycle and sperm parameters were not examined. At the highest dosage, two females lost their entire litter. At the highest dose, impairment of embryonic or foetal development occurred (reduced number of live foetuses/total number of foetuses, increased number of stillbirths/total births, reduced numbers of juveniles/litter on day 4 of lactation). Postnatally, the weight of the young animals was reduced as well as their general condition; especially changes in the skin were noted. Among the stillbirths, one was with cleft palate and oedema. Among the stillbirths and live births several animals showed telangiectasia, dermal hypoplasia, or desquamation. This study showed a NOAEL fertility of ≥ 750 mg/(kg bw x d) and a $NOAEL_{maternal}$ and $NOAEL_{development}$ of 225 mg/(kg bw x d).

As a follow-up to this screening study, an extended one-generation study (EOGRTS, in accordance with OECD 443 reproductive toxicity with developmental neurotoxicity) was conducted in rats. The study is described in the ECHA Chemicals Database (2022), in a detailed summary by the AIR (2022), and in detail in a CLH report (Ministry of Health, 2023) and by the RAC (2025a, b), which provided the basis for the following overview:

Sprague-Dawley rats (24 M + 24 F/parental group, 20 – 21 M + 20 – F/offspring cohort 1A (only 10 M in high-dose) and 1B (not enough pups for high dose), 10 M + 10 F/group in cohort 2A + B for developmental neurotoxicity (2A: 5 M +5 F /high dose, 2 B: not enough pups for high dose) received 0, 75, 225 or 500 mg acetophenone/(kg bw x d) by gavage in aqueous solutions with

carboxymethylcellulose and emulsifier (Tween 80). At the beginning of the mating period, the parent animals had already been exposed for ten weeks. Exposure continued during the two-week mating period (females only until successful mating) and then both sexes were exposed for a further 6 weeks until the end of the lactation period. The cohorts of offspring 1A, 1B and 2A were also exposed directly from the 22nd day (weaning phase). Cohort 2B was not directly exposed.

Clinical signs were observed in the parental animals (all doses: burrowing activity and ptyalism, mid and high dose: hypoactivity and half-closed eyes, high dose: chewing movement, staggering gait and recumbency) and similarly, in the subsequent generations. Organ weight changes included an increased relative and absolute liver weight at the medium and high dose (some changes were also observed regarding kidney weight but were not consistent in both sexes and not dose-dependent in females). At all doses, histopathology showed dose-dependent hepatocellular hypertrophy, tubular basophilia and accumulation of hyaline droplets in the kidney, brown pigmentation in the spleen, and hyperkeratosis in the forestomach. At the highest dose, effects noted included follicular cell hypertrophy in the thyroid gland, an increased incidence of vaginal enlargement and a decrease in the number of females in the prooestrus, oestrus, metoestrus and dioestrus phases of the cycle (25% vs. 61%), but no effect on sperm quality and mating behaviour.

Three females at the low dose, one at the middle and three at the high dose had to be sacrificed prematurely between GD 23 and 26 as they had difficulty giving birth (dystocia). In these potential litters, 1 out of 11 and 6 out of 15 foetuses were dead. There were three females with dead litters in the medium dose and eleven in the highest dose group. It was noted that the substance did not cause marked systemic toxicity, and that only the dystocia was the trigger of the sacrifices of the females at delivery (RAC, 2025a). The live birth indices (day 1) and viability indices (day 4) for the control, low, intermediate, and highest dose groups were 96.8, 94.4, 79.6 and 34.1 %, and 96.3, 92.9, 77.7, and 38.1 %, respectively. During lactation, adverse clinical findings attributed to a lack of maternal care increased in the offspring from the middle dose onwards: hypothermic pups, dehydration, hypoactivity and thin appearance. In addition to hypoactivity and half-closed eyes, unsteady gait and loss of balance were observed in the middle dose group in the young animals that were also directly exposed after lactation. Significantly increased organ weights were also reported in these offspring with dose-dependent centrilobular hepatocellular hypertrophy, tubular basophilia and hyaline droplets in the kidneys of the males and pigment deposition in the spleen. Small hippocampal values were also reported (AIR, 2022; Ministry of Health, 2023).

The lowest dose of 75 mg/(kg bw x d) is considered to be the LOAEL (P0 females, sexual function and fertility), due to the clear evidence of dystocia (difficulty to deliver) (AIR, 2022; ECHA Chemicals Database, 2022; Ministry of Health, 2023; RAC, 2025a).

Developmental toxicity

Two developmental toxicity studies according to OECD guideline 414 were conducted with rats and rabbits, respectively.

Pregnant Wistar rats (35 each in control and high dose group, otherwise 25 each) received 0, 125, 300 or 750 mg/(kg bw x d) acetophenone in maize oil on GD5 – 19 by gavage and delivered by caesarean section on GD 20. At the highest dosage, clinical effects were observed in the dams immediately after administration, but also several hours later, as signs of a central nervous effect (slightly to significantly reduced spontaneous activity, eyelid closure, crouching, ataxia, apathy) as well as piloerection and salivation. Slightly reduced spontaneous activity was also observed in three animals in the medium dose group immediately after administration of acetophenone on

individual days. From the middle dose on, weight gain (77 and 63 % of the control), feed intake and uterine weight were significantly reduced. In the foetuses, body weight was reduced from the middle dose onwards, while the highest dose showed increased skeletal variations in the pelvic girdle area. In this study the NOAEL was 125 mg/(kg bw x d) for maternal and developmental toxicity (AIR, 2022; ECHA Chemicals Database, 2022).

In the corresponding study with pregnant rabbits (22 F/group), the animals received 0, 60, 170, or 500 mg acetophenone/(kg bw x d) on GD 6 – 28. Pups were examined after caesarean section. At the highest dose, two females aborted and a third was found dead with red discharge, and transient clinical signs indicating CNS effects (decreased activity, abnormal gait, shallow breathing). Food intake and interim reduced body weight gain were noted at >= 170 mg/(kg bw x d). The number of resorptions was but non-significantly increased at the highest dose, whereas the foetal weight was significantly reduced at the highest dose. A NOAEL of 170 mg/(kg bw x d) for maternal and developmental toxicity is reported (AIR, 2022; ECHA Chemicals Database, 2022).

3.5.5 Odour perception

The odour of acetophenone is described as characteristically “sweet orange blossom” (ECHA Chemicals Database, 2022), but also as sweet, pungent, almond-like or reminiscent of river water (AIHA, 2013). An odour threshold of 2.9 µg/m^3 is reported for acetophenone (AIR, 2022).

3.5.6 Existing regulations and classifications

There is currently no harmonised classification for acetophenone regarding carcinogenicity, mutagenicity, or toxicity to reproduction, but only for acute toxicity (Acute Tox 4*, H302) and eye irritation (Eye Irrit. 2, H319) (ECHA C&L Inventory, 2024).

However, the RAC (2025b) proposed an additional harmonised classification and labelling for acetophenone with respect to reproductive toxicity (Category 1B, H360FD). The proposal regarding effects on sexual function and fertility (Repr.1B; H360F) is based on the severity of the dystocia observed in an OECD TG 443 study with rats along with the decreased mating index and the delayed sexual maturity. The proposal regarding developmental toxicity is based on decreased offspring viability and the reduction in pup/foetus body weight consistently observed across studies along with developmental neurotoxicity and effects on immunophenotyping observed in the OECD TG 443 study and the skeletal malformations observed in the OECD TG 414 study in rats.

Additionally, it is proposed to classify acetophenone as STOT SE 3; H336 (may cause drowsiness or dizziness) based on its historical use as a hypnotic agent in human medicine and narcotic effects transiently observed in experimental animals. It is also proposed to remove the existing classification as Acute Tox. 4* (H302). The classification criteria for acute oral toxicity are not fulfilled, since the lowest LD50 in the most reliable studies exceed 2 000 mg/kg bw (RAC, 2025b).

Existing guide values acetophenone in air are summarised in Table 14.

A DNEL of 0.22 mg/m^3 is reported in the registration dossier for the protection of the general population via inhalation route. The derivation is based on a route-to-route extrapolation using the LOAEL of 75 mg/(kg bw x d) from the EOGRTS with rats (see chapter 3.5.4) as POD. Conversion of oral exposure (rat) to inhalation exposure (human) was performed using a default factor of 1.15 m^3/kg and a default factor of 0.5 for differences between oral absorption (assumed to be 50 %) and absorption by inhalation (assumed to be 100 %). A standard assessment factor of 3 was used for the extrapolation of a NOAEL from a LOAEL and a factor of 2 for time

extrapolation (the critical effect was foetal lethality caused by dystocia of the pregnant females which were exposed for a subchronic period of time). Standard factors of 2.5 and 10 were used for interspecies and intraspecies extrapolation, respectively (ECHA Chemicals Database, 2022).

The German Committee on Indoor Air Guide Values (AIR) based the derivation of their guide values I and II also on the LOAEC of 75 mg/(kg bw x d) obtained in the EOGRTS with rats since neither human studies nor suitable inhalation studies with experimental animals were available. Route-to-route-extrapolation was performed with default assumptions of allometric factor of 4 for rat to human, a breath volume of 20 m^3/d for a 70 kg person and an oral absorption rate of 50 % (and 100 % for inhalation). A factor of 2 was applied for the subchronic study duration, a factor of 2.5 for the possible interspecies toxicodynamic differences and a factor of 10 for the interindividual variability. To account for the severity of the effect and the uncertainty that this effect has no NOAEL in this study, an additional factor of 3 was applied for the derivation of the guide value II (hazard value). For the precautionary value, this additional factor was set to 10. This led to a guide value II of 220 µg/m^3 and a guide value I of 66 µg/m^3 for acetophenone in indoor air (AIR, 2022).

A NIK value ("adopted EU-LCI value") of 0.49 mg/m^3 is reported by AGBB (2024) for acetophenone.

The German TRGS 900 and the MAK-commission have not specified workplace limit values for acetophenone (AGS, 2023; DFG, 2024). In 1992, ACGIH published a TLV TWA of 50 mg/m^3(10 ppm), which is intended to protect against systemic and reproductive toxic effects and reduce the probability of sensory irritation (ACGIH, 2009). It must be noted that this value was published before the EOGRT study on rats was performed and its results published in the registration dossier for acetophenone.

3.5.7 Derivation of an EU-LCI value

Acetophenone was marketed around the turn of the 20th century as a hypnotic (brand name "Hypnon") because of the sedative-hypnotic effect ascribed to it; however, this effect has also been called questionable. There are no usable human data available for the health assessment of repeated inhalation exposure to acetophenone.

Thus, animal experiments are used to derive guide values. There is also little information available from animal experiments on the inhalation toxicity of acetophenone. Studies on mice on the respiratory irritant effect of acetophenone provided RD50 in the range of 500 mg/m^3 (100 ppm). In a subacute inhalation study in mice, inhalation for two weeks at the only tested concentration of 1500 mg/m^3 did not lead to histologically detectable damage in the nasal epithelia or in deeper sections of the respiratory tract; other tissues and organs were not examined (Zissu, 1995).

An inhalation study in rats reported that histological changes of mitral cells in the olfactory bulb occur after continuous subacute exposure to 8.9 mg/m^3 (Pinching and Døving, 1974). The adversity of these changes cannot be clarified from the information provided in the study.

The data basis is considered insufficient for the derivation of toxicological reference values based on inhalation studies.

Toxicokinetic data (see chapter 3.4) indicate that qualitatively and quantitatively comparable metabolite patterns occur with oral and intraperitoneal administration. It is concluded that the metabolism of acetophenone is not subject to a pronounced first-pass effect in the liver. Furthermore, the findings on central nervous acute effects indicate that the effective dose is not

significantly determined by the uptake pathway. Thus, the present findings do not provide evidence against a route-to-route extrapolation.

Oral exposure of rats was associated with central nervous system effects, which manifested as movement disorders immediately following gavage, i.e. bolus administration. The effective oral doses were in the range of 500-700 mg/kg bw and thus in the same dose range as intraperitoneally administered doses (400-500 mg/kg bw), which produced corresponding central nervous effects in mice.

With continued oral exposure, non-specific effects such as reduced weight gain and changes in haematological or clinical chemical parameters occurred. These were of mild nature and partly in the range of historical controls. Increased liver weight was also observed without histologically detectable cytological damage. According to the registrant, a NOAEL of 250 mg/(kg KG x d) can be obtained from a subchronic toxicity study. However, the registrant also noted that *"based on the histopathological findings the NOEL of Acetophenone could not be established"* (ECHA Chemicals Database, 2022). Thus, considering the dose-dependent increase in the relative liver weight as adverse, the NOAEL could be set to 125 mg/(kg bw x d).

The available results of *in vitro* and *in vivo* genotoxicity studies do not indicate concern for such effects, with the exception of a weakly positive finding on the induction of chromosomal aberrations in the presence of exogenous metabolising system. There are no studies available on the carcinogenic effect of acetophenone. A study carried out within the framework of the NTP with 1-phenyl-ethan-1-ol, which is metabolised to acetophenone, showed an increased nephropathy and hyperplasia of the renal tubule cells in male rats and an increased incidence of tumours of the renal tubules ("some evidence of carcinogenicity") (NTP, 1990). In a subchronic feeding study, acetophenone led to hyaline inclusions in the kidney of male rats with detection of α2u microglobulin (ECHA Chemicals Database, 2022). This form of α2u nephropathy and the associated formation of renal tumours is considered a species- and sex-specific process that is not relevant for risk assessment in humans (Swenberg and Lehman-McKeeman, 1999). Accordingly, the EFSA concluded that, despite some evidence of positive genotoxic effects *in vitro,* there is no cause for concern for a carcinogenic effect of acetophenone (and 1-phenylethanol) in humans (EFSA, 2008).

The extended one-generation reproductive toxicity study (EOGRTS, OECD guideline 443) is used as the key study for the derivation of an EU-LCI value for acetophenone. In that study, the lowest dose of 75 mg/(kg bw x d) is considered to be the LOAEL (P0 females, sexual function and fertility), due to the clear evidence of dystocia (difficulty to deliver) (AIR, 2022; ECHA Chemicals Database, 2022; Ministry of Health, 2023; RAC, 2025a).

The key study provided a LOAEL, but not a NOAEL. An inspection of the data showed that a benchmark calculation of a BMD is not possible (analysis not shown). Therefore, a LOAEL-to-NOAEL extrapolation was performed.

The AIR (2022) pointed out that effects on reproduction and/or developmental (abortion, post implantation and litter losses) were observed at 500 or 750 mg/(kg bw x d), respectively, in studies with exposure duration of the parents for 14 to 46 days (chapter 3.5.4), whereas the longer (subchronic) exposure duration in the EOGRTS provided a much lower LOAEL of 75 mg/(kg bw x d).

Therefore, it seems justified to use an assessment factor of 2 to adjust for study length. Overall, the following assessment factors are used (EC, 2013):

- Route-to-route extrapolation: 1.15 m^3/kg bw x d

- Standard factor for differences between inhalation and oral absorption: 2
- LOAEL to NOAEL: 3
- Severity of effect: 3 (because the critical effect is a severe outcome: foetal lethality)
- Adjusted study length factor: 2
- Interspecies extrapolation: 2.5
- Intraspecies extrapolation (interindividual variability, general population): 10

Route-to-route extrapolation of LOAEL: 75 mg/(kg bw x d) : 1.15 m^3/(kg bw x d) : 2 = 32.6 mg/m^3

Total assessment factor: 450, leading to a value of 0.072 mg/m^3 (rounded to 70 µg/m^3).

An EU-LCI value of 70 µg/m^3 is proposed for acetophenone.

In the literature, an odour threshold of 2.9 µg/m^3 is reported for acetophenone (AIR, 2022). Therefore, it is expected that the odour will be perceivable at the proposed EU-LCI value.

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The links listed in the bibliography were last checked and confirmed on 2. June 2025.

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C Appendix

C.1 Data collection and fact sheet for acetophenone

Table 14: Data collection sheet for acetophenone

Compound	**1,4-Butanediol**	**Data collection sheet**	
Nº CAS: 98-86-2 1 ppm = 4.95 mg/m³ at 23 °C	**EU-Classification:** **CLP, harmonised classification:** none		
Organisation name	**AgBB**	**REACH registrant**	**AIR Germany**
Risk value name	NIK ('Lowest Concentration of Interest')	DNEL (chronic, general population)	Guide value II Guide value I
Risk value (mg/m³)	0.49	0.22	Guide value II: 0.22 Guide value I: 0.066
Reference period	Chronic (general population)	Chronic (general population)	Chronic (general population)
Risk value (mg/m³) Short term (15 min)	-	-	-
Year	2024	2022	2022
Key study	-	Not reported	ECHA Dissemination (2022)
Study type	-	Not reported	EOGRTS
Species	-	Rat	Rat
Duration of exposure in key study	-	Subchronic (no further data)	Subchronic
Critical effect	-	Not reported	Foetal lethality
Critical dose value	-	LOAEL, oral: 75 mg/(kg bw x d)	LOAEL, oral: 75 mg/(kg bw x d)
Adjusted critical dose	-	LOAEC: 33 mg/m³	LOAEC: 32.8 mg/m³

Compound	1,4-Butanediol	Data collection sheet	
Single assessment factors	-	UF_L 3, UF_S 2, UF_A 2.5, UF_H 10	Guide value II: UF_S 2, UF_A 2.5, UF_H 10, UF 3 (severity of effect) Guide value I: UF_L 10, UF_S 2, UF_A 4 x 2.5, UF_H 10, UF 10 (severity of effect)
Other effects			
Remarks	Adoption of ascribed EU-LCI value	Conversion of oral exposure (rat) to inhalation exposure (human): 1.15 m^3/kg bw x d, $Abs_{oral/ihl}$: 0.5	Conversion of oral LOAEL (rat) to inhalation LOAEC (human): LOAEL x 0.5 $Abs_{oral/ihl}$: 4 : (20 m^3/70 kg bw x d)

AgBB = Committee for Health-related Evaluation of Building Products

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

Table 15: Fact sheet for acetophenone

Compound	Acetophenone C8H9O		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	4400
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2025
General information			
CLP-Index No.	4	INDEX	606-042-00-1
EC-No.	5	EINECS	202-708-7
CAS-No.	6	Chemical Abstract Service number	98-86-2
Harmonised CLP classification	7	Human health risk related classification	Acute Tox. 4 H302, Eye irrit. 2 H319; proposed: Eye irrit. 2 H319, Repr. 1B, H360FD, STOT SE 3, H336
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	120.2 1 ppm = 4.95 mg/m³
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	ECHA Dissemination (2022) Extended One-generation reproductive toxicity study (OECD guideline 443)
Read across compound	10	Where applicable	-
Species	11	Rat, human, etc.	Rat, Sprague-Dawley
Route / type of study	12	Inhalation, oral feed, etc.	Oral gavage
Study length	13	Days, subchronic, chronic, etc.	Subchronic
Exposure duration	14	h/d, d/w	daily
Critical endpoint	15	Effect (s), site of	Foetal lethality
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	LOAEL
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	75 mg/(kg bw x d)
Assessment factors (AF)			
Adjustment for exposure duration	19	Study exposure h/d, d/w	1
Study length	20	sa→sc→c	2
Route-to-route extrapolation factor	21	-	1.15 m³/kg bw x 2

Compound	Acetophenone C8H9O		Fact sheet
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	3
	22b	Severity of effect (R8 6d)	3
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	1
	23b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		1
Other adjustment factors Quality of database	26	Quality of database	1
Results			
Summary of assessment factors	27	Total Assessment Factor	450 x 1.15 x 2
POD/TAF	28	Calculated value [µg/m³ and ppb]	72.5 µg/m³ and 14.5 ppb
Molar adjustment factor	29		
Rounded value	30	[µg/m³]	70
Additional comments	31		
Rationale selection	32		

Rationale for critical effects

Acetophenone (phenylethanone, methylphenylketone) is a colourless, low-volatility, low-melting solid at room temperature. The odour is described as sweetish and pungent, but also as almond-like, orange and jasmine scented or reminiscent of river water (AIHA, 2013; HSDB, 2010). The reported odour threshold of acetophenone is very low (2.9 µg/m^3 or 0.00059 ppm) (AIR, 2022).

