Compound	Butyl glycolate		*Data collection sheet (1/1)*
N°CAS 7397-62-8 **1 ppm ~5.44 mg/m³**	**CLP: No harmonised classification**		
Organisation name	**ANSES**	**Denmark**	**REACH Registrants**
Risk value name	CLI (= LCI)	OEL	DNEL (General population, long-term, inhalation, systemic)
Risk value (µg/m³)	1300	136000	1740
Risk value (ppb)	240	25000 (provisional)	320
Reference period	Chronic	Chronic	Chronic
Year	2004	1994	2018
Key study	OEL Denmark	N/A	Study report (2013)
Study type	N/A	N/A	90-day repeated dose oral gavage study
Species	N/A	N/A	Male rats
Duration of exposure	N/A	N/A	Daily exposure for 13 weeks
Critical effect	N/A	N/A	Nephropathy
Critical dose value	OEL	N/A	NOAEL
	135 mg/m³ (25 ppm)	N/A	100 mg/kg bw/day
Adjusted critical dose	N/A	N/A	NOAEC
	N/A	N/A	100/1.15 m³/kg bw = 86.96 mg/m³
Single assessment factors	Total assessment factor of 100	N/A	UF_S 2; UF_{other} 2.5; UF_H 10
Other effects	N/A	N/A	N/A
UF_H Intraspecies variability; UF_A interspecies variability; UF_S Used subchronic study			

Compound	**Butyl glycolate C6H12O3**		***Factsheet***
Parameter	**Note**	**Comments**	**Value / descriptor**
EU-LCI value and status			
EU-LCI value	1	Mass/volume [µg/m^3]	900
EU-LCI status	2	Draft/Final	Final
EU-LCI year of issue	3	Year when the EU-LCI value has been issued	2019
General information			
CLP-INDEX-No.	4	INDEX	none
EC-No.	5	EINECS – ELINCS - NLP	230-991-7
CAS-No.	6	Chemical Abstracts Service number	7397-62-8
Harmonised CLP classification	7	Human Health Risk related classification	No harmonised classification
Molar mass and conversion factor	8	[g/mol] and [ppm – mg/m^3]