Acetophenone is a large-scale industrial product (tonnage band in the EU 10000 to 100000 tonnes/year). The substance also occurs naturally as a component of vegetable essential oils and in food (HSDB, 2010).

According to the registration dossier, consumer products in which acetophenone is used include coatings, cements and fillers, modelling clay, lubricants and greases, detergents and cleaning agents, air fresheners and finger paints (ECHA Chemicals Database, 2022). At the turn of the 20th century, acetophenone was marketed under the name of "hypnon" as a sleeping aid because of the sedative-hypnotic effect attributed to it (Fischer, 1893; Schneider, 1969).

Data on the occurrence of acetophenone in indoor air from studies carried out in Germany showed that the substance could be detected in about 33 % of the samples (412 of 1252 samples), normally at low concentrations around 2 µg/m^3 but reaching 2300 µg/m^3 in extreme cases (Hofmann and Plieninger, 2008). A possible source of acetophenone in indoor air is

polystyrene-based insulation materials, which can cause acetophenone emissions (Scherer, 2011).

Acetophenone can be detected as a component of various foods, e. g. honey, hazelnuts, nectarines, or cheese (HSDB, 2010, Adda et al., 1978). It can therefore be assumed that small amounts of acetophenone are taken up with food; a 95th percentile consumer exposure of 0.53 µg/(kg bw x d) was estimated, based on production volume data and assumptions on the proportion of the exposed population (Api et al., 2018; WHO, 2001).

Systemic effects after oral and dermal exposure and excretion of metabolites after oral administration demonstrate the bioavailability after exposure to acetophenone via these pathways. Bioavailability after inhalation exposure is to be assumed. However, more precise quantitative data on absorption availability are not available.

In vitro studies of cytosolic and microsomal fractions from rat and rabbit liver showed that acetophenone can be reduced to 1-phenylethanol by cytosolic alcohol dehydrogenases as well as aldehyde and keton reductase. Corresponding activity has also been demonstrated in the kidney, heart and lungs, but not in the brain (Leibman, 1971; U.S.EPA, 1987). Conversely, 1-phenylethanol is oxidised to acetophenone, both substances are thus convertible into each other and provide similar excretion products (WHO, 2001).

The excretion of acetophenone and metabolites takes place largely with urine. The path of application and the species only have little influence on the metabolite spectrum. Several studies carried out at the beginning and in the middle of the 20th century showed that after oral administration of acetophenone or α-methylbenzyl alcohol (1-phenylethan-1-ol, the corresponding alcohol) to rabbits, about half of the administered dose is excreted in the form of metabolites in urine within 24 h, primarily as (-)1-phenylethanol glucuronide (approx. 47 %) but also as sulfate (3 %). Dogs also excreted about half of a dose of acetophenone administered in food within the first 12 h and in subsequent 12 h urine samples (U.S.EPA, 1987; WHO, 2001).

(-)1-phenylethanol was also detected in urine of rabbits, in addition to ω-hydroxyacetophenone and p- and m-hydroxyacetophenone, phenol, mandelic acid, hippuric acid, and traces of unchanged acetophenone. In contrast, an older study described that the largest proportion in the urine of dogs was due to unchanged acetophenone (WHO, 2001). Studies in rats with ^{14}C-methyl labelled acetophenone also showed the formation of mandelic acid, and the excretion of $^{14}CO_2$ in the exhaled air indicates the formation of benzoic or hippuric acid (Sullivan et al., 1976).

Older sources report that after oral ingestion of acetophenone as a drug in humans, the exhaled air smelled strongly of acetophenone (Lewin, 1899); it can therefore be assumed that part of the substance is exhaled unchanged.

No toxicity data on acute inhalation exposure are available other than data from an older study. According to this, exposure of rats for up to 8 hours in an atmosphere saturated with acetophenone at room temperature did not lead to lethal effects (no further details available) (ECHA Chemicals Database, 2022).

After a single oral administration in rats, LD50 values slightly below 1000 mg/kg bw were reported in older studies, but in more recent studies according to or similar to OECD guidelines, LD50 values were consistently > 2000 mg/kg bw. In one of these studies, 710 mg acetophenone/kg bw led to clinical symptoms within 15 min after oral administration (central nervous effects: unsteady gait, impaired reflexes, ptosis and slowed breathing, as well as watery eyes) (ECHA Chemicals Database, 2022). In mice, clear symptoms of a central nervous hypnotic effect occurred after intraperitoneal administration of 400 – 500 mg/kg bw (ACGIH, 2009). Systemic effects also occurred after dermal exposure of rats in a test conducted according to

OECD guidelines (at ≥ 1820 mg/kg bw: reduced activity, ptosis, unsteady gait, also lacrimation), the LD50 value was 3300 mg/kg (ECHA Chemicals Database, 2022; Ministry of Health, 2023).

Acute signs of CNS effects occurred in rats after oral administration in several studies. Reduced spontaneous activity and initially also ataxia were observed in a subchronic oral toxicity study with rats after the gavage administration of 500 mg/(kg bw x d), but not at 250 mg/(kg bw x d). Movement coordination disorders (unsteady gait) and urinary discolouration of the coat were observed in rats following administration of 750 mg/(kg bw x d), but not 225 mg/(kg bw x d) in a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test. Transient hypoactivity and half-closed eyes were noted at the lowest of 255 mg/(kg bw x d) in an Extended One-Generation Reproductive Toxicity Study (EOGRT). In developmental toxicity studies, reduced spontaneous activity after administration was observed in rats at 300 mg/(kg bw x d) and also abnormal gait in rabbits at 500 mg/(kg bw x d) (ECHA Chemicals Database, 2022; Ministry of Health, 2023; US EPA, 2011).

In humans there are no findings relevant for evaluation after inhalation exposure against acetophenone. At the turn of the 20th century acetophenone was sold as hypnotic pharmaceutical due to the sedative-hypnotic effects attributed to the substance. Orally administered doses of 0.2 – 0.5 g were given (Fischer, 1893); however, the effect at this dose is said to have occurred only in individual cases and was not reproducible. No corresponding effect was reported in monkeys either (Lewin, 1899). The undiluted substance is said to cause severe irritation of the stomach wall; irritation of the nasal cavity and slight coughing attacks have also been described (Fischer, 1893; Lewin, 1899).

Sensory irritation was observed in Alarie tests with mice. RD50 (concentration leading to a decrease in breathing rate by 50 % as sign of respiratory irritation) of 554 mg/m^3 (about 112 ppm) and of 102 ppm (505 mg/m^3) were reported (Zissu, 1995; Lehmann et al., 2016).

Liquid acetophenone caused only slight, temporary irritation on the skin of rabbits and did not irritate the eyes of rabbits. In older studies, however, temporary eye irritation was reported (ECHA Chemicals Database, 2022).

Acetophenone was not sensitising in a patch test in humans and in a modified Draize test with guinea pigs (ECHA Chemicals Database, 2022).

There are no studies in humans available with repeated administration of acetophenone.

In male mice (10/group, control: 5) exposed to a concentration of 1500 mg acetophenon/m^3 (303 ppm) for 2 weeks at 6 h/d, 5 d/week, no changes were detected in the histological examination in the nasal olfactory and respiratory epithelium or in deeper sections of the respiratory tract (NOAEC ≥ 1500 mg/m^3) (Zissu, 1995).

Effects of inhalation exposure to acetophenone on olfactory mitral cells were studied in male Wistar rats (Pinching and Døving, 1974). Four animals were continuously exposed to 7.4 x 10^{-8}M (8.9 mg/m^3) acetophenone or filtered air (control) for one week and five weeks. At the end of the exposure, light microscopically moderately pronounced changes in the mitral cells were observed like darkening and shrinking of the cell body, which was considered cell degeneration. However, the authors point out that this "degeneration" does not imply cell death at all and mention unpublished findings according to which even highly "degenerated" areas react physiologically "normally". Effects of acetophenone exposure on other tissues or organs were not investigated in this study. In another study by the same group, male Wistar rats were exposed to acetophenone for different periods of time (Dalland and Døving, 1981). Comparable findings on mitral cells as in the first study are mentioned. In addition, responses to conditioning stimuli under different exposure conditions were examined. However, the description of the

experimental design, the exposure situation and the results does not allow an evaluation of the study.

In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test according to OECD Guideline 422, Sprague-Dawley rats (10 M + 10 F/dose each) were treated for at least 46 d with 0, 75, 225 or 750 mg/(kg bw x d) acetophenone in corn oil by gavage. Exposure started at least 14 d before mating and continued throughout the gestation period until day 3 of lactation (ECHA Chemicals Database, 2022; U.S.EPA, 2011). No lethal effects occurred. In the high-dose group, movement coordination disorders (unsteady gait) and urinary discolouration of the coat were observed following administration. On the 29th day of treatment, the grip strength of the front legs and the average motor activity of the males were reduced. An initially slightly reduced weight gain as well as significant changes in haematological and clinical-chemical parameters, which remained within the range of historical controls, was not considered toxicologically relevant. A dose-dependent increase in total protein, albumin and globulin in serum correlated with a dose-dependent increase in liver weight (significant only at the highest dose, +15 % in males, +40 % in females). Males showed minimal to mild nephropathy with hyaline droplets at all doses. This study resulted in a NOAEL of 225 mg/(kg bw x d). (The results of this screening study regarding reproductive toxic effects are described below).

In a study conducted by the US American FDA, rats (10 M + 10 F/group) were exposed to acetophenone in their feed for 17 weeks (Hagan et al., 1967). The nominal concentrations were 0, 1000, 2500 and 10 000 mg/kg feed, but losses, probably mainly due to evaporation, resulted in a 31 % loss on day seven of the concentration determination at the end of each week. Taking this information into account, the US EPA concluded that the highest concentration of the administered body dose of 423 mg/(kg bw x d) had a correction factor of 0.845 (U.S.EPA, 1988). In the study, no effects were found for the investigated endpoints body weight, feed intake, clinical symptoms, haematology, organ weights and histology (including bone marrow and muscle) up to the highest dose (NOAEL ≥ 423 mg/(kg bw x d)).

A subchronic study according to OECD Guideline 408 was conducted with Wistar rats (10 M + 10 F/dose) which received 0, 125, 250 or 500 mg/(kg bw x d) acetophenone in corn oil for 90 d. At the highest dose, clinical signs of central nervous effects (reduced spontaneous activity, initially also ataxia) were observed. There were no substance-related lethal effects. In males, weight gain was delayed at the highest dose level (-15 %), while weight gain was only initially and slightly reduced at the mid-dose level, but not during the course of the study. Slight changes in several haematological and clinical-chemical parameters were noted. In a FOB, reduced spontaneous activity was observed from the middle dose onwards. Also, from the middle dose on, the absolute and relative liver weight was increased (absolute increase at middle dose 18 – 20 %, at highest dose 26 – 32 %). Histologically, slight hepatocellular hypertrophy was observed in the liver of some animals, especially in males. In the kidney of male rats hyaline inclusions with detection of α2u-microglobulin increased dose-dependent. The registrant concluded that the NOAEL in this study was 250 mg/(kg KG x d), based on reduced body weight gain, reduced spontaneous activity and increased percentage of reticulocytes. However, it was also noted that *"based on the histopathological findings the NOEL of Acetophenone could not be established"* (ECHA Chemicals Database, 2022). Considering the dose-dependent increase in the relative liver weight as adverse, the NOAEL could be set to 125 mg/(kg bw x d).

Regarding genotoxicity *in vitro*, acetophenone was not mutagenic or DNA-damaging in the presence or absence of exogenous metabolic activation system (S9-mix) in bacteria. The simultaneous exposure of isolated DNA to UV light and acetophenone has been described to cause the formation of base dimers, primarily thymidine dimers, and DNA strand breaks. In a

bacterial strain with defective base excision repair (Escherichia coli B/r, WU-11 as well as E. coli WP2) the co-exposure of acetophenone and UV light (313 nm) led to an increased mutation rate (ECHA Chemicals Database, 2022).

In mammalian cells *in vitro*, acetophenone showed no mutagenic effects in mouse L5178Y lymphoma cells and in a test for chromosomal aberrations on Chinese hamster V79 cells in the presence and absence of a S9-mix. In a study published in Japanese with an English summary, a weak clastogenic effect (induction of chromosomal aberrations) of acetophenone is reported on Chinese hamster lung cells in the presence, but not in the absence of exogenous metabolising system (ECHA Chemicals Database, 2022).

In vivo, a micronucleus test on mice did not lead to an increased formation of micronuclei in peripheral erythrocytes after a single oral administration of up to 515 mg acetophenone/kg bw (ECHA Chemicals Database, 2022).

There are no data available in humans or experimental animals on the carcinogenic effect of acetophenone.

Read-across: No evidence of carcinogenic effects was observed in female rats and in both sexes of mice in a NTP-study with oral administration of α-methylbenzyl alcohol (1-phenylethan-1-ol, as racemate, in corn oil) by gavage for two years. In male rats, in addition to increased nephropathy and hyperplasia of the renal tubule cells, an increased incidence of adenomas and of the combined incidence of adenomas and carcinomas of the renal tubules ("some evidence of carcinogenicity") was observed. However, the sensitivity of the study was compromised by the high mortality in both exposed groups of male rats and in the female rats of the high-dose group (NTP, 1990).

In an assessment carried out on behalf of EFSA, the committee concluded that, despite some evidence of positive genotoxic effects *in vitro*, there is no cause for concern for a carcinogenic effect of acetophenone (and 1-phenylethanol) in humans, as the results of the NTP study with 1-phenylethan-1-ol in rats and mice give no cause for concern (EFSA, 2008).

In a combined study according to OECD Guideline 422 on toxicity after continued administration/reproductive toxicity in rats, adverse effects on the parent animals were found at the highest dose of 750 mg/(kg bw x d) (see above). The weight gain of pregnant females was significantly reduced at the highest dose of GD 0-7, the weight development gradually became similar to that of the control group during the further course of gestation. No impairment of fertility (mating and fertility index, gestation duration) occurred up to the highest dose tested; however, oestrus cycle and sperm parameters were not examined. At the highest dose, two females lost their entire litter. Also, impairment of embryonic or foetal development occurred (reduced number of live foetuses/total number of foetuses, increased number of stillbirths/total births, reduced numbers of juveniles/litter on day 4 of lactation). Postnatally, the weight of the young animals was reduced as well as their general condition; especially changes in the skin were noted. Among the stillbirths, one was with cleft palate and oedema. Among the stillbirths and live births, several animals showed telangiectasia, dermal hypoplasia, or desquamation. This study showed a NOAEL fertility of ≥ 750 mg/(kg bw x d) and a $NOAEL_{maternal}$ and $NOAEL_{development}$ of 225 mg/(kg bw x d) (ECHA Chemicals Database, 2022).

As a follow-up to this screening study, an extended one-generation study (EOGRTS, in accordance with OECD 443 reproductive toxicity with developmental neurotoxicity) was conducted in rats. The study is described in the ECHA Chemicals Database (2022), in a detailed summary by the AIR (2022), and in detail in a CLH report (Ministry of Health, 2023) and by the RAC (2025a, b), which provided the basis for the following overview:

Sprague-Dawley rats (24 M + 24 F/parental group, 20 – 21 M + 20 – F/offspring cohort 1A (only 10 M in high-dose) and 1B (not enough pups for high dose), 10 M + 10 F/group in cohort 2A + B for developmental neurotoxicity (2A: 5 M +5 F /high dose, 2 B: not enough pups for high dose) received 0, 75, 225 or 500 mg acetophenone/(kg bw x d) by gavage in aqueous solutions with carboxymethylcellulose and emulsifier (Tween 80). At the beginning of the mating period, the parent animals had already been exposed for ten weeks. Exposure continued during the two-week mating period (females only until successful mating) and then both sexes were exposed for further 6 weeks until the end of the lactation period. The cohorts of offspring 1A, 1B and 2A were also exposed directly from the 22nd day (weaning phase). Cohort 2B was not directly exposed.

Clinical signs were observed in the parental animals (all doses: burrowing activity and ptyalism, mid and high dose: hypoactivity and half-closed eyes, high dose: chewing movement, staggering gait and recumbency) and similarly, in the subsequent generations. Organ weight changes included increased relative and absolute liver weight at the mid- and high-dose (some changes were also observed regarding kidney weight but were not consistent in both sexes and not dose-dependent in females). At all doses, histopathology showed dose-dependent hepatocellular hypertrophy, tubular basophilia and accumulation of hyaline droplets in the kidney, brown pigmentation in the spleen, and hyperkeratosis in the forestomach. At the highest dose, effects noted included follicular cell hypertrophy in the thyroid gland, increased incidence of vaginal enlargement and decrease in the number of females in the proestrus, oestrus, metoestrus and dioestrus phases of the cycle (25% vs. 61%), but no effect on sperm quality and mating behaviour.

Three females at the low dose, one at the middle and three at the high dose had to be sacrificed prematurely between GD 23 and 26 as they had difficulty giving birth (dystocia). In these potential litters, 1 out of 11 and 6 out of 15 foetuses were dead. There were three females with dead litters in the mid-dose and eleven in the highest dose group. It was noted that the substance did not cause marked systemic toxicity, and that only the dystocia was the trigger of the sacrifices of the females at delivery (RAC, 2025a). The live birth indices (day 1) and viability indices (day 4) for the control, low, intermediate, and highest dose groups were 96.8, 94.4, 79.6 and 34.1 %, and 96.3, 92.9, 77.7, and 38.1 %, respectively. During lactation, adverse clinical findings attributed to a lack of maternal care increased in the offspring from the mid-dose onwards: hypothermic pups, dehydration, hypoactivity and thin appearance. In addition to hypoactivity and half-closed eyes, unsteady gait and loss of balance were observed in the mid-dose group in the young animals that were also directly exposed after lactation. Significantly increased organ weights were also reported in these offspring with dose-dependent centrilobular hepatocellular hypertrophy, tubular basophilia and hyaline droplets in the kidneys of the males and pigment deposition in the spleen. Small hippocampal values were also reported (Ministry of Health, 2023; AIR, 2022).

The lowest dose of 75 mg/(kg bw x d) is considered to be the LOAEL (P0 females, sexual function and fertility), due to the clear evidence of dystocia (difficulty to deliver) (RAC, 2025a; Ministry of Health, 2023; AIR, 2022; ECHA Chemicals Database, 2022).

Two developmental toxicity studies according to OECD guideline 414 were conducted with rats and rabbits, respectively.

Pregnant Wistar rats (35 each in control and high dose group, otherwise 25 each) received 0, 125, 300 or 750 mg/(kg bw x d) acetophenone in maize oil on GD5 – 19 by gavage and delivered by caesarean section on GD 20. At the highest dosage, clinical effects were observed in the dams immediately after administration, but also several hours later, as signs of a central nervous effect

(slightly to significantly reduced spontaneous activity, eyelid closure, crouching, ataxia, apathy) as well as piloerection and salivation. Slightly reduced spontaneous activity was also observed in three animals in the mid-dose group immediately after administration of acetophenone on individual days. From the mid-dose on, weight gain (77 and 63 % of the control), feed intake and uterine weight were significantly reduced. In the foetuses, body weight was reduced from the mid-dose onwards, while the highest dose showed increased skeletal variations in the pelvic girdle area. In this study the NOAEL was 125 mg/(kg bw x d) for maternal and developmental toxicity (Echa Chemicals Database, 2022, AIR, 2022).

In the corresponding study with pregnant rabbits (22 F/group), the animals received 0, 60, 170, or 500 mg acetophenone/(kg bw x d) on GD 6 – 28. Pups were examined after caesarean section. At the highest dose, two females aborted and a third was found dead with red discharge, and transient clinical signs indicating CNS effects (decreased activity, abnormal gait, shallow breathing). Food intake and interim reduced body weight gain were noted at >= 170 mg/(kg bw x d). The number of resorptions was but non-significantly increased at the highest dose, whereas the foetal weight was significantly reduced at the highest dose. A NOAEL of 170 mg/(kg bw x d) for maternal and developmental toxicity is reported (ECHA Chemicals Database, 2022; Ministry of Health, 2023).

The AIR (2022) points out that effects on reproduction and/or developmental (abortion, post implantation and litter losses) were observed at 500 or 750 mg/(kg bw x d), respectively, in studies with exposure duration of the parents for 14 to 46 days, whereas longer exposure duration in the EOGRTS provided a LOAEL of 75 mg/(kg bw x d).

Rationale for starting point

The extended one-generation reproductive toxicity study (OECD guideline 443) (ECHA Chemicals Database, 2022) summarised above is used as the key study for the derivation of an EU-LCI value for acetophenone. In this study, foetal lethality was observed at all tested doses. The LOAEL of 75 mg/(kg bw x d) from this study is used as POD for the calculation.

Toxicokinetic findings show that qualitatively and quantitatively comparable metabolite patterns occur with oral and intraperitoneal administration. This is seen as an indication that the metabolism of acetophenone is not subject to a pronounced first-pass effect in the liver. These data thus do not provide evidence against a route-to-route extrapolation.

Rationale for assessment factors

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

- Route-to-route extrapolation: 1.15 m^3/kg bw x d
- Standard factor for differences between oral and inhalation absorption, $ABS_{oral/ihl}$: 2
- LOAEL to NOAEL: 3
- Severity of effect: 3
- Adjusted study length factor: 2
- Interspecies extrapolation: 2.5
- Intraspecies extrapolation (interindividual variability, general population): 10

Route-to-route extrapolation of LOAEL: 75 mg/(kg bw x d) : 1.15 m^3/(kg bw x d) : 2 = 32.6 mg/m^3

Total assessment factor: 450, leading to a value of 0.072 mg/m³ (rounded to 70 µg/m³).

An EU-LCI value of 70 µg/m³ is proposed for acetophenone.

In the literature, an odour threshold of 2.9 µg/m³ is reported for acetophenone (AIR, 2022). Therefore, it is expected that the odour will be perceivable at the proposed EU-LCI value.

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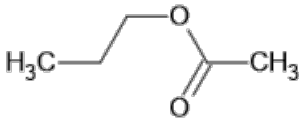
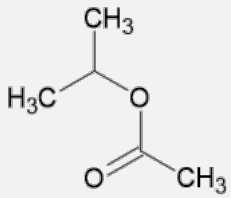
4 Toxicological evaluation of n- and isopropyl acetate as basis for the derivation of an EU-LCI value

4.1 Substance identification

Both propyl acetates belong to the group of aliphatic esters. Substance identification data of n- and isopropyl acetate are shown in Table 16.

Table 16: Substance identification of n- and isopropyl acetate (ECHA Chemicals Database, 2020; ECHA Chemicals Database, 2024)

CAS-No. EC-No. CLP-Index-No.	Systematic name, common name	Sum formula	Structural formula
109-60-4 203-686-1 607-024-00-6-	n-propyl ethanoate, n-propyl acetate, 1-acetoxypropane, acetic acid n-propyl ester	$C_5H_{10}O_2$	
108-21-4 203-561-1 607-024-00-6	2-propyl ethanoate, isopropyl acetate, 2-propyl acetate, 2-acetoxypropane, acetic acid isopropyl ester	$C_5H_{10}O_2$	

4.2 Substance properties and uses

The physiochemical properties of n- and isopropyl acetate are shown in Table 17.

At room temperature, both compounds are colourless liquids with a pleasant fruity odour (n-propyl acetate: pear and raspberry; isopropyl acetate: apple-like). Both are moderately soluble in water, but miscible with alcohols, ketones, esters, and hydrocarbons. Both esters occur naturally in many fruits or fruit juices, e. g., apples, nectarines, grapefruits (PubChem, 2024a; PubChem, 2024b).

Table 17: Physicochemical properties of n- and isopropyl acetate (DFG, 1999; ECHA Chemicals Database, 2020; ECHA Chemicals Database, 2024)

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa) at 20 °C	Conversion 1 ppm = x mg/m³ at 23 °C	log pow at 25 °C	Solubility in water (g/L) at 20 °C
n-Propyl acetate						
102.1	-93	101.5	33	4.20	1.4	18.9
Isopropyl acetate						
102.1	-73.6	88.6	60.7	4.20	1.18	30.9

According to REACH, n- and isopropyl acetate are both registered in a total tonnage band ≥ 10000 to < 100000 tonnes/a. The substances are used as a solvent or processing aids in a wide variety of products such as coatings and paints, inks, and adhesives (ECHA Chemicals Database, 2020; ECHA Chemicals Database, 2024). Further uses include cleaning and household care products, cosmetics such as perfumes and use as a flavouring agent, e. g. in beverages, chewing gum or soft candy (PubChem, 2024a; PubChem, 2024b).

4.3 Exposure

4.3.1 Indoor air

Data on the occurrence of n- and isopropyl acetate are presented in Table 18. Both compounds could rarely be detected in indoor air, and if, mostly at very low concentrations (Hofmann and Plieninger, 2008). No data were reported for n- or isopropyl acetate in the German Environmental Survey for Children and Adolescents 2014–2017 (GerES V, Part 2: Indoor Air Quality) (Lahore et al., 2025).

Table 18: Data on the occurrence of n- and isopropyl acetate in indoor air

Indoor location	N	LoD (µg/m³)	N > LoD	Median (µg/m³)	P95 (µg/m³)	Maximum (µg/m³)	Source
n-Propyl acetate							
Not further specified, Germany, 2006-2012	1250	not reported	34	1.0	1.3	52	(Hofmann and Plieninger, 2008)
Isopropyl acetate							
Not further specified, Germany, 2006-2012	1501	not reported	117	0.9	2.0	107	(Hofmann and Plieninger, 2008)

4.3.2 Other sources

Since n-propyl and/or isopropyl acetate can be detected as a volatile constituent in many fruits or fruit products, e. g. grape juice, nectarines, and apples, but also in the volatiles from cold-stored milk, oral exposure of humans is to be expected. Furthermore, dermal exposure may occur from the use of these esters in perfumes and other cosmetics (PubChem, 2024a; PubChem, 2024b). However, data are insufficient to quantitatively estimate human exposure.

4.4 Toxicokinetics

Data regarding the hydrolysis of the esters are available from respiratory bioavailability studies in rats. Inhalation exposure of rats with 2000 ppm n-propyl acetate or isopropyl acetate, respectively, demonstrated the rapid hydrolysis of the esters with the formation of the corresponding alcohol. Blood levels of n-propyl alcohol were about 2.6 to 7.7fold higher than that of n-propyl acetate and that of isopropyl alcohol were between 2 and 10fold higher than that of isopropyl acetate within the 90 min exposure interval (OECD SIDS, 2005; 2009).

Thus, as with similar other alkyl acetates, e. g. ethyl and n-butyl acetate, n-propyl acetate and isopropyl acetate can be expected to be hydrolysed following contact with the mucous membranes or absorption into the organism. In a study with butyl acetates, hydrolysis was detected in rat nasal tissue preparations *in vitro* (AGS, 2018; ECHA Chemicals Database, 2020; ECHA Chemicals Database, 2024; WHO, 2005).

Following enzymatic hydrolysis of n-propyl acetate by esterases, the n-propanol formed is oxidised to propanal and further to propanoic acid, which is an endogenous substance in mammalian metabolism. Propanoic acid is further metabolised via the methylmalonyl pathway and may enter the citric acid cycle (AIR, 2022).

In case of isopropyl acetate, the hydrolysis product isopropanol is oxidised in a first step to acetone by the alcohol dehydrogenase of the liver. Acetone is either exhaled or eliminated unchanged in the urine or further metabolised via hydroxypropanone (hydroxyacetone) in further metabolic reactions involving microsomal monooxygenases and other enzymes. Minor amounts of isopropanol are conjugated and excreted as glucuronide in the urine (AIR, 2021).

Acetic acid formed during the hydrolysis of these esters is largely utilised via the citric acid cycle or for the synthesis of fatty acids (AIR, 2023).

4.5 Health effects

4.5.1 Acute toxicity, sensory irritation, and local effects

Acute toxicity

The acute toxicity of n-propyl acetate and isopropyl acetate in animals is low.

All six rats survived a 30 min, but not a 60 min exposure to an atmosphere almost saturated with n-propyl acetate vapour (no further details reported). In another study, all six rats survived a 4-hour exposure with 4000 ppm (about 16800 mg/m^3). 4 of 6 rats died at 8000 ppm (about 33600 mg/m^3), and all 6 rats died at 16000 ppm (about 67200 mg/m^3). A 4-h LC50 of about 7620 ppm (32000 mg/m^3) was calculated based on these data (ECHA Chemicals Database, 2024). In this study, animals were inactive at 4000 ppm and became unconscious during exposure with the two higher concentrations. At necropsy, animals dying during exposure showed pulmonary haemorrhages, and necropsy of surviving animals revealed evidence of earlier lung damage (OECD, 2009). For isopropyl acetate, an 8-hour LC50 of 12114 ppm (about 50900 mg/m^3) is reported for female rats. A 4-hour exposure of rats led to the death of one of the six 6 animals exposed to 32000 ppm and 5 of the 6 rats at 32000 ppm (OECD SIDS, 2005).

Oral LD50 of 8700 mg n-propyl acetate/kg bw and of 9370 mg n-propyl acetate/kg bw are reported for male or male and female rats, respectively. A dermal LD50 of > 17800 mg n-propyl acetate/kg bw is reported for male rabbits (ECHA Chemicals Database, 2024). For isopropyl acetate, oral LD50 in the range of 3000 to 14964 mg/kg bw are reported for rats and 6650 and 6945 mg/kg bw for mice and rabbits, respectively. A dermal LD50 of > 17400 mg isopropyl acetate/kg bw is reported for male rabbits (ECHA Chemicals Database, 2020).

Irritation

Sensory irritation was observed at high concentrations of n- and isopropyl acetate in Alarie tests with mice: An RD50 (concentration leading to a decrease in breathing rate by 50 % as sign of respiratory irritation) of 3311 mg/m^3 (about 788 ppm) is reported for n-propyl acetate and of 17783 mg/m^3 (about 4234 ppm) for isopropyl acetate (Bos et al., 1992; Muller and Greff, 1984).

Limited data are available from studies with humans, mostly from older studies and with limited exposure measurements and data presentation. The results were summarised as follows (DFG, 1999).

Irritation of the skin, eyes and mucous membranes was reported after exposure with propyl acetates. Furthermore, effects on the central nervous systems (CNS) and even narcosis are to be expected at higher concentrations, but no data for the effect thresholds are available. Some

information can be gathered from earlier studies with volunteers: Exposure for 5 min in a room in which 3 min before n-propyl acetate had been sprayed and distributed evenly, led to mild irritation of the airways, the eyes, nose and throat at the low concentration of 1000 mg/m^3. At 15000 mg/m^3 all these symptoms were still described as weak. The volunteers felt cold and reported dryness in the throat and airways and slight lacrimation. In another study with exposure to n-propyl acetate for about 2 sec, a threshold value of 17600 ppm was given for nasal irritation in anosmic persons (DFG, 1999).

In another study, during exposure for 15 minutes to isopropyl acetate, most of the 12 volunteers found 200 ppm to be irritative for the eyes and concentrations above 200 ppm also for nose and throat. The odour nuisance of 200 ppm was reported to be slight. 100 ppm was regarded by the test persons as acceptable for an 8-hour exposure (DFG, 1999).

Liquid n-propyl acetate (0.5 ml undiluted) led to diffuse corneal injury (Grade 2 on Draize) which healed quickly and was thus regarded as irritating to eyes. Similarly, Grade 2 corneal necrosis was reported following instillation of 0.5 ml undiluted isopropyl acetate into rabbit eyes. Furthermore, two clinical cases from an occupational survey are mentioned in which isopropyl acetate caused chemical burns and healing was slow (3 – 10 d) after mechanical removal of the affected epithelium cells (ECHA Chemicals Database, 2020; ECHA Chemicals Database, 2024).

On the skin of rabbits, n-propyl acetate and isopropyl acetate caused at most very slightly erythema and no oedema in irritation studies (ECHA Chemicals Database, 2020; ECHA Chemicals Database, 2024; OECD SIDS, 2005)). Application of large amounts of n-propyl acetate at concentrations up to 10 ml/kg bw in guinea pigs or 20 ml/kg bw in rabbits under occluded conditions, however, led to erythema, desquamation and necrosis (OECD SIDS, 2009).

Sensitisation

No skin sensitisation was observed in a maximisation test with closed patch application of n-propyl acetate (2 % in petrolatum) in humans (9 M + 16 F) (ECHA Chemicals Database, 2024).

In vivo animal studies with n-propyl acetate regarding skin sensitisation are not available. The results on an *in vitro* test (OECD Guideline 442D: *In Vitro* Skin Sensitisation: ARE-Nrf2 luciferase KeratinoSens™ test method) and of QSAR calculations were considered negative (ECHA Chemicals Database, 2024). No data are available for isopropyl acetate. It was noted that other analogue alcohol esters of acetic acid, for example ethyl acetate and butyl acetates, have been studied and are not dermal sensitisers (ECHA Chemicals Database, 2020).

No data are available on respiratory sensitising effects of n- or isopropyl acetate.

4.5.2 Repeated dose toxicity

Human data

No studies are available with repeated exposure to n- or isopropyl acetate, respectively.

Animal data

Local irritation of eyes with lacrimation, salivation, and CNS-depressant effects were observed in two cats exposed to about 5200 ppm n-propyl acetate (about 21840 mg/m^3) 6 h/d for five times. Autopsy in one cat revealed tracheitis, bronchitis, lung emphysema, and fatty liver. No clinical signs were observed in the other animal during a several week follow-up period (DFG, 1999).

In a 14-day range finding inhalation toxicity study conducted prior to a subchronic study (see below), Wistar rats (4 M + 4F/group) were exposed whole-body to 0, 1000, or 3000 ppm (0,

4200, 12600 mg/m³) n-propyl acetate 6 h/day on 14 consecutive days. At 3000 ppm, local effects in the nasal epithelia were observed (minimal to severe multifocal degeneration/ regeneration of olfactory epithelium) in all male and female animals. Systemic effects observed were reduced mean body weight in males and reduced body weight change in both males and females, and, accordingly, lower terminal body weight of both males and females compared to control. The local effect in the nasal cavity was also observed at 1000 ppm, though less severe. Reduced body weight change was observed only in females at the low concentration (ECHA Chemicals Database, 2024).

In a subchronic inhalation toxicity study (OECD guideline 413) with n-propyl acetate, Wistar rats (10 M + 10 F/group) were exposed "whole body" to 0, 150, 500, or 1500 ppm of vapour (0, 630, 2100, 6300 mg/m³) 6 h/d, 5 d/week for 13 weeks. The analytically determined concentrations of n-propyl acetate (148.5, 505.2, 1528.7 ppm) were very close to the target concentrations.

Transiently reduced attention, probably due to a narcotic effect of the test substance, was observed in both male and female animals during exposure to 1500 ppm from day 14 to 44 in males and 13 to 43 in females. The effect was no longer observed shortly after the termination of each daily exposure. No other substance-related clinical signs of toxicity or any abnormalities during examinations of FOB and MA were observed. Effects on body weight or weight gain and food consumption were noted at 1500 ppm. The lowered mean body weight or mean body weight gains were consistent with the reduced food consumption. The same tendency was observed in males at 500 ppm. The mean terminal body weight of male animals was significantly lower than the concurrent control. The effects were likely secondary to the local effects observed in nasal cavity (see below). No adverse histological findings in other organs were observed. Weight changes of different organs (kidney, liver, adrenal glands, uterus, brain, testes, lungs, and heart) were considered as secondary to the changes of body weights (ECHA Chemicals Database, 2024).

The target organ was the nasal cavity where concentration-dependent effects were observed in the olfactory epithelium. Six male and female animals at 500 ppm and all males and females at 1500 ppm showed a focal or multifocal degeneration and/ or regeneration in the olfactory epithelium at different levels at the dorsal part of septum, nasoturbinate, and/or ethmoid turbinate of the nasal cavity. The severity ranged from minimal to severe. No effects were observed at 150 ppm (630 mg/m³) (NOAEC) (ECHA Chemicals Database, 2024).

The only identified study with repeated exposure to isopropyl acetate must be considered unreliable. In this study, mice (no further data) were exposed to a single concentration of 200000 mg/m³ isopropyl acetate 4 h/d, 5 d/week for 4 weeks and maintained for 2 weeks after exposure. No effects were seen in general appearance, and there were no significant effects on body weight. The authors conclude that isopropyl acetate is faintly narcotic. No further details were available (ECHA Chemicals Database, 2020). It must be noted that the reported exposure level exceeds the saturated vapour concentration.

4.5.3 Genotoxicity and carcinogenicity

Genotoxicity

Regarding genotoxicity, n-propyl acetate was not mutagenic *in vitro* in the presence or absence of exogenous metabolic activation system (S9-mix) in OECD guideline tests in bacteria and in mammalian cells (HPRT-assay in CHO cells and micronucleus assay in TK6 cells) (ECHA Chemicals Database, 2024).

Isopropyl acetate was not mutagenic *in vitro* in the presence or absence of exogenous metabolic activation system (S9-mix) in OECD guideline tests in bacteria. Isopropanol, the alcohol

produced by hydrolysis of isopropyl acetate, was not mutagenic with and without S9-mix in a HPRT assay in CHO cells (ECHA Chemicals Database, 2020).

In vivo data are not available for both compounds. Isopropanol did not induce micronuclei in the bone marrow of mice after intraperitoneal injection of up to 2500 mg/kg bw (ECHA Chemicals Database, 2020). No valid study could be identified for n-propanol.

Mutagenic effects of acetic acid observed in some studies on bacteria and mammalian cells are attributed to the non-physiological acidification of the culture medium and not to a substance-specific effect (Heldreth, 2012).

Carcinogenicity

Carcinogenicity studies with n- or isopropyl acetate are not available. The available genotoxicity data do not raise concern for a genotoxic non-threshold carcinogenic effect of both compounds.

Inhalation carcinogenicity studies conducted with isopropyl alcohol in rats and mice have shown that isopropyl alcohol does not exhibit carcinogenic potential relevant to humans. Testicular tumours seen in isopropyl alcohol-exposed male rats are considered to have no significance for human cancer risk assessment (Burleigh-Flayer et al., 1997; OECD SIDS, 2005).

Overall, the data for C_2 – C_4 alkyl acetate esters reveal that the chemicals of this group have no mutagenic or genotoxic potential (AICIS, 2014).

4.5.4 Toxicity to reproduction

Fertility

An extended one-generation reproductive toxicity (EOGRT) study according to OECD guideline 443 was conducted with oral n-propyl acetate exposure of rats. In the parental generation, the animals (28 M + 28 F/group) received 0, 100, 300, or 1000 mg/(kg bw x d) for two weeks prior to mating, during mating (two weeks), gestation (three weeks) and lactation (three weeks). In cohort 1A, pups (20 M + 20 F/group) selected from different litters of the parental generation received the same doses as their parents from day 21 of age up to day 72 – 78. No other treatment-related effects than salivation could be observed. Cohort 1B (25 M + 25 F/group) selected from different litters of the parental generation received the same doses as note above for 10 days prior to breeding (from day 21 of age), during mating (two weeks), gestation (three weeks) and lactation (three weeks). In the parental generation, cohort A and B, salivation at 1000 mg/(kg bw x d) was the only sign related to treatment. No other treatment-related effects were seen in any parameters investigated. 1000 mg/(kg bw x d), the highest dose tested, was considered the NOAEL for systemic toxicity, reproductive toxicity and pup development (ECHA Chemicals Database, 2024).

In a range-finding study for a reproduction/developmental toxicity screening test (following OECD Guideline 421), Wistar rats received 0, 300, or 1000 mg n-propyl acetate/(kg bw x d) per gavage for 4 weeks before pairing and during gestation and lactation periods. 10 M + 10 F pups were selected (F1 generation) to evaluate the effect of the test item on offspring, dosed for a total of 7 days from weaning (from day 21 to day 28 of age). In addition, reproductive performance such as conception, development of the conceptus and parturition was also examined. Salivation was occurred in males and females treated with ≥ 300 mg/(kg bw x d). This observation was considered to be a test item-related effect, but non-adverse. Up to the highest dose level of 1000 mg/(kg bw x d) tested, there were no substance-related effects on fertility or development (ECHA Chemicals Database, 2024).

Developmental toxicity

In a developmental toxicity study following OECD guideline 414, 25 pregnant Wistar rats/group received 0, 100, 300, or 1000 mg n-propyl acetate/(kg bw x d) in corn oil via gavage on GD 6 – 19. Analytical data showed that that the actual concentration of the low dose was 138 mg/(kg bw x d). There were no test substance-related adverse effects on dams, gestational parameters or foetuses at any dose level of n-propyl acetate. The NOAEL was thus assessed as 1000 mg/(kg bw x d), the highest dose tested, for maternal and foetal developmental toxicity (ECHA Chemicals Database, 2024).

In a similar OECD guideline 414 study, pregnant New Zealand White Rabbits (24 F/group) were given 0, 100, 300, or 1000 mg/(kg bw x d) of n-propyl acetate in 0.5 % methylcellulose in water by gavage on GD 7 – 27. Treatment-related effects were observed in dams at 1000 mg/(kg bw x d): an increased incidence of transiently decreased faeces and a mean body weight loss from GD 7 – 10 with concomitant decreases in feed consumption, leading to an overall 22.5 % decrease in body weight gain from GD 7 – 28 compared to controls. Body weights were decreased at 300 mg/(kg bw x d) on GD 7 – 10 compared to controls, but overall, weight gains were similar to controls over the entire treatment period (GD 7 – 28). There were no treatment-related differences in gross pathologic observations or maternal kidney or liver weights and no indications of embryo/foetal toxicity or teratogenicity at any dose level. The reported NOAEL for maternal toxicity was 300 mg/(kg bw x d) and for developmental toxicity 1000 mg/(kg bw x d), the highest dose tested (ECHA Chemicals Database, 2024).

No reproductive toxicity studies are available for isopropyl acetate. However, studies were performed with isopropanol. The results are summarised as follows:

A 2-generation study (according to OECD guideline 416) was conducted in rats with gavage administration of 0, 100, 500 or 1000 mg/(kg bw x d). The animals were exposed from the 10th week before mating. At ≥ 500 mg/(kg bw x d), weight gain during lactation was increased in the female animals and liver and kidney weights were increased in both sexes. In the F1 generation of the high-dose group, body weight was reduced and mortality increased in the early postnatal period. The F2 offspring in the high-dose group again had a reduced body weight. At the highest dose, the mating index of the males of the F1 generation was statistically significantly reduced from 93.3 to 73.1 % compared to the control. Benchmark calculations were carried out for the endpoints "reduced postnatal survival rate" in the F1 and F2 generations. These resulted in BMDL10 of 449 and 418 mg/(kg bw x d), respectively. A BMDL5 of 407 mg/(kg bw x d) was calculated for the endpoint "male mating index". Further details on the calculation are not available (AIR, 2021; OECD SIDS, 2005).

The developmental toxicity of isopropanol via inhalation exposure was studied in pregnant rats. The animals were exposed whole body to measured concentrations of 3500, 7000 and 10000 ppm of substance vapour for 7 h/d on GD 0 – 19. In dams, narcotic effects, reduced body weight gain and reduced food intake were observed at ≥ 7000 ppm. Effects were severe in the high-dose group, and the number of offspring in the high-dose group was reduced. There was a dose dependent drop in foetal body weight across all groups. This effect was small (4 %) in the low-dose group and considered close to a NOAEC. The NOAEC for both developmental and maternal effects was determined to be 3500 ppm (equivalent to about 875 mg/(kg bw x d)) (ECHA Chemicals Database, 2020).

In a study with pregnant rats exposed via gavage to 0, 400, 800, or 1200 mg/(kg bw x d) on GD 6 – 15, the NOAEL for maternal toxicity was 400 mg/(kg bw x d), based on a small increase in mortality at higher doses. Gravid uterine weight and male and female average foetal weights were reduced by about 5 % at the mid-dose and more in the high-dose group. At the highest

dose, gestational weight gain was reduced. There was no evidence of teratogenicity up to the maximum tested dose of 1200 mg/(kg bw x d). The NOAEL for maternal and foetal toxicity was 400 mg/(kg bw x d) (ECHA Chemicals Database, 2020).

In a similarly conducted developmental toxicity study with pregnant New Zealand rabbits treated during GD 6 – 18 at doses of 120, 240 and 480 mg isopropanol/(kg bw x d) by gavage, the NOAEL for maternal toxicity was 240 mg/(kg bw x d) with no evidence of teratogenicity up to the maximum tested dose of 480 mg/(kg bw x d) (ECHA Chemicals Database, 2020).

Exposure of pregnant rats 0, 0.5, 1.25 and 2.5 % isopropanol in drinking water (0, 596, 1242 and 1605 mg/(kg bw x d)) during GD6 – 16 provided a NOAEL for maternal and developmental effects of 596 mg/(kg bw x d). Maternal toxicity at the two higher doses manifested in the form of a reduced food and water intake along with a suppression in body weight growth. All reproductive parameters were normal across all dose groups. The only sign of foetotoxicity was a slight reduction in average litter weights in the medium and high dose groups, probably reflecting the weight loss seen in the dams. No external or visceral malformations were seen (ECHA Chemicals Database, 2020).

Regarding acetic acid, the German MAK commission stated that the active principle of any potential prenatal toxicity of acetic acid could be acidosis. However, inhalation exposure to a very high concentration of 54000 mg n-propyl acetate/m^3 for two hours did not lead to such an effect. Also, exposure of rabbits on GD 6 – 18 to vinegar (about 80 mg acetic acid/(kg bw x d)) did not lead to maternal or developmental toxicity (DFG, 1999).

4.5.5 Odour perception

The odour of both esters is described as fruity and reminiscent of pear or raspberry (n-propyl acetate) or apple-like (isopropyl acetate) (PubChem, 2024a; PubChem, 2024b). An odour threshold is reported of 0.24 ppm (1.008 mg/m^3) for n-propyl acetate and of 0.16 ppm (0. 672 mg/m^3) for isopropyl acetate (Nagata, 2003).

4.6 Evaluation

4.6.1 Existing regulations and classifications

There is no harmonised classification for n-propyl or isopropyl acetate with respect to carcinogenicity, mutagenicity, or toxicity to reproduction. However, n-propyl and isopropyl acetate are both classified for Eye Irritation 2 (H319) and for STOT SE 3 (Specific target organ toxicity) (H336: may cause drowsiness or dizziness) (ECHA C&L Inventory, 2024).

Existing guide values for n-propyl and isopropyl acetate in air are summarised in Table 20 and Table 21, respectively.

n-Propyl acetate

A DNEL of 150 mg/m^3 is reported in the registration dossier for the protection of the general population via inhalation route. This DNEL was derived from the corresponding DNEL of 100 ppm (420 mg/m^3) for workers, which in turn was adopted from the 8-hour limit value of 100 ppm (420 mg/m^3) for n-propyl and isopropyl acetate determined by the German MAK commission. The MAK value was corrected by a factor of 2.8 (20/10 x 7/5) to convert the worker DNEL to the consumer DNEL, considering that workers have a respiratory volume of 10 m^3/8h exposure whereas consumers have a respiratory volume of 20 m^3/24 h and because consumers may be exposed for 7 d/week instead of 5 d/week (workers) (ECHA Chemicals Database, 2024).

For the derivation of the German MAK value of 100 ppm (420 mg/m³) for n- and isopropyl acetate, the irritative effects of the propyl acetates on the eyes and mucous membranes of the upper respiratory tract are the critical effects. The MAK commission noted that the first, weak irritative effects were reported at concentrations of about 200 ppm. The MAK value for both propyl acetate isomers has therefore provisionally been set to 100 ppm. The commission further stated that this value is supported by the data for irritation of other alkyl acetates, which show that the irritation strength increases with chain length. The MAK value for the shorter chained ethyl acetate is 400 ml/m³ and that for the longer chained n-butyl acetate 100 ppm (DFG, 1999).

A NIK value ("adopted EU-LCI value") of 4.2 mg/m³ is reported by AGBB (2024).

Isopropyl acetate

DNELs for the protection of the general population via inhalation route of 168 mg/m³ for systemic effects and 136 mg/m³ for local effects, respectively, are reported in the registration dossier. A factor of 2 was used for the extrapolation from subchronic to chronic extrapolation and a factor of 5 for intraspecies differences. Regarding the interspecies differences for local effects on the respiratory tract epithelia, an interspecies factor of 0.2 was applied because *"the PBPK model (see below) shows that for the end point that give the most conservative (lowest) value for the point of departure, the difference between the inhaled concentrations required to deliver the same concentrations of acetic acid in rats versus humans is a factor of 5.8. This is rounded down to 5 to give an AF for interspecies difference other than allometry of 0.2."* (ECHA Chemicals Database, 2020).

The registrant further stated that "adequate studies of the repeated dose toxicity of isopropyl acetate were not found. The repeated dose toxicity of the in vivo hydrolysis product, isopropanol, has been studied by inhalation in rats and mice. The NOAEL of 500 ppm isopropanol seen in the rat and mouse corresponds to 394 ppm (1.675 mg/l) isopropyl acetate and a LOAEL of 1500 ppm isopropyl alcohol corresponds to 1181 ppm (4.9 mg/l) isopropyl acetate after correcting for differences in total respiratory bioavailability. … Exposure to high concentrations of isopropyl acetate or the in vivo hydrolysis product isopropanol have been reported to produce narcosis in exposed rats. No persistent neurotoxicity was seen in subchronic studies of isopropanol. … Data on ethyl acetate can be used to predict the potential for local effects through hydrolysis in the URT. Based on this available data, the BMDL10 for isopropyl acetate is predicted to be in the region 272 – 523 mg/m³". (ECHA Chemicals Database, 2020).

The data base for the derivation of the German MAK value for isopropyl and n-propyl acetate is described above.

A NIK value ("adopted EU-LCI value") of 4.2 mg/m³ is reported by AGBB (2024).

4.6.2 Derivation of an EU-LCI value

n-Propyl acetate

The subchronic inhalation toxicity study with n-propyl acetate on rats (ECHA Chemicals Database, 2024b) is taken as the basis for the derivation of the EU-LCI. This study provided a NOAEC of 150 ppm n-propyl acetate (630 mg/m³).

The following assessment factors are used:

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

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

Total assessment factor: 280 leading to a value of 150 ppm: 280 = 0.536 ppm (2250 µg/m³, rounded to 2300 µg/m³).

An EU-LCI value of 2300 µg/m³ is proposed for n-propyl acetate.

An odour threshold of 0.24 ppm (1008 µg/m³) was determined by Nagata (2003). It is expected that the odour will be perceivable at the proposed EU-LCI value.

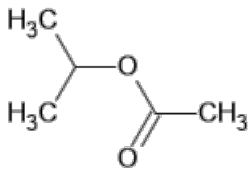
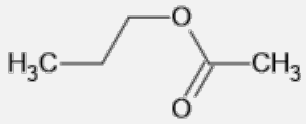
Isopropyl acetate

The EU-LCI derivation for isopropyl acetate was conducted via read-across with n-propyl acetate, following the principles described in (EC, 2013). The key assumption is that n-propyl acetate is the closest homologue with sufficient existing toxicological data and an already proposed EU-LCI value (see above):

- Data poor compound: insufficient data for isopropyl acetate.
- Read-across from n-propyl acetate: within the chemical group of "propyl acetates", n-propyl acetate is the closest homologue compound with an adequate data base. The only difference between the two substances is the branched propyl group, i. e. a 2-methylethyl group in isopropyl acetate instead of the straight-chain propyl group in n-propyl acetate,
- Toxicological critical endpoint for n-propyl acetate: degeneration and/or regeneration of the olfactory nasal epithelium.

The key assumption underlying the read-across of the EU-LCI value from n-propyl acetate to isopropyl acetate is that both compounds have the same critical endpoint and this is caused by their common chemical structure as an alkyl acetate. The effect is associated with the local formation of acetic acid by hydrolysis of the acetate ester, which, after exceeding the specific buffer capacity of the cells, leads to acidification and consequently cytotoxic damage (Hardisty et al., 1999).

Table 19: Comparison of the structure and molar mass of n- and isopropyl acetate

Compound	Structure	Molar mass (g/mol)	EU-LCI value
Isopropyl acetate (iPA)		102.1	Read-across Proposed: 2300 µg/m³
n-Propyl acetate (nPA)		102.1	Proposed: 2300 µg/m³ (rounded value)

- No cut-off rule in place: no difference in chain length between the two homologue compounds n-propyl acetate and isopropyl acetate.
- The derived EU-LCI value for n-propyl acetate of 2300 µg/m³ may be applied to isopropyl acetate without modification.

For the derivation of an EU-LCI value for isopropyl acetate, it is proposed to perform the read-across from n-propyl acetate.

An EU-LCI value of 2300 µg/m^3 is proposed for isopropyl acetate.

An odour threshold is reported for isopropyl acetate of 0.16 ppm (672 µg/m^3) (Nagata, 2003). It is expected that the odour of isopropyl acetate will be perceivable at the proposed EU-LCI value.

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D Appendix

D.1 Data collection and fact sheet for n- and isopropyl acetate

Table 20: Data collection sheet for n-propyl acetate

Compound	**n-Propyl acetate**	**Data collection sheet**		
Nº CAS: 109-60-4 1 ppm = 4.20 mg/m³ at 23 °C	**EU-Classification:** **CLP, harmonised classification:** Eye Irrit. 2, H319 ; STOT SE 3, H336			
Organisation name	**REACH registrants**	**AgBB**	**REACH registrants**	**DFG**
Risk value name	DNEL (general population)	NIK ('Lowest Concentration of Interest')	DNEL (workers)	MAK value (workplace)
Risk value (mg/m³)	150	4.2	420	420
Reference period	Chronic		Chronic (workplace)	Chronic (workplace)
Risk value (mg/m³) **Short term (15 min)**	300		840	840 ("excursion factor 2")
Year	2024	2024	2024	1999
Key study			Silverman et al., 1946	Silverman et al., 1946
Study type	Clinical study		Clinical study	Clinical study
Species	Human		Human	Human
Duration of exposure in key study	15 min		15 min	15 min

Compound	n-Propyl acetate	Data collection sheet		
Critical effect	Irritation of eyes and respiratory tract		Irritation of eyes and respiratory tract	Irritation of eyes and respiratory tract
Critical dose value	200 ppm (440 mg/m³)		200 ppm (440 mg/m³)	200 ppm (420 mg/m³)
Adjusted critical dose				
Single assessment factors	20 m³/10 m³ x 7 d/5 d = 2.8		2	2
Other effects				
Remarks	Derivation based on German MAK value of 100 ppm (420 mg/m³ for local effects; “no hazard identified” regarding systemic toxicity	Adopted ascribed EU-LCI-value	The German MAK value of 100 ppm (420 mg/m³) was adopted for local effects; “no hazard identified” regarding systemic toxicity	Peak limitation for category I substances (local irritant effect is limit-determining): exceedance factor 1

AgBB = Committee for Health-related Evaluation of Building Products

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

Table 21: Data collection sheet for isopropyl acetate

Compound	**n-Propyl acetate**	**Data collection sheet**		
N° CAS: 108-21-4 1 ppm = 4.20 mg/m³ at 23 °C	**EU-Classification:** **CLP, harmonised classification:** Eye Irrit. 2, H319; STOT SE 3, H336			
Organisation name	**REACH registrants**	**AgBB**	**REACH registrants**	**DFG**
Risk value name	DNEL (general population)	NIK ('Lowest Concentration of Interest')	DNEL (workers)	MAK value (workplace)
Risk value (mg/m³)	168 (systemic) 136 (local)	4.2	275 (systemic) 227 (local)	420
Reference period	Chronic		Chronic	Chronic
Risk value (mg/m³) **Short term (15 min)**	335		558 (systemic) - (local)	840 ("excursion factor 2")
Year	2020	2024	2020	1999
Key study	Burleigh-Flayer et al. (1997) (study with isopropanol)	See below	Burleigh-Flayer et al. (1997) (study with isopropanol)	Silverman et al., 1946 (study with isopropyl acetate)
Study type	Inhalation study		Inhalation study	Clinical study
Species	Rat		Rat	Human
Duration of exposure in key study	Subchronic		Subchronic	15 min
Critical effect	Decreases in red blood cell parameters and the during-exposure clinical signs		Decreases in red blood cell parameters and the during-exposure clinical signs	Irritation of eyes and respiratory tract
Critical dose value	NOAEC: 1675 mg/m³ (systemic)* BMCL10: 272 mg/m³ (local)		NOAEC: 1650 mg/m³ (systemic)* BMCL10: 272 mg/m³ (local)	200 ppm (420 mg/m³)

Compound	**n-Propyl acetate**	**Data collection sheet**		
Adjusted critical dose				
Single assessment factors	UF_S 2, UF_H 5 (systemic) UF_S 2, UF_A 0.2, UF_H 5 (local)		UF_H 3, UF_S 2 (systemic) UF_S 2, UF_A 0.2, UF_H 3 (local) (local)	2
Other effects				
Remarks	See below*	Adopted ascribed EU-LCI-value	See below*	Peak limitation for category I substances (local irritant effect is limit-determining): exceedance factor 1

AgBB = Committee for Health-related Evaluation of Building Products

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

*: *"Adequate studies of the repeated dose toxicity of isopropyl acetate were not found. The repeated dose toxicity of the in vivo hydrolysis product, isopropanol, has been studied by inhalation in rats and mice. The NOAEL of 500 ppm isopropanol seen in the rat and mouse corresponds to 394 ppm (1.675 mg/L) isopropyl acetate and a LOAEL of 1500 ppm isopropyl alcohol corresponds to 1181 ppm (4.9 mg/L) isopropyl acetate after correcting for differences in total respiratory bioavailability* [no further explanation given].

"Exposure to high concentrations of isopropyl acetate or the in vivo hydrolysis product isopropanol have been reported to produce narcosis in exposed rats. No persistent neurotoxicity was seen in subchronic studies of isopropanol. Data on ethyl acetate can be used to predict the potential for local effects through hydrolysis in the URT. Based on this available data, the BMDL10 for isopropyl acetate is predicted to be in the region 272 – 523mg/m³." (ECHA Chemicals Database, 2020).

"The PBPK model [no further explanation provided] *shows that for the end point that give the most conservative (lowest) value for the point of departure, the difference between the inhaled concentrations required to deliver the same concentrations of acetic acid in rats versus humans is a factor of 5.8. This is rounded down to 5 to give an AF for interspecies difference other than allometry of 0.2."* (ECHA Chemicals Database, 2020).

Table 22: Fact sheet for n-propyl acetate (nPA)

Compound	n-Propyl acetate C5H10O2		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	2300
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2025
General information			
CLP-Index No.	4	INDEX	607-024-00-6 (identical with that for isopropyl acetate)
EC-No.	5	EINECS	203-686-1
CAS-No.	6	Chemical Abstract Service number	109-60-4
Harmonised CLP classification	7	Human health risk related classification	Eye Irrit. 2, H319 STOT SE 3, H336
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	102.1 1 ppm = 4.20 mg/m³ 1 mg/m³ = 0.24 ppm
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	ECHA Dissemination (2024)
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
Exposure duration	14	h/d, d/w	6 h/d, 5 d/week
Critical endpoint	15	Effect (s), site of	Effects in nasal cavity: degeneration and/or regeneration of the olfactory epithelium
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEC
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	150 ppm
Assessment factors (AF)			
Adjustment for exposure duration	19	Study exposure h/d, d/w	5.6
Study length	20	sa→sc→c	2

Compound	n-Propyl acetate C5H10O2		Fact sheet
Route-to-route extrapolation factor	21	-	1
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	1
	22b	Severity of effect (R8 6d)	1
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	1
	23b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		1
Other adjustment factors Quality of database	26	Quality of database	1
Results			
Summary of assessment factors	27	Total Assessment Factor	280
POD/TAF	28	Calculated value [µg/m³ and ppb]	2251 µg/m³ and 536 ppb
Molar adjustment factor	29		
Rounded value	30	[µg/m³]	2300
Additional comments	31		
Rationale selection	32		

Rationale for critical effects

The two isomer aliphatic esters, n-propyl acetate (nPA) and isopropyl acetate (iPA), are colourless, only slightly water-soluble liquids with a moderate vapour pressure (at 20 °C) of 33 hPa (nPA) or 60.3 hPa (iPA), respectively (ECHA Chemicals Database, 2020, 2024). Both esters have a fruity odour. The reported odour thresholds are 0.24 ppm (1.01 mg/m^3) for nPA and 0.16 ppm (0.67 mg/m^3) for iPA (Nagata, 2003).

Both compounds are large-scale industrial products (EU tonnage band ≥ 10000 – < 100000 t/a) which, as similar alkyl acetates, are used as solvents in a variety of applications, e.g. for coatings and in printing, but also as synthetic flavour and adjuvant in food (OECD SIDS, 2005; 2009).

Data on the occurrence of n- and isopropyl acetate in indoor air from studies carried out in Germany showed that nPA could be detected in about 3 % of 1250 measurements and iPA in about 8 % of 1501 measurements, with concentrations mostly around 1 – 2 µg/m^3 with maximum values of 50 or 100 µg/m^3, respectively (Hofmann and Plieninger, 2008).

Toxicokinetic data regarding the hydrolysis of the esters are available from respiratory bioavailability studies in rats. Inhalation exposure of rats with 2000 ppm nPA or iPA,

respectively, demonstrated the rapid hydrolysis of the esters with the formation of the corresponding alcohol. Blood levels of n-propyl alcohol were about 2.6 to 7.7fold higher than that of nPA and that of isopropyl alcohol were between 2 and 10fold higher than that of iPA within the 90 min exposure interval (OECD 2005; 2009).

Thus, as with similar other alkyl acetates, e. g. ethyl and n-butyl acetate, nPA and iPA can be expected to be hydrolysed following contact with the mucous membranes or absorption into the organism. In a study with butyl acetates, hydrolysis was detected in rat nasal tissue preparations *in vitro* (AGS, 2018; ECHA Dissemination, 2024; WHO, 2005).

Following enzymatic hydrolysis of nPA by esterases, the n-propanol formed is oxidised to propanal and further to propanoic acid, which is an endogenous substance in mammalian metabolism. Propanoic acid is further metabolised via the methylmalonyl pathway and may enter the citric acid cycle (AIR, 2022, 2023).

In case of iPA, the hydrolysis product isopropanol is oxidised in a first step to acetone by the alcohol dehydrogenase of the liver. Acetone is either exhaled or eliminated unchanged in the urine or further metabolised via hydroxypropanone (hydroxyacetone) in further metabolic reactions involving microsomal monooxygenases and other enzymes. Minor amounts of isopropanol are conjugated and excreted as glucuronide in the urine (AIR, 2021).

Acetic acid formed during the hydrolysis of these esters is largely utilised via the citric acid cycle or for the synthesis of fatty acids.

The acute toxicity of nPA and iPA in animals is low.

All six rats survived a 30 min, but not a 60 min exposure to an atmosphere almost saturated with nPA vapour (no further details reported). In another study, all six rats survived a 4-hour exposure with 4000 ppm (about 16800 mg/m^3) nPA. 4 of 6 rats died at 8000 ppm (about 33600 mg/m^3), and all 6 rats died at 16000 ppm (about 67200 mg/m^3). A 4-h LC50 of about 7620 ppm (32000 mg/m^3) nPA was calculated based on these data (ECHA Chemicals Database, 2020). In this study, animals were inactive at 4000 ppm and became unconscious during exposure with the two higher concentrations. At necropsy, animals dying during exposure showed pulmonary haemorrhages, and necropsy of surviving animals revealed evidence of earlier lung damage (OECD, 2009). For iPA, an 8-hour LC50 of 12114 ppm (about 50900 mg/m^3) is reported for female rats. A 4-hour exposure of rats led to the death of one of the six 6 animals exposed to 32000 ppm and 5 of the 6 rats at 32000 ppm iPA (OECD, 2005).

Oral LD50 of 8700 mg nPA/kg bw and of 9370 mg iPA/kg bw are reported for male or male and female rats, respectively. A dermal LD50 of > 17800 mg nPA/kg bw is reported for male rabbits (ECHA Chemicals Database, 2024). For iPA, oral LD50 in the range of 3000 to 14964 mg/kg bw are reported for rats and 6650 and 6945 mg/kg bw for mice and rabbits, respectively. A dermal LD50 of > 17400 mg iPA/kg bw is reported for male rabbits (ECHA Chemicals Database, 2020).

Sensory irritation was observed at high concentrations of n- and isopropyl acetate in Alarie tests with mice: An RD50 (concentration leading to a decrease in breathing rate by 50 % as sign of respiratory irritation) of 3311 mg/m^3 (about 788 ppm) is reported for n-propyl acetate and of 17783 mg/m^3 (about 4234 ppm) for isopropyl acetate (Bos et al., 1992; Muller and Greff, 1984).

Limited data are available from studies with humans, mostly from older studies and with limited exposure measurements and data presentation. The results were summarised as follows (DFG, 1999):

Irritation of the skin, eyes and mucous membranes was reported after exposure with propyl acetates. Furthermore, effects on the central nervous systems (CNS) and even narcosis are to be

expected at higher concentrations, but no data for the effect thresholds are available. Some information can be gathered from earlier studies with volunteers: Exposure for 5 min in a room in which 3 min before n-propyl acetate had been sprayed and distributed evenly, led to mild irritation of the airways, the eyes, nose and throat at the low concentration of 1000 mg/m^3. At 15000 mg/m^3 all these symptoms were still described as weak. The volunteers felt cold and reported dryness in the throat and airways and slight lacrimation. In another study with exposure to n-propyl acetate for about 2 sec, a threshold value of 17600 ppm was given for nasal irritation in anosmic persons (DFG, 1999).

In another study, during exposure for 15 minutes to isopropyl acetate, most of the 12 volunteers found 200 ppm to be irritative for the eyes and concentrations above 200 ppm also for nose and throat. The odour nuisance of 200 ppm was reported to be slight. 100 ppm was regarded by the test persons as acceptable for an 8-hour exposure (DFG, 1999).

Liquid nPA (0.5 ml undiluted) led to diffuse corneal injury (Grade 2 on Draize) which healed quickly and was thus regarded as irritating to eyes. Similarly, Grade 2 corneal necrosis was reported following instillation of 0.5 ml undiluted iPA into rabbit eyes. Furthermore, two clinical cases from an occupational survey are mentioned in which iPA caused chemical burns and healing was slow (3 – 10 d) after mechanical removal of the affected epithelium cells (ECHA Chemicals Database, 2020, 2024).

On the skin of rabbits, nPA and iPA caused at most very slightly erythema and no oedema in irritation studies (ECHA Chemicals Database, 2024a, b; OECD, 2005). Application of large amounts of nPA at concentrations up to 10 ml/kg bw in guinea pigs or 20 ml/kg bw in rabbits under occluded conditions, however, led to erythema, desquamation and necrosis (OECD, 2009).

No skin sensitisation was observed in a maximisation test with closed patch application of nPA (2 % in petrolatum) in humans (9 M + 16 F) (ECHA Chemicals Database, 2024).

In vivo animal studies with nPA regarding skin sensitisation are not available. The results on an *in vitro* test (OECD Guideline 442D: *In Vitro* Skin Sensitisation: ARE-Nrf2 luciferase KeratinoSens™ test method) and of QSAR calculations were considered negative (ECHA Chemicals Database, 2024b). No data are available for iPA. It was noted that other analogue alcohol esters of acetic acid, for example ethyl acetate and butyl acetates, have been studied and are not dermal sensitisers (ECHA Chemicals Database, 2024).

No data are available on respiratory sensitising effects of nPA or iPA.

Repeated dose toxicity studies with n- or isopropyl acetate in humans are not available.

Local irritation of eyes with lacrimation, salivation, and CNS-depressant effects were observed in two cats exposed to about 5200 ppm n-propyl acetate (about 21840 mg/m^3) 6 h/d for five times. Autopsy in one cat revealed tracheitis, bronchitis, lung emphysema, and fatty liver. No clinical signs were observed in the other animal during a several week follow-up period (DFG, 1999).

In a 14-day range finding inhalation toxicity study conducted prior to a subchronic study (see below), Wistar rats (4 M + 4F/group) were exposed whole-body to 0, 1000, or 3000 ppm (0, 4200, 12600 mg/m^3) n-propyl acetate 6 h/day on 14 consecutive days. At 3000 ppm, local effects in the nasal epithelia were observed (minimal to severe multifocal degeneration/regeneration of olfactory epithelium) in all male and female animals. Systemic effects observed were reduced mean body weight in males and reduced body weight change in both males and females, and, accordingly, lower terminal body weight of both males and females compared to control. The local effect in the nasal cavity was also observed at 1000 ppm, though

less severe. Reduced body weight change was observed only in females at the low concentration (ECHA Chemicals Database, 2024).

In a subchronic inhalation toxicity study (OECD guideline 413) with n-propyl acetate, Wistar rats (10 M + 10 F/group) were exposed "whole body" to 0, 150, 500, or 1500 ppm of vapour (0, 630, 2100, 6300 mg/m^3) 6 h/d, 5 d/week for 13 weeks. The analytically determined concentrations of nPA (148.5, 505.2, 1528.7 ppm) were very close to the target concentrations.

Transiently reduced attention, probably due to a narcotic effect of the test substance, was observed in both male and female animals during exposure to 1500 ppm from day 14 to 44 in males and 13 to 43 in females. The effect was no longer observed shortly after the termination of each daily exposure. No other substance-related clinical signs of toxicity or any abnormalities during examinations of FOB and MA were observed. Effects on body weight or weight gain and food consumption were noted at 1500 ppm. The lowered mean body weight or mean body weight gains were consistent with the reduced food consumption. The same tendency was observed in males at 500 ppm. The mean terminal body weight of male animals was significantly lower than the concurrent control. The effects were likely secondary to the local effects observed in nasal cavity (see below). No adverse histological findings in other organs were observed. Weight changes of different organs (kidney, liver, adrenal glands, uterus, brain, testes, lungs, and heart) were considered as secondary to the changes of body weights (ECHA Chemicals Database, 2024).

The target organ was the nasal cavity where concentration-dependent effects were observed in the olfactory epithelium. Six male and female animals at 500 ppm and all males and females at 1500 ppm showed a focal or multifocal degeneration and/ or regeneration in the olfactory epithelium at different levels at the dorsal part of septum, nasoturbinate, and/or ethmoid turbinate of the nasal cavity. The severity ranged from minimal to severe. No effects were observed at 150 ppm (630 mg/m^3) (NOAEC) (ECHA Chemicals Database, 2024).

The only identified study with repeated exposure to isopropyl acetate must be considered unreliable. In this study, mice (no further data) were exposed to a single concentration of 200000 mg/m^3 isopropyl acetate 4 h/d, 5 d/week for 4 weeks and maintained for 2 weeks after exposure. No effects were seen in general appearance, and there were no significant effects on body weight. The authors conclude that isopropyl acetate is faintly narcotic. Note that the reported exposure level exceeds the saturated vapour concentration (ECHA Chemicals Database, 2020). No further details were available.

Regarding genotoxicity, n-propyl acetate was not mutagenic *in vitro* in the presence or absence of exogenous metabolic activation system (S9-mix) in OECD guideline tests in bacteria and in mammalian cells (HPRT-assay in CHO cells and micronucleus assay in TK6 cells). (ECHA Chemicals Database, 2024).

Isopropyl acetate was not mutagenic *in vitro* in the presence or absence of exogenous metabolic activation system (S9-mix) in OECD guideline tests in bacteria. Isopropanol, the alcohol produced by hydrolysis of iPA, was not mutagenic with and without S9-mix in a HPRT assay in CHO cells (ECHA Chemicals Database, 2020).

In vivo data are not available for both compounds. Isopropanol did not induce micronuclei in the bone marrow of mice after intraperitoneal injection of up to 2500 mg/kg bw (ECHA Chemicals Database, 2020). No valid study could be identified for n-propanol.

Mutagenic effects of acetic acid observed in some studies on bacteria and mammalian cells are attributed to the non-physiological acidification of the culture medium and not to a substance-specific effect (Heldreth, 2012).

Carcinogenicity studies with n- or isopropyl acetate are not available. The available genotoxicity data do not raise concern for a genotoxic non-threshold carcinogenic effect of both compounds.

Inhalation carcinogenicity studies conducted with isopropyl alcohol in rats and mice have shown that isopropyl alcohol does not exhibit carcinogenic potential relevant to humans. Testicular tumours seen in isopropanol-exposed male rats are considered to have no significance for human cancer risk assessment (Burleigh-Flayer et al., 1997; OECD SIDS, 2005).

Overall, the data for C_2 – C_4 alkyl acetate esters reveal that the chemicals of this group have no mutagenic or genotoxic potential (AICIS, 2014).

An extended one-generation reproductive toxicity (EOGRT) study according to OECD guideline 443 was conducted with oral n-propyl acetate exposure of rats. In the parental generation, the animals (28 M + 28 F/group) received 0, 100, 300, or 1000 mg/(kg bw x d) for two weeks prior to mating, during mating (two weeks), gestation (three weeks) and lactation (three weeks). In cohort 1A, pups (20 M + 20 F/group) selected from different litters of the parental generation received the same doses as their parents from day 21 of age up to day 72 – 78. Again, no other treatment-related effects than salivation could be observed. Cohort 1B (25 M + 25 F/group) selected from different litters of the parental generation received the same doses as note above for 10 days prior to breeding (from day 21 of age), during mating (two weeks), gestation (three weeks) and lactation (three weeks). In the parental generation, cohort A and B, salivation at 1000 mg/(kg bw x d) was the only sign related to treatment. No other treatment-related effects were seen in any parameters investigated. 1000 mg/(kg bw x d), the highest dose tested, was considered the NOAEL for systemic toxicity, reproductive toxicity and pup development (ECHA Chemicals Database, 2024).

In a range-finding study for a reproduction/developmental toxicity screening test (following OECD Guideline 421), Wistar rats received 0, 300, or 1000 mg nPA/(kg bw x d) per gavage for 4 weeks before pairing and during gestation and lactation periods. 10 M + 10 F pups were selected (F1 generation) to evaluate the effect of the test item on offspring, dosed for a total of 7 days from weaning (from day 21 to day 28 of age). In addition, reproductive performance such as conception, development of the conceptus and parturition was also examined. Salivation occurred in males and females treated with ≥ 300 mg/(kg bw x d). This sign was considered to be a test item-related effect, but non-adverse. Up to the highest dose level of 1000 mg/(kg bw x d) tested, there were no substance-related effects on fertility or development (ECHA Chemicals Database, 2024).

In a developmental toxicity study following OECD guideline 414, 25 pregnant Wistar rats/group received 0, 100, 300, or 1000 mg nPA/(kg bw x d) nPA in corn oil via gavage on GD 6 – 19. Analytical data showed that that the actual concentration of the low dose was 138 mg/(kg bw x d). There were no test substance-related adverse effects on dams, gestational parameters or foetuses at any dose level of n-propyl acetate. The NOAEL was thus assessed as 1000 mg/(kg bw x d), the highest dose tested, for maternal and foetal developmental toxicity (ECHA Chemicals Database, 2024).

In a similar OECD guideline 414 study, pregnant New Zealand White Rabbits (24 F/group) were given 0, 100, 300, or 1000 mg/(kg bw x d) of nPA in 0.5 % methylcellulose in water by gavage on GD 7 – 27. Treatment-related effects were observed in dams at 1000 mg/(kg bw x d): an increased incidence of transiently decreased faeces and a mean body weight loss from GD 7 – 10 with concomitant decreases in feed consumption, leading to an overall 22.5 % decrease in body weight gain from GD 7 – 28 compared to controls. Body weights were decreased at 300 mg/(kg bw x d) on GD 7 – 10 compared to controls, but overall, weight gains were similar to controls over the entire treatment period (GD 7 – 28). There were no treatment-related differences in

gross pathologic observations or maternal kidney or liver weights and no indications of embryo/foetal toxicity or teratogenicity at any dose level. The reported NOAEL for maternal toxicity was 300 mg/(kg bw x d) and for developmental toxicity 1000 mg/(kg bw x d), the highest dose tested (ECHA Chemicals Database, 2024).

No reproductive toxicity studies are available for isopropyl acetate. However, studies were performed with isopropanol. The results are summarised as follows:

A 2-generation study (according to OECD guideline 416) was conducted in rats with gavage administration of 0, 100, 500 or 1000 mg isopropanol/(kg bw x d). The animals were exposed from the 10th week before mating. At ≥ 500 mg/(kg bw x d), weight gain during lactation was increased in the female animals and liver and kidney weights were increased in both sexes. In the F1 generation of the high-dose group, body weight was reduced and mortality increased in the early postnatal period. The F2 offspring in the high-dose group again had a reduced body weight. At the highest dose, the mating index of the males of the F1 generation was statistically significantly reduced from 93.3 to 73.1 % compared to the control. Benchmark calculations were carried out for the endpoints "reduced postnatal survival rate" in the F1 and F2 generations. These resulted in a BMDL10 of 449 and 418 mg/(kg bw x d), respectively. A BMDL5 of 407 mg/(kg bw x d) was calculated for the endpoint "male mating index". Further details on the calculation are not available (AIR, 2021; OECD, 2005).

The developmental toxicity of isopropanol via inhalation exposure was studied in pregnant rats. The animals were exposed whole body to measured concentrations of 3500, 7000 and 10000 ppm of substance vapour for 7 h/d on GD 0 – 19. In dams, narcotic effects, reduced body weight gain and reduced food intake were observed at ≥ 7000 ppm. Effects were severe in the high-dose group, and the number of offspring in the high-dose group was reduced. There was a dose dependent drop in foetal body weight across all groups. This effect was small (4 %) in the low-dose group and considered close to a NOAEC. The NOAEC for both developmental and maternal effects was determined to be 3500 ppm (equivalent to about 875 mg/(kg bw x d)) (ECHA Chemicals Database, 2020).

In a study with pregnant rats exposed via gavage to 0, 400, 800, or 1200 mg/(kg bw x d) on GD 6 – 15, the NOAEL for maternal toxicity was 400 mg/(kg bw x d), based on a small increase in mortality at higher doses. Gravid uterine weight and male and female average foetal weights were reduced by about 5 % at the mid-dose and more in the high-dose group. At the highest dose, gestational weight gain was reduced. There was no evidence of teratogenicity up to the maximum tested dose of 1200 mg/(kg bw x d). The NOAEL for maternal and foetal toxicity was 400 mg/(kg bw x d) (ECHA Chemicals Database, 2020).

In a similarly conducted developmental toxicity study with pregnant New Zealand rabbits treated during GD 6 – 18 at doses of 120, 240 and 480 mg isopropanol/(kg bw x d) by gavage, the NOAEL for maternal toxicity was 240 mg/(kg bw x d) with no evidence of teratogenicity up to the maximum tested dose of 480 mg/(kg bw x d) (ECHA Chemicals Database, 2024a).

Exposure of pregnant rats 0, 0.5, 1.25 and 2.5 % isopropanol in drinking water (0, 596, 1242 and 1605 mg/(kg bw x d)) during GD6 – 16 provided a NOAEL for maternal and developmental effects of 596 mg/(kg bw x d). Maternal toxicity at the two higher doses manifested in the form of a reduced food and water intake along with a suppression in body weight growth. All reproductive parameters were normal across all dose groups. The only sign of foetotoxicity was a slight reduction in average litter weights in the mid- and high-dose groups, probably reflecting the weight loss seen in the dams. No external or visceral malformations were seen (ECHA Chemicals Database, 2020).

Regarding acetic acid, the German MAK commission stated that the active principle of any potential prenatal toxicity of acetic acid could be acidosis. However, inhalation exposure to a very high concentration of 54000 mg nPA/m^3 for two hours did not lead to such an effect. Also, exposure of rabbits on GD 6 – 18 to vinegar (about 80 mg acetic acid/(kg bw x d)) did not lead to maternal or developmental toxicity (DFG, 1999).

Rationale for starting point for n-propyl acetate

The subchronic inhalation toxicity study with n-propyl acetate on rats (ECHA Chemicals Database, 2024) is taken as the basis for the derivation of the EU-LCI. This study provided a NOAEC of 150 ppm (630 mg/m^3).

Rationale for assessment factors

The NOAEC of 150 ppm was chosen as POD. The following assessment factors are used:

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

Total assessment factor: 280 leading to a value of 150 ppm: 280 = 0.536 ppm (2250 µg/m^3, rounded to 2300 µg/m^3).

An EU-LCI value of 2300 µg/m^3 is proposed for n-propyl acetate.

An odour threshold of 0.24 ppm (1008 µg/m^3) was determined by Nagata (2003). It is expected that the odour will be perceivable at the proposed EU-LCI value.

Table 23: Fact sheet for isopropyl acetate (iPA)

Compound	Isopropyl acetate C5H10O2		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	2300
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2025
General information			
CLP-Index No.	4	INDEX	607-024-00-6 (identical with that for n-propyl acetate)
EC-No.	5	EINECS	203-561-1
CAS-No.	6	Chemical Abstract Service number	108-21-4
Harmonised CLP classification	7	Human health risk related classification	Eye Irrit. 2 (H319), STOT SE 3 (H336)
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	102.1 1 ppm = 4.20 mg/m³ 1 mg/m³ = 0.24 ppm
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	n-Propyl acetate
Species	11	Rat, human, etc.	
Route / type of study	12	Inhalation, oral feed, etc.	
Study length	13	Days, subchronic, chronic, etc.	
Exposure duration	14	h/d, d/w	
Critical endpoint	15	Effect (s), site of	
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	
POD value	17	[mg/m³] or ppm or [mg/kg_{BW}×d]	EU-LCI value of n-propyl acetate
Assessment factors (AF)			
Adjustment for exposure duration	19	Study exposure h/d, d/w	-
Study length	20	sa→sc→c	-
Route-to-route extrapolation factor	21	-	-

Compound	Isopropyl acetate C5H10O2		Fact sheet
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	-
	22b	Severity of effect (R8 6d)	-
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	-
	23b	Kinetic + dynamic	-
Intraspecies differences	24	Kinetic + dynamic General population	-
AF (sensitive population)	25		-
Other adjustment factors Quality of database	26	Quality of database	-
Results			
Summary of assessment factors	27	Total Assessment Factor	-
POD/TAF	28	Calculated value [µg/m³ and ppb]	
Molar adjustment factor	29		1
Rounded value	30	[µg/m³]	2300
Additional comments	31		
Rationale selection	32		

Rationale for read-across

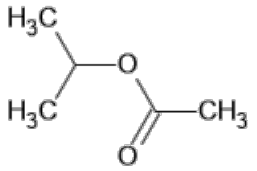
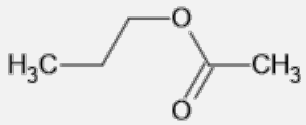
The EU-LCI derivation for isopropyl acetate (iPA) was conducted via read-across with n-propyl acetate (nPA), following the principles described in EC (2013). The key assumption is that nPA is the closest homologue with sufficient existing toxicological data and an already derived EU-LCI value:

- Data poor compound: insufficient data for iPA.
- Read-across from nPA: within the chemical group of "propyl acetates", nPA is the closest homologue compound with an adequate data base. The only difference between the two substances is the branched propyl group, i. e. a 2-methylethyl group in iPA instead of the straight-chain propyl group in nPA.
- Toxicological critical endpoint for nPA: degeneration and/or regeneration of the olfactory nasal epithelium.

The key assumption underlying the read-across of the EU-LCI value from nPA to iPA is that both compounds have the same critical endpoint and this is caused by their common chemical structure as an alkyl acetate. The effect is associated with the local formation of acetic acid by

hydrolysis of the acetate ester, which, after exceeding the specific buffer capacity of the cells, leads to acidification and consequently cytotoxic damage (Hardisty et al., 1999).

Table 24: Comparison of the structure and molar mass of n- and isopropyl acetate

Compound	Structure	Molar mass (g/mol)	EU-LCI value
Isopropyl acetate (iPA)		102.1	Read-across Proposed: 2300 µg/m³
n-Propyl acetate (nPA)		102.1	Proposed: 2300 µg/m³ (rounded value)

- No cut-off rule in place: no difference in chain length between the two homologue compounds nPA and iPA.
- The derived EU-LCI value for nPA of 2300 µg/m³ may be applied to iPA without modification.

For the derivation of an EU-LCI value for isopropyl acetate, it is proposed to perform the read-across from n-propyl acetate.

An EU-LCI value of 2300 µg/m³ is proposed for isopropyl acetate.

An odour threshold is reported for iPA of 0.16 ppm (672 µg/m³) (Nagata, 2003). It is expected that the odour of isopropyl acetate will be perceivable at the proposed EU-LCI value.

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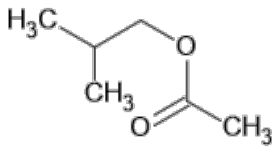
5 Toxicological evaluation of isobutyl acetate as basis for the derivation of an EU-LCI value

5.1 Substance identification

Isobutyl acetate (2-methylpropyl ethanoate) belongs to the group of aliphatic esters. Substance identification data of isobutyl acetate are shown in Table 25.

Table 25: Substance identification of isobutyl acetate (ECHA Chemicals Database, 2019)

CAS-No. EC-No. CLP-Index-No.	Systematic name, common name	Sum formula	Structural formula
110-19-0 203-745-1 607-026-00-7	2-methylpropyl ethanoate, isobutyl acetate, acetic acid isobutyl ester	$C_6H_{12}O_2$	

5.2 Substance properties and uses

The physiochemical properties of isobutyl acetate are shown in Table 26.

At room temperature, isobutyl acetate is a colourless liquid with a fruity odour. The substance is moderately soluble in water, soluble in acetone, and miscible with methanol, ethanol, and diethyl ether. It occurs naturally in fruits, e. g., apples, pears, nectarines, pineapples, and bananas (ECHA Chemicals Database, 2019; PubChem, 2024).

Table 26: Physicochemical properties of isobutyl acetate (ECHA Chemicals Database, 2019)

Molar mass (g/mol)	Melting point (°C)	Boiling point (°C)	Vapour pressure (hPa) at 20 °C	Conversion 1 ppm = x mg/m³ at 23 °C	log pow at 25 °C	Solubility in water (g/L) at 20 °C
116.2	-90	117	21		2.3	5.6

According to REACH, isobutyl acetate is registered in a total tonnage band ≥ 10000 to < 100000 tonnes/a. The substance is used as a solvent in a wide variety of products such as coatings and paints, thinners, paint removers, in cleaning agents and in the manufacture of other chemicals. Isobutyl acetate is also used in personal care products such as cosmetics, perfumes, and fragrances, and as a flavouring agent (ECHA Chemicals Database, 2019; PubChem, 2024).

5.3 Exposure

5.3.1 Indoor air

Data on the occurrence of isobutyl acetate are presented in Table 27.

Indoor releases into the air may occur from consumer products but also from natural sources such as fruits and food (PubChem, 2024). Isobutyl acetate is among those substances which are very often measured in indoor air, but concentrations rarely exceed 10 µg/m^3 (Hofmann and

Plieninger, 2008; Ostendorp and Heinzow, 2013; Ostendorp et al., 2009), including measurements conducted after complaints about indoor air quality (Petzold, 2015).

Within the substance group of carboxylic acid esters, n-butyl acetate was detected in almost all households (97 %) above the limit of quantification in the German Environmental Survey for Children and Adolescents 2014–2017 (GerES V, Part 2: Indoor Air Quality), however, no data were reported for isobutyl acetate (Lahore et al., 2025).

Table 27: Data on the occurrence of isobutyl acetate in indoor air

Indoor location	N	LoD (µg/m³)	N > LoD	Median (µg/m³)	P95 (µg/m³)	Maximum (µg/m³)	Source
Not further specified, Germany, 2006-2012	2143	not reported	517	0.5	9.7	46.2	(Hofmann and Plieninger, 2008)
Schools, kindergartens, Schleswig-Holstein, Germany, 2005-2007	285	2	6	< 2	< 2	26	(Ostendorp et al., 2009)
Public buildings: retirement and care homes, Schleswig-Holstein, Germany, 2012-2013	44	Not reported	1	-	-	2.0	(Ostendorp and Heinzow, 2013)
Schools, kindergartens and office workplaces, complaint-related measurements, Schleswig-Holstein, Germany, 2006-2011	1897	Not reported	22	< 1	< 1	14	(Petzold, 2015)

5.3.2 Other sources

Since isobutyl acetate is a naturally occurring constituent of many fruits, oral exposure of humans is to be expected. Furthermore, dermal exposure may occur from the use of isobutyl acetate in perfumes and other cosmetics. However, data are insufficient to estimate human exposure from all routes (WHO, 2005).

5.4 Toxicokinetics

It is assumed that isobutyl acetate is rapidly absorbed after inhalation exposure; quantitative data are, however, not available. For the isomeric n-butyl acetate, it is stated that about 50 % of the inhaled compound is found in the exhaled air after inhalation exposure with 42 ppm (about 200 mg/m^3). According to animal data, n-butyl acetate is well absorbed in the lungs (100 % of alveolar ventilation), and the maximum concentration in the blood after inhalation of 2000 ppm (about 9600 mg/m^3) will be reached within 10 min (ECHA Chemicals Database, 2019; SCOEL, 2016).

Regarding the metabolism of isobutyl acetate, no relevant qualitative species differences in mammals are known. In the initial step, isobutyl acetate, n butyl acetate, and *sec*-butyl acetate are rapidly hydrolysed to acetic acid and the respective alcohols in blood, liver, small intestine, and respiratory tract, as has been shown in a number of *in vitro* experiments using homogenates

from liver, small intestinal mucosa, and ethmoturbinates (AGS, 2018; ECHA Chemicals Database, 2019; SCOEL, 2016).

Enzymatic hydrolysis of isobutyl acetate to isobutanol (2-methylpropan-1-ol) and acetic acid already occurs at contact of the ester with the mucous membranes of the upper respiratory tract. In rat nasal tissue preparations *in vitro,* hydrolysis was detectable for all butyl acetate isomers including isobutyl acetate; the reaction rate decreased with increasing degree of branching. An inhalation experiment in rats *in vivo* with isobutyl acetate confirmed the rapid hydrolysis of the ester: Upon exposure to 200 ppm isobutyl acetate, the concentration of the hydrolysis product isobutanol in the blood of the animals was already twice as high as that of isobutyl acetate itself 5 min after the start of exposure (AGS, 2018; ECHA Dissemination, 2024; WHO, 2005).

In S9-mix from rat liver, the rate of enzymatic hydrolysis of isobutyl acetate was comparable (87 %) to that of n-butyl acetate. Following enzymatic hydrolysis of isobutyl acetate by esterases, isobutanol is conjugated to a minor extent with glucuronic acid or sulphate and excreted as conjugates in the urine. Very small amounts of isobutanol may be excreted unchanged via urine or exhaled breath. The major pathway involves oxidation of isobutanol to the corresponding aldehyde and further to isobutanoic acid (isobutyric acid, 2-methylpropanoic acid). The latter is metabolised via methylmalonic acid to succinic acid which is utilised in the citric acid cycle. Acetic acid formed during the hydrolysis of isobutyl acetate is also largely utilised via the citric acid cycle or for the synthesis of fatty acids (AGS, 2018; ECHA Chemicals Database, 2019; SCOEL, 2016).

5.5 Health effects

The data base regarding the toxicity of isobutyl acetate is limited. Read-across using data from studies with n-butyl acetate or, in case of systemic effects, additionally from studies with isobutanol are used for the evaluation.

5.5.1 Acute toxicity, sensory irritation, and local effects

Acute toxicity

No data are available regarding acute systemic toxic effects of isobutyl acetate in humans. The structural isomer n-butyl acetate did not cause any significant central nervous system symptoms (headache, vertigo, nausea and tiredness) during or after exposure with up to 1400 mg/m^3 (Iregren et al., 1993; SCOEL, 2016).

Based on animal data, high vapour concentrations of isobutyl acetate are likely to cause narcotic effects on the CNS with, e.g., drowsiness and dizziness. However, no information is available on the concentrations of isobutyl acetate at or above such effects are to be expected in humans (AGS, 2018; DFG, 1999).

The acute toxicity of isobutyl acetate in animals is low:

All six rats survived a one-hour exposure to an atmosphere almost saturated with isobutyl acetate vapour (approx. 20000 ppm, corresponding to about 97400 mg/m^3), as well as six hours of exposure to 3500 ppm (about 17000 mg/m^3). All six female rats survived an exposure to 4000 ppm (about 19500 mg/m^3) for 4 hours; at 8000 ppm (about 39000 mg/m^3) 4 of the 6 animals died; at 16000 ppm (about 78000 mg/m^3) all 6 animals died between the third and fourth hour of exposure. Clinical symptoms during exposure included an anaesthetic effect of isobutyl acetate, and death occurred due to damage to the capillaries in the lung. A 4-h-LC50 of

6200 ppm (about 30200 mg/m^3) was estimated from these data (AGS, 2018; ECHA Chemicals Database, 2019).

An oral LD50 of 13413 mg/kg bw was determined for male rats, clinical signs and the cause of death were not reported. For rabbits, an LD50 of 4763 mg/kg bw is presented, referring to deaths occurring within 24 hours. A narcotic dose (ND50) of 4298 mg/kg bw is also reported, higher doses caused disappearance of corneal reflexes, nystagmus, dyspnea, and bradycardia (ECHA Chemicals Database, 2019).

In a dermal toxicity study, male rabbits were exposed for 24 h to isobutyl acetate (occlusive wrap, 14 days post-observation, no further details). The acute dermal LD50 for isobutyl acetate was determined to be > 17400 mg/kg bw (ECHA Chemicals Database, 2019).

Irritation

No acute inhalation studies with iBA are available in humans.

Read-across: However, some data are available for n-butyl acetate from older studies (nominal concentrations reported): Overall, effects of n-butyl acetate may be expected at ≥ 200 ppm (about 970 mg/m^3) after short-term exposure for 5 to 20 minutes. Irritation of the throat was described by volunteers exposed for 3 – 5 min to 200 – 300 ppm and, additionally, of eyes and nose at 300 ppm. Moderate irritation effects were reported after inhalation of 2100 ppm for 5 min (AGS, 2018; SCOEL, 2016).

A clinical study on irritation effects of n-butyl acetate was conducted in human volunteers without previous occupational exposure (Iregren et al., 1993; SCOEL, 2016). Three experiments with different exposure levels were conducted:

1. Four 20-minute sessions with 24-hour intervals at 350, 700, 1050 and 1400 mg/m^3 (72, 145, 217 and 290 ppm) (n=24 volunteers). Under these conditions, irritation ratings were not significantly different from baseline level before exposure for any of the exposure concentrations. However, subjects reported borderline statistically significant “irritation to the throat” and “difficulties in breathing” (p=0.06), whereas “sensation of a bad smell” (p<0.05) was statistically significant. According to the authors, the odour of the compound is suggested to play a role in the irritation rating.
2. Two 20-minute sessions, 7 days apart, at 70 and 1400 mg/m^3 (14 and 290 ppm) (n=23 volunteers). Subjective ratings for irritation differed significantly between 70 mg/m^3 (regarded as “control level”) and 1400 mg/m^3. However, the rated levels of irritation were very low. The eye blinking frequency was unchanged during the control exposure (12/min), but increased at 1400 mg/m^3 from 9/min to 12/min. The authors stated that interpretation of the results was difficult since the difference found was mainly due to a difference in baseline levels before exposure. No substantial effects were observed on the lipid layer of the eyes. Only minor changes in pulmonary functional parameter were noted at 1400 mg/m^3 (FEV1 unchanged, FVC slightly lower), but bronchial responsiveness was significantly increased after exposure to 1400 mg/m^3.
3. Two 4-hour exposures with a 7-day interval and exposure concentrations of 70 and 700 mg/^{3} (14 and 145 ppm) (n=12 volunteers). Subjective throat irritation, difficulties in breathing and sensation of a bad smell were increased at the higher concentration, but not ocular and nasal irritation. Pulmonary function measures were unchanged during the exposure except for an increase in bronchial responsiveness and the maximum expiratory flow at 25 % at the end of the exposure. Eye redness was increased in 50 % of the subjects after exposure to 700 mg/m^3 as compared to 17 % during control conditions.

In animals, sensory irritation was observed at high concentrations of isobutyl acetate in an Alarie test with Swiss OF1 mice. An RD50 (concentration leading to a decrease in breathing rate by 50 % as sign of respiratory irritation) of 818 ppm (about 3910 mg/m^3) was determined for isobutyl acetate. This RD50 value is very similar to the RD50 of 730 ppm (about 3490 mg/m^3) determined for n-butyl acetate in the same study, indicating a comparable sensory irritation potency of both isomers (AGS, 2018; Alarie et al., 1998).

Limited data indicate that liquid isobutyl acetate is at most minimally irritating to the eyes and on the skin in tests on animals (ECHA Chemicals Database, 2019; OECD SIDS, 2009; WHO, 2005).

In a primary eye irritation test (not according to guidelines), 0.5 ml of undiluted isobutyl acetate caused an injury grade 2 of a scale with a maximum score of 10 within 24 hours (no further data). In a study comparable to OECD guideline 405, a 4-hour occlusive treatment of rabbit eyes with 0.5 ml of n-butyl acetate caused only barely perceptible effects on the cornea (score:1) and the conjunctivae (redness score:1, chemosis score: 1), which were all reversible within a maximum of 14 days (ECHA Chemicals Database, 2019).

In a primary skin irritation test (not according to guidelines), 0.01 ml isobutyl acetate was not irritating to rabbit skin (primary irritation index 1 on a scale of 10). In a further study, isobutyl acetate was reported to be moderately irritating (24 hours occlusive exposure, concentration and amount applied not mentioned, no further data). In a study comparable to OECD guideline 404, a 4-hour occlusive treatment of rabbits with 0.5 ml of n-butyl acetate did not reveal any irritating potential (ECHA Chemicals Database, 2019).

Sensitisation

Isobutyl acetate was not reported to be a skin sensitiser in a 48-hour closed patch test and in a maximisation test on 28 human volunteers with 2 % isobutyl acetate in petrolatum (ECHA Chemicals Database, 2019; SCOEL, 2016).

Isobutyl acetate also was not sensitising in a guinea pig maximisation test (comparable with OECD guideline 406). In this study, 20 animals were induced by intradermal injection of 0.1 ml of isobutyl acetate in maize oil and 0.1 ml of 10 % isobutyl acetate in a 1:1 mixture of Freund's complete adjuvant (FCA) and maize oil. For the topical application, the injection site was treated 7 days after the initial injection for 48 hours with undiluted isobutyl acetate (patch application). Challenge exposure after 14 days was performed with pure isobutyl acetate applied for 24 hours to one flank of the test animals. No skin reactions in any of the test animals were observed either at 48 hours or at 72 hours after the start of the challenge application (ECHA Chemicals Database, 2019; SCOEL, 2016).

No data are available on respiratory sensitising effects of isobutyl acetate.

5.5.2 Repeated dose toxicity

Human data

No studies are available with repeated exposure to isobutyl acetate.

Animal data

No studies are available with repeated exposure to isobutyl acetate.

Read-across: A subchronic inhalation toxicity study following the then current version of EPA-guideline OTS 798.2450 (comparable with OECD guideline 413) was performed with Sprague-Dawley rats. The animals (15 M + 15 F/group) were exposed to n-butyl acetate with nominal concentrations of 0, 500, 1500, or 3000 ppm (0, 2390, 7170, 14340 mg/m^3) on 6 h/d, 5 d/week,

for 13 weeks. The time-weighted average analytical concentrations were within 10 % of the target concentrations (David et al., 2001; ECHA Chemicals Database, 2019).

Narcotic effects (transient signs of sedation) occurred during the exposure to 1500 and 3000 ppm. Over the course of the study, body weights and feed consumption were significantly lower in the mid- and high-concentration groups compared to the control group. The overall weight gains at 3000 ppm were 62 % (males) and 78 % (females) of those for the control group; at 1500 ppm, weight gains were 77 % (males) and 70 % (females) of weight gains for the control group. Regarding organ weights, the mean absolute liver, spleen and kidney weights were significantly lower than for the control groups for the 1500 ppm (except kidney weights for males) and 3000 ppm male and females. The mean relative spleen weight was also significantly lower for the 3000 ppm males. The relative testes and adrenal gland weights for the mid and high concentration groups and the relative lung weights for the 3000 ppm males were significantly higher than for the control group. However, histopathology revealed no systemic organ-specific toxicity. Females showed signs of irritation of the glandular stomach and necrosis in the non-glandular stomach at 3000 ppm (David et al., 2001; ECHA Chemicals Database, 2019).

Local exposure-related histopathological effects were observed in the nasal epithelia of rats exposed at 1500 and 3000 ppm. All male and female animals at 3000 ppm and 4/10 males and 6/10 females at 1500 ppm developed degeneration of the olfactory nasal epithelium (mild to moderate for the 3000-ppm group, minimal to mild for the 1500 ppm group). No lesions were observed in the nasal passages at 500 ppm or in the control group. A NOAEC for local and systemic effects of 500 ppm n-butyl acetate (2390 mg/m^3) could be identified in this study (David et al., 2001; ECHA Chemicals Database, 2019).

In a further subchronic inhalation study, the neurotoxicity of n-butyl acetate was studied in Sprague-Dawley rats (10 M + 10 F/group fed as-libitum and 10 M/group with food restriction) at the same concentrations as indicated above. Endpoints for neurotoxicity included a functional observed battery (FOB), motor activity, operant behaviour (food-restricted rats), and neuro-histopathology (ad-libitum fed rats). At 3000 ppm and, from the 2nd day on, also at 1500 ppm, the animals were sedated (reduced activity and response to stimuli) during the exposure, no behavioural effects could be observed 30 – 60 min after cessation of exposure. Besides this transient effect, no evidence of neurotoxicity could be observed on any other endpoints. Body weight gain was significantly reduced at ≥ 1500 ppm compared to the ad-libitum fed control group. A NOAEC of 500 ppm (2390 mg/m^3) was obtained in this study, based on the transient sedation and hypoactivity seen at ≥ 1500 ppm (David et al., 1998; ECHA Chemicals Database, 2019).

Similarly, a subchronic inhalation neurotoxicity study with isobutanol (comparable to OECD guideline 424) was conducted with Sprague-Dawley rats (20 M + 10 F/group, including 10 M/group with food restriction). The animals were exposed to 0, 250, 1000, or 2500 ppm isobutanol 6 h/day, 5 d/week for 13 weeks. At all concentrations of isobutanol, the animals showed a slightly decreased responsiveness to external stimuli during the exposure but not afterwards. There were no treatment related effects on mortality, clinical signs, body weight, organ weights or gross and histologic pathology or neuropathology. FOB and motor activity testing revealed no treatment-related effects. A NOAEC for neurotoxicity of 2500 ppm, the highest concentration tested, was reported by the registrant (ECHA Chemicals Database, 2019).

The same NOAEC of 2500 ppm, the highest concentration tested, was also reported for a schedule-controlled operant behaviour subchronic inhalation study with male rats exposed as indicated above (ECHA Chemicals Database, 2019)

Furthermore, data are available from a subchronic oral toxicity study with isobutyl isobutyrate (purity ≥ 98 %) in which rats (15 M + 15 F/group) received 0, 10, 100, or 1000 mg/(kg bw x d) via gavage for 18 weeks. Compared to the corresponding OECD guideline, the observation parameters were slightly reduced (no behavioural/neurological observations, limited blood parameters, no clinical chemistry). No treatment related effects were observed up to the highest dose level in male and female rats (ECHA Chemicals Database, 2019).

5.5.3 Genotoxicity and carcinogenicity

Genotoxicity

Isobutyl acetate was not mutagenic *in vitro* in the presence or absence of exogenous metabolic activation system (S9-mix) in bacteria (*Salmonella typhimurium* TA TA98, TA100, TA 1535, TA1537, TA 1538 and TA100, *Escherichia coli* WP2uvrA) and did not induce chromosomal aberrations in mammalian cells (V79 cells from Chinese hamster) up to cytotoxic concentrations. Also, the metabolite isobutanol (2-methylpropan-1-ol) was not mutagenic with or without S9-mix in L5178Y cells from mice (AGS, 2018; ECHA Chemicals Database, 2019). Mutagenic effects of acetic acid observed in some studies on bacteria and mammalian cells are attributed to the non-physiological acidification of the culture medium and not to a substance-specific effect (Heldreth, 2012).

No substance-specific data are available for isobutyl acetate *in vivo.* Isobutanol was not clastogenic (no induction of micronuclei) in the bone marrow of mice in a micronucleus test after oral administration of up to 2000 mg/kg bw (ECHA Chemicals Database, 2019).

No substance-specific data are available for isobutyl acetate *in vivo.* Isobutanol was not clastogenic (no induction of micronuclei) in the bone marrow of NMRI mice (5 M + 5F/group) in a micronucleus test after oral administration of up to 2000 mg/kg bw which caused systemic toxicity (ECHA Chemicals Database, 2019).

Carcinogenicity

Carcinogenicity studies with isobutyl acetate are not available. The available genotoxicity data for isobutyl acetate and isobutanol do not raise concern for a genotoxic non-threshold carcinogenic effect of iBA.

5.5.4 Toxicity to reproduction

No studies with iBA are available regarding reproductive and developmental toxicity.

Fertility

Read-Across: The reproductive toxicity of isobutanol was examined in a two-generation inhalation study following EPA OPPTS 870.3800 guideline. Sprague-Dawley rats (30 F + 30 M/group) were exposed whole body against 0, 500, 1000 and 2500 ppm (0, 1476, 2952, and 7380 mg/m^3) 6 h/d, 7 d/week, from the beginning of the study (F0 generation) or PND 28 (F1 generation) until sacrifice after weaning of the pups (F0: PND 28, F1: PND 21). For dams, exposure was discontinued after day 20 of gestation until lactation day 5. There were no adverse effects observed on parental systemic, reproductive, and neonatal toxicity up to 2500 ppm (NOAEC), the highest concentration tested (ECHA Chemicals Database, 2019). (Note: referred to isobutyl acetate, 2500 ppm corresponds to 11950 mg/m^3 at 23 °C).

Developmental toxicity

In a prenatal developmental toxicity study according to OECD TG 414, pregnant Wistar rats (25/dose group) were exposed by inhalation to vapour concentrations 0, 500, 2500, or

10000 mg isobutanol/m^3 for 6 h/d on GD 6 – 15. All animals were killed on day 20 of gestation; the foetuses were removed and examined for exposure-related effects. No treatment-related effects could be noted on maternal toxicity (mortality, clinical signs, body weight development, gross pathology) up to the highest concentration tested. Similarly, no signs of treatment-related embryo-/foetotoxicity or teratogenic effects were observed in the foetuses. The NOAEC for maternal and developmental toxicity was 10000 mg/m^3, the highest concentration tested (ECHA Chemicals Database, 2019).

In a corresponding study following OECD guideline 414, pregnant Himalayan rabbits (15/group) were exposed to vapours of 0, 500, 2500, or 10000 mg isobutanol/m^3 for 6 h/d on GD 7 – 19 of gestation. All animals were killed on day 29 of gestation, and the foetuses were removed and examined for compound-related effects. Signs of maternal toxicity (retardation in body weight gain) was observed at the highest concentration of 10000 mg/m^3. However, no signs of treatment-related embryo-/foetotoxicity or teratogenic effects were observed in the foetuses at any concentration. The NOAEC for maternal toxicity was 2500 mg/m^3 (LOAEC: 10000 mg/m^3) and the NOAEC for developmental toxicity was 10000 mg/m^3, the highest concentration tested (ECHA Chemicals Database, 2019).

5.5.5 Odour perception

The odour of isobutyl acetate is described as fruity or floral (SCOEL, 2016) and reminiscent of banana, currant, pear, hyacinth or rose, but also of nail polish (PubChem, 2024). An odour threshold of 0.008 ppm (0.038 mg/m^3) is reported (Nagata, 2003).

5.6 Evaluation

5.6.1 Existing regulations and classifications

There is no harmonised classification for isobutyl acetate regarding toxicity (ECHA C&L Inventory, 2024).

Existing guide values for isobutyl acetate in air are summarised in Table 29.

A DNEL of 35.7 mg/m^3 is reported in the registration dossier for the protection of the general population via inhalation route. This DNEL was derived from the DNEL for workers, which was adopted from the legally binding 8-hour limit value (AGW) of 300 mg/m^3 for isobutyl acetate in Germany. The AGW was corrected for continuous exposure over 24 hours for the general population instead of 8 hours for workers and 7 days instead of 5 days. An additional assessment factor of 2 was considered for intraspecies differences (quotient of default value for general population of 10 versus that of 5 for workers): 300 mg/m^3 x (8 h/24 h) x (5 d/7 d) x (5/10) = 35.7 mg/m^3 (7 ppm) (ECHA Chemicals Database, 2019).

The German AGW is based on the NOAEC of 500 ppm obtained in each of two subchronic studies with n-butyl acetate (AGS, 2018; David et al., 2001; 1998). In one of the studies, a dose dependent reduced body weight gain was observed at ≥ 1500, respectively, and, more important, a dose dependent necrosis of olfactory epithelium starting at 1500 ppm was noted in the other study. The NOAEC of 500 ppm was corrected from the experimental exposure regimen (6 h) to shift exposure (8 h). A time extrapolation factor of 2 was applied for extrapolation from subchronic to chronic exposure. Additionally, an overall combined inter- and intraspecies variability factor of 3 was applied due to substance specific data (higher sensitivity of rats, unspecific cytotoxic effects responsible for irritating effects) (AGS, 2018; ECHA Chemicals Database, 2019).

The MAK commission based the derivation of a MAK value for isobutyl acetate on a read-across using data for n-butyl acetate, assuming that the irritation threshold for isobutyl acetate "is not very different from the irritation threshold of the better investigated 1-butyl acetate.." Several studies with controlled exposure of humans to n-butyl acetate showed that this substance is irritating to mucous membranes, and the MAK-commission stated that "… 200 ppm does not offer sufficient protection against the reactive effect of the substance…. It will therefore be lowered to 100 ppm." (DFG, 2003a; DFG, 2003b). Individual assessment factors were not reported.

The 8-h TWA derived by SCOEL (2016) is also based on read-across using data for n-butyl acetate (Iregren et al., 1993). In that study, controlled human inhalation exposure to 145 ppm (700 mg/m^3) n-butyl acetate for 4 hours led to throat irritation, breathing difficulties, and eye redness. This concentration was considered to represent a LOAEC. An uncertainty factor of 3 was considered sufficient – since the described effects were regarded as minimal – to derive an OEL of 50 ppm (240 mg/m^3) (SCOEL, 2016).

A TLV-TWA of 1500 ppm (713 ppm) isobutyl acetate was derived for the protection of workers by ACGIH (2001). No details regarding the derivation are available.

A NIK value ("adopted EU-LCI value") of 4.8 mg/m^3 is reported by AGBB (2024).

5.6.2 Derivation of an EU-LCI value

The data base regarding the toxicity of isobutyl acetate is limited. Therefore, read-across using data from studies with n-butyl acetate is used for the assessment of isobutyl acetate.

In a subchronic inhalation toxicity study (comparable with OECD Guideline 413), rats were exposed "whole body" to 0, 500, 1500, or 3000 ppm of n-butyl acetate vapour (0, 2390, 7170, 14340 mg/m^3) 6 h/d, 5 d/week for 13 weeks. Clinical effects were noted during exposure, i.e. transient sedation of the animals at ≥ 1500 ppm. Body weight gain and food consumption were lower at these concentrations. Local effects in the nasal epithelia were also reported. These included degeneration of the olfactory epithelium along the dorsal medial meatus and ethmoturbinates of the nasal passages. The severity was mild to moderate at 3000 ppm group and minimal to mild at 1500 ppm group. No effect was observed at 500 ppm. Thus, a NOAEC for local and systemic effects of 500 ppm n-butyl acetate (2390 mg/m^3) could be identified in this study (David et al., 2001; ECHA Chemicals Database, 2019).

A subchronic neurotoxicity study with n-butyl acetate was also performed with rats at the same exposure concentrations as described above. At 3000 ppm and, from the 2nd day on, also at 1500 ppm, the animals were sedated; however, no behavioural effects could be observed 30 – 60 min after cessation of exposure. Besides this transient effect, no evidence of neurotoxicity could be observed on any other endpoints. Body weight gain was significantly reduced at ≥ 1500 ppm (David et al., 1998; ECHA Chemicals Database, 2019).

Regarding genotoxicity, isobutyl acetate was not mutagenic *in vitro* in the presence or absence of exogenous metabolic activation system (S9-mix) in bacteria and did not induce chromosomal aberrations in mammalian cells (V79 cells from Chinese hamster) up to cytotoxic concentrations. Also, isobutanol (2-methylpropan-1-ol) was not mutagenic with or without S9-mix in L5178Y cells from mice (AGS, 2018; ECHA Chemicals Database, 2019).

Mutagenic effects of acetic acid observed in some studies on bacteria and mammalian cells are attributed to the non-physiological acidification of the culture medium and not to a substance-specific effect (Heldreth, 2012).

No substance-specific data are available for isobutyl acetate *in vivo*. Isobutanol was not clastogenic in the bone marrow of mice in a micronucleus test after oral administration of up to 2000 mg/kg bw (ECHA Chemicals Database, 2019).

Carcinogenicity studies with isobutyl acetate are not available. The available genotoxicity data for isobutyl acetate and isobutanol do not raise concern for a genotoxic non-threshold carcinogenic effect of iBA.

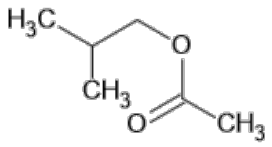
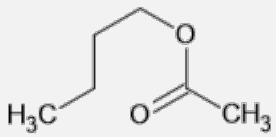
No studies with isobutyl acetate are available regarding reproductive and developmental toxicity. The available data for the metabolites isobutanol and acetic acid do not raise concern for such effects of isobutyl acetate.

The EU-LCI derivation for isobutyl acetate (iBA) is conducted via read-across with n-butyl acetate, following the principles described in (EC, 2013). The key assumption is that n-butyl acetate is the closest homologue with sufficient existing toxicological data and an already published EU-LCI value:

- Data poor compound: insufficient data for iBA, *de novo* derivation of EU-LCI for isobutyl acetate not possible.
- Read-across from n-butyl acetate: within the chemical group of "butyl acetates", n-butyl acetate is the closest homologue compound with an adequate data base. The only difference between the two substances is the branched butyl group, i. e. a 2-methylpropyl group in isobutyl acetate instead of the straight-chain butyl group in n-butyl acetate.
- Toxicological critical endpoint for n-butyl acetate: local irritation of upper respiratory tract and eyes.

The key assumption underlying the read-across of the EU-LCI value from n-butyl acetate to isobutyl acetate is that both compounds have the same critical endpoint (irritation), and this is caused by their common chemical structure as an alkyl acetate. The effect is associated with the local formation of acetic acid by hydrolysis of the acetate ester, which, after exceeding the specific buffer capacity of the cells, leads to acidification and consequently cytotoxic damage (Hardisty et al., 1999).

Table 28: Comparison of the structure and molar mass of n- and isobutyl acetate

Compound	Structure	Molar mass (g/mol)	EU-LCI value
Isobutyl acetate (iBA)		116.16	Read-across Proposed: 8500 µg/m³
n-Butyl acetate (nBA)		116.16	Derived: 8500 µg/m³ (rounded value)

- No cut-off rule in place: no difference in chain length between the two homologue compounds n-butyl acetate and iBA isobutyl acetate.
- The derived EU-LCI value for n-butyl acetate of 8500 µg/m³ may be applied to isobutyl acetate without modification.

For the derivation of an EU-LCI value for isobutyl acetate, it is proposed to perform the read-across from n-butyl acetate.

An EU-LCI value of 8500 µg/m^3 is proposed for isobutyl acetate (iBA).

An odour threshold of 8 ppb (38 µg/m^3) is reported for isobutyl acetate (Nagata, 2003), which is several orders of magnitude below the proposed EU-LCI value. Thus, it is expected that the odour of isobutyl acetate will be perceivable at the proposed EU-LCI value.

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E Appendix

E.1 Data collection and fact sheet for isobutyl acetate (iBA)

Table 29: Data collection sheet for isobutyl acetate (iBA)

Compound	**Isobutyl acetate**	**Data collection sheet**				
Nº CAS: 110-19-0 1 ppm = 4.78 mg/m³ at 23 °C	**EU-Classification:** **CLP, harmonised classification:** – with respect to toxicity					
Organisation name	**REACH registrants**	**AgBB**	**German AGS**	**German DFG**	**SCOEL**	**ACGIH**
Risk value name	DNEL (general population)	NIK ('Lowest Concentration of Interest')	AGW (workplace)	MAK	OEL	TLV-TWA
Risk value (mg/m³)	35.7	4.8	300 (62 ppm)	480 (100 ppm)	240 (50 ppm)	713 (150 ppm)
Reference period	Chronic (general population)	Chronic	8 h TWA (chronic, workplace)	8 h TWA (chronic, workplace)	8 h TWA (chronic, workplace)	8 h TWA (chronic, workplace)
Risk value (mg/m³) **Short term (15 min)**	300		600	960 (200 ppm)	700 (150 ppm)	
Year	2019	2024	2012, 2018	2003	2016	2001
Key study		See below	David et al. (2001)	Iregren et al. (1993)	Iregren et al. (1993)	Not reported
Study type			Subchronic inhalation toxicity study	Acute inhalation study with volunteers	Acute inhalation study with volunteers	

Compound	Isobutyl acetate	Data collection sheet				
Species			Rat, Wistar (n = 15 M + 15 F/group)	Human	Human	
Duration of exposure in key study			6 h/d, 5 d/week, 13 weeks	20 min/4 h	4 h	
Critical effect	Irritation of respiratory tract		Irritation of respiratory tract	Irritation of eyes and respiratory tract	Irritation of throat, difficulties in breathing	Ocular and upper respiratory tract irritation
Critical dose value			NOAEC: 500 ppm	"no sufficient protection against the irritating effect of the substance at 200 ppm"	LOAEC: 150 ppm	
Adjusted critical dose			375 ppm (6 h/8 h)			
Single assessment factors	UF_S 2 UF_H 6 (reduced intraspecies factor 3 for workers due to unspecific cytotoxic effect and additional factor 2 for general population). Value further corrected for the exposure of the general population for 7 days instead of 5 days for workers		UF_S 2 UF_H 3 (reduced intraspecies factor 3 for workers due to unspecific cytotoxic effect)	Not reported	UF_L 3	Not reported
Other effects						

Compound	Isobutyl acetate	Data collection sheet				
Remarks	Derivation based on German OEL (AGW)	Adopted ascribed EU-LCI-value	Based on read-across using animal data for n-butyl acetate	Based on read-across using data for n-butyl acetate	Based on read-across using data for n-butyl acetate	Based on limited data and by analogy with n-butyl acetate

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

Table 30: Fact sheet for n-butyl acetate (nBA)*

Compound	n-Butyl acetate C6H12O2		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	8500
EU-LCI status	2	Draft/Final	Final
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2022
General information			
CLP-Index No.	4	INDEX	607-025-00-1
EC-No.	5	EINECS	204-658-1
CAS-No.	6	Chemical Abstract Service number	123-86-4
Harmonised CLP classification	7	Human health risk related classification	STOT SE 3, H336
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	116.2 1 ppm = 4.78 mg/m³ 1 mg/m³ = 0.21 ppm
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	David et al. (2001)
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
Exposure duration	14	h/d, d/w	6 h/d, 5 d/week
Critical endpoint	15	Effect (s), site of	Effects in nasal cavity transient signs of sedation, reduced body weight
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	NOAEC
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	500 ppm
Assessment factors (AF)			
Adjustment for exposure duration	19	Study exposure h/d, d/w	5.6
Study length	20	sa→sc→c	2
Route-to-route extrapolation factor	21	-	1

Compound	n-Butyl acetate C6H12O2		Fact sheet
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	1
	22b	Severity of effect (R8 6d)	1
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	1
	23b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic General population	10
AF (sensitive population)	25		1
Other adjustment factors Quality of database	26	Quality of database	
Results			
Summary of assessment factors	27	Total Assessment Factor	280
POD/TAF	28	Calculated value [µg/m³ and ppb]	8537 µg/m³ and 1786 ppb
Molar adjustment factor	29		
Rounded value	30	[µg/m³]	8500
Additional comments	31		
Rationale selection	32		

*: according to https://ec.europa.eu/docsroom/documents/55996

Table 31: Fact sheet for isobutyl acetate (iBA)

Compound	Isobutyl acetate C6H12O2		Fact sheet
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	[µg/m³]	8500
EU-LCI status	2	Draft/Final	Draft
EU-LCI year of issue	3	Year when EU-LCI value has been issued	2025
General information			
CLP-Index No.	4	INDEX	607-026-00-7
EC-No.	5	EINECS	203-745-1
CAS-No.	6	Chemical Abstract Service number	110-19-0
Harmonised CLP classification	7	Human health risk related classification	-
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m³]	116.2 1 ppm = 4.78 mg/m³ 1 mg/m³ = 0.21 ppm
Key data / database			
Key study, authors, year	9	Critical study with lowest relevant effect level	
Read across compound	10	Where applicable	n-Butyl acetate
Species	11	Rat, human, etc.	
Route / type of study	12	Inhalation, oral feed, etc.	
Study length	13	Days, subchronic, chronic, etc.	
Exposure duration	14	h/d, d/w	
Critical endpoint	15	Effect (s), site of	
Point of departure (POD)	16	LOAEC, NOAEC, BMD, etc.	
POD value	17	[mg/m³] or ppm or [mg/kg$_{BW}$×d]	EU-LCI value of n-butyl acetate
Assessment factors (AF)			
Adjustment for exposure duration	19	Study exposure h/d, d/w	-
Study length	20	sa→sc→c	-
Route-to-route extrapolation factor	21	-	-

Compound	Isobutyl acetate C6H12O2		Fact sheet
Dose-response	22a	Reliability of dose-response, LOAEL to NOAEL	-
	22b	Severity of effect (R8 6d)	-
Interspecies differences	23a	Allometric Metabolic rate (R8-3)	-
	23b	Kinetic + dynamic	-
Intraspecies differences	24	Kinetic + dynamic General population	-
AF (sensitive population)	25		-
Other adjustment factors Quality of database	26	Quality of database	-
Results			
Summary of assessment factors	27	Total Assessment Factor	-
POD/TAF	28	Calculated value [µg/m³ and ppb]	-
Molar adjustment factor	29		1
Rounded value	30	[µg/m³]	8500
Additional comments	31		
Rationale selection	32		

Rationale for starting point

Isobutyl acetate (iBA), an aliphatic ester, is a colourless liquid with a moderate vapour pressure (20 hPa) at room temperature. The saturated vapour concentration of isobutyl acetate in air is about 95000 mg/m^3 at 20°C. The hardly water-soluble substance has a distinct fruity or floral odour reminiscent of pineapple and banana and occurs naturally in many fruits. The odour threshold is given as 0.008 ppm (0.038 mg/m^3) (Nagata, 2003). Isobutyl acetate is also a large-scale industrial product (EU tonnage band ≥ 10000 – < 100000 t/a) which is primarily used as a solvent in a variety of ways, e.g. for coatings, adhesives, printing inks, sealants and cleaning agents, but also in cosmetics and as a flavouring agent in food and beverages (ECHA Chemicals Database, 2019; OECD SIDS, 2009).

Data on the occurrence of isobutyl acetate in indoor air from studies carried out in Germany showed that the substance could be detected quite often (in about 25 % of 2143 measurements), with concentrations mostly below 10 µg/m^3 but reaching 1660 µg/m^3 in extreme cases (Hofmann and Plieninger, 2008).

Isobutyl acetate is rapidly absorbed after inhalation exposure; quantitative data are, however, not available. For the isomeric n-butyl acetate, it is stated that about 50 % of the inhaled compound is found in the exhaled air after inhalation exposure with 42 ppm (about 200 mg/m^3). According to animal data, n-butyl acetate is well absorbed in the lungs (100 % of

alveolar ventilation), and the maximum concentration in the blood after inhalation of 2000 ppm (about 9600 mg/m^3) was reached within 10 min (SCOEL, 2016; ECHA Chemicals Database, 2019).

Following contact with the mucous membranes or absorption into the organism, iBA is hydrolysed to isobutanol (2-methylpropan-1-ol) and acetic acid. In rat nasal tissue preparations *in vitro,* hydrolysis was detectable for all butyl acetate isomers including iBA; the reaction rate decreased with increasing degree of branching. An inhalation experiment in rats *in vivo* with iBA confirmed the rapid hydrolysis of the ester: upon exposure to 200 ppm iBA, the concentration of the hydrolysis product, isobutanol, in the blood of the animals was already twice as high as that of iBA itself 5 min after the start of exposure (AGS, 2018; ECHA Chemicals Database, 2019; WHO, 2005).

Regarding the metabolism of iBA, no relevant species differences are known. Enzymatic hydrolysis has been shown in several *in vitro* experiments using homogenates from liver, small intestinal mucosa, and nasal epithelia. In S9-mix from rat liver, the rate of enzymatic hydrolysis of iBA was comparable (87 %) to that of n-butyl acetate. Following enzymatic hydrolysis of iBA by esterases, isobutanol is conjugated to a minor extent with glucuronic acid or sulphate and excreted as conjugates in the urine. The major pathway involves oxidation of isobutanol to the corresponding aldehyde and further to isobutyric acid (2-methylpropanoic acid). The latter is metabolised via methylmalonic acid to succinic acid which is utilised in the citric acid cycle. Acetic acid formed during the hydrolysis of iBA is also largely utilised via the citric acid cycle or for the synthesis of fatty acids (AGS, 208; ECHA Chemicals Database, 2019; SCOEL, 2016).

The data base regarding the toxicity of isobutyl acetate (iBA) is limited.

The acute toxicity of iBA in animals is low. All six rats survived a one hour exposure to an atmosphere almost saturated with iBA vapour (approx. 20000 ppm, corresponding to about 97400 mg/m^3), as well as six hours of exposure to 3500 ppm (about 17000 mg/m^3). All six female rats survived an exposure to 4000 ppm (about 19500 mg/m^3) for 4 hours; at 8000 ppm (about 39000 mg/m^3) 4 of the 6 animals died, at 16000 ppm (about 78000 mg/m^3) all 6 animals died between the third and fourth hour of exposure. Clinical symptoms during exposure included an anaesthetic effect of iBA, and death occurred as a result of damage to the capillaries in the lung. A 4-h LC50 of 6200 ppm (about 30200 mg/m^3) was estimated from these data (ECHA Chemicals Database, 2019; AGS, 2018).

An oral LD50 of 13413 mg/kg bw was determined for male rats and a dermal LD50 of > 17,400 mg/kg bw in male rabbits (ECHA Chemicals Database, 2019).

Liquid iBA is at most minimally irritating to the eyes and on the skin in tests on animals (OECD SIDS, 2009; ECHA Chemicals Database, 2019; WHO, 2005).

Isobutyl acetate was not reported to be a skin sensitiser in a patch test and a maximisation test in human volunteers with 2 % iBA and in a guinea pig maximisation test (ECHA Chemicals Database, 2019; SCOEL, 2016). No data are available on respiratory sensitising effects of iBA.

Sensory irritation was observed at high concentrations of iBA in an Alarie test with mice: An RD50 (concentration leading to a decrease in breathing rate by 50 % as sign of respiratory irritation) of 818 ppm (about 3910 mg/m^3) was determined for iBA. This RD50 value is very similar to the RD50 of 730 ppm (about 3490 mg/m^3) determined for n-butyl acetate, indicating a comparable sensory irritation potency of both isomers (AGS, 2018; Alarie et al., 1998).

No acute inhalation studies with iBA are available in humans. However, some data are available for n-butyl acetate from older studies (nominal concentrations reported): Overall, effects of n-butyl acetate may be expected at ≥ 200 ppm (about 970 mg/m^3) after short-term exposure for 5

to 20 minutes. Irritation of the throat was described by volunteers exposed for 3 – 5 min to 200 – 300 ppm and, additionally, of eyes and nose at 300 ppm. Moderate irritation effects were reported after inhalation of 2100 ppm for 5 min (SCOEL, 2016, AGS, 2018).

A clinical study on irritation effects of n-butyl acetate in human volunteers without previous occupational exposure was published by Iregren et al. (1993). Three experiments with different exposure levels were conducted: 1) four 20-minute sessions with 24-hour intervals at 72, 145, 217 and 290 ppm (n=24); 2) two 20-minute sessions, 7 days apart, at 14 and 290 ppm (n=23); and 3) two 4-hour exposures with a 7-day interval and exposure concentrations of 14 and 145 ppm (n=12). Only minimal irritation effects in the throat were reported after exposure with up to 290 ppm for 20 min, and these were not significantly different from the control values. The described throat effects were accompanied by the sensation of a bad smell. However, throat irritation and breathing difficulties occurred at 145 ppm after 4 hours of exposure, and eye redness was found in 50 % of the exposed and 17 % of the control subjects. Bronchial responsiveness (breathing difficulties) was also significantly increased (EU-LCI Working Group, 2023; AGS, 2018; SCOEL, 2016; ECHA Chemicals Database, 2019; HCN, 2001).

Repeated dose toxicity studies with iBA in humans or animals are not available.

Read-across: In a subchronic inhalation toxicity study, Sprague-Dawley rats (15 M + 15 F/group) were exposed "whole body" to 0, 500, 1500, or 3000 ppm of n-butyl acetate (nBA) vapour (0, 2390, 7170, 14340 mg/m^3) 6 h/d, 5 d/week for 13 weeks. The study was conducted comparable with the then current version of EPA-guideline OTS 798.2450 (comparable with OECD Guideline 413). The time-weighted analytical concentrations of the test compound were within 10 % of the target concentrations. Clinical effects were noted during exposure, i.e. transient sedation of the animals at ≥ 1500 ppm. Also, body weight gain and food consumption were lower at these concentrations. Several changes of organ weights were noted. At 3000 ppm, the absolute weight of liver, kidney and spleen were significantly lower and the lung weight significantly higher than for the control group in male rats. The testes and adrenals weights were significantly increased in males at ≥ 1500 ppm. However, histopathology revealed no systemic organ-specific toxicity. Females showed signs of irritation of the glandular stomach and necrosis in the non-glandular stomach at 3000 ppm (David et al., 2001; ECHA Chemicals Database, 2019).

Local effects in the nasal epithelia were also reported. These included degeneration of the olfactory epithelium along the dorsal medial meatus and ethmoturbinates of the nasal passages. The severity was mild to moderate at 3000 ppm group and minimal to mild at 1500 ppm group. No effect was observed at 500 ppm. Thus, a NOAEC for local and systemic effects of 500 ppm nBA (2390 mg/m^3) could be identified in this study (David et al., 2001; ECHA Chemicals Database, 2019).

In a further subchronic inhalation study, the neurotoxicity of n-butyl acetate (nBA) was studied in Sprague-Dawley rats (10 M + 10 F/group fed as-libitum and 10 M/group with food restriction) at the same concentrations as indicated above. Endpoints for neurotoxicity included a functional observed battery, (FOB), motor activity, operant behaviour (food-restricted rats), and neuro-histopathology (ad-libitum fed rats). At 3000 ppm and, from the 2nd day on, also at 1500 ppm, the animals were sedated (reduced activity and response to stimuli) during the exposure, no behavioural effects could be observed 30 – 60 min after cessation of exposure. Besides this transient effect, no evidence of neurotoxicity could be observed on any other endpoints. Body weight gain was significantly reduced at ≥ 1500 ppm compared to the ad-libitum fed control group. A NOAEC of 500 ppm (2390 mg/m^3) was obtained in this study, based

on the transient sedation and hypoactivity seen at ≥ 1500 ppm (David et al., 1998; SCOEL, 2016; ECHA Chemicals Database, 2019).

Furthermore, no treatment related effects were observed up to the highest dose of 1000 mg/(kg x bw x d) after oral administration of isobutyl isobutyrate to male and female rats via gavage for 18 weeks (ECHA Chemicals Database, 2019).

Regarding genotoxicity, iBA was not mutagenic *in vitro* in the presence or absence of exogenous metabolic activation system (S9-mix) in bacteria and did not induce chromosomal aberrations in mammalian cells (V79 cells from Chinese hamster) up to cytotoxic concentrations. Also, isobutanol (2-methylpropan-1-ol) was not mutagenic with or without S9-mix in L5178Y cells from mice (AGS, 2018; ECHA Chemicals Database, 2019). Mutagenic effects of acetic acid observed in some studies on bacteria and mammalian cells are attributed to the non-physiological acidification of the culture medium and not to a substance-specific effect (Heldreth, 2012).

No substance-specific data are available regarding genotoxicity of iBA *in vivo*.

Read-across: Isobutanol was not clastogenic (no induction of micronuclei) in the bone marrow of mice in a micronucleus test after oral administration of up to 2000 mg/kg bw (ECHA Chemicals Database, 2019).

Carcinogenicity studies with iBA are not available. The available genotoxicity data for iBA and isobutanol do not raise concern for a genotoxic non-threshold carcinogenic effect of iBA.

No studies with iBA are available regarding reproductive and developmental toxicity.

Read-across: In a two-generation study with inhalation exposure of rats to isobutanol, no adverse effects were observed on parental systemic, reproductive, and neonatal toxicity up to 2500 ppm (about 7400 mg/m^3), the highest concentration tested (SCOEL, 2016; ECHA Chemicals Database, 2019).

In a developmental toxicity study with isobutanol in rats, inhalation exposure on gestational day (GD) 6 – 15 did not lead to treatment-related maternal toxicity or to signs of treatment-related embryo-/fetotoxicity or teratogenicity up to the highest concentration of 10000/m^3 (about 2090 ppm) tested. In rabbits (inhalation exposure on GD 7 – 19), maternal toxicity was observed at the highest concentration of 10000 mg/m^3 (NOAEC: 2500 mg/m^3, about 520 ppm), but there were no signs of developmental toxicity (NOAEC: 10000 mg/m^3, about 2090 ppm) (SCOEL, 2016; ECHA Chemicals Database, 2019).

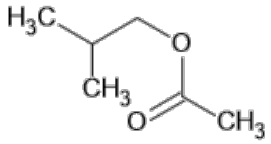
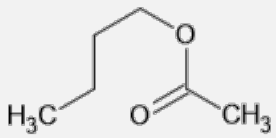
Rationale for read-across

The EU-LCI derivation for isobutyl acetate (iBA) is conducted via read-across with n-butyl acetate (nBA), following the principles described in EC (2013). The key assumption is that nBA is the closest homologue with sufficient existing toxicological data and an already published EU-LCI value:

- Data poor compound: insufficient data for iBA, *de novo* derivation of EU-LCI for iBA not possible.
- Read-across from nBA: within the chemical group of "butyl acetates", nBA is the closest homologue compound with an adequate data base. The only difference between the two substances is the branched butyl group, i. e. a 2-methylpropyl group in iBA instead of the straight-chain butyl group in nBA.
- Toxicological critical endpoint for nBA: local irritation of upper respiratory tract and eyes.

The key assumption underlying the read-across of the EU-LCI value from nBA to iBA is that both compounds have the same critical endpoint (irritation) and this is caused by their common chemical structure as an alkyl acetate. The effect is associated with the local formation of acetic acid by hydrolysis of the acetate ester, which, after exceeding the specific buffer capacity of the cells, leads to acidification and consequently cytotoxic damage (Hardisty et al., 1999).

Table 32: Comparison of the structure and molar mass of n- and isobutyl acetate

Compound	Structure	Molar mass (g/mol)	EU-LCI value
Isobutyl acetate (iBA)		116.16	Read-across Proposed: 8500 µg/m³
n-Butyl acetate (nBA)		116.16	Derived: 8500 µg/m³ (rounded value)

- No cut-off rule in place: no difference in chain length between the two homologue compounds nBA and iBA.
- The derived EU-LCI value for nBA of 8500 µg/m³ may be applied to iBA without modification.

For the derivation of an EU-LCI value for isobutyl acetate, it is proposed to perform the read-across from n-butyl acetate.

An EU-LCI value of 8500 µg/m³ is proposed for isobutyl acetate (iBA).

An odour threshold of 8 ppb (38 µg/m³) is reported for isobutyl acetate (Nagata, 2003), which is several orders of magnitude below the proposed EU-LCI value. Thus, it is expected that the odour of isobutyl acetate will be perceivable at the proposed EU-LCI value.

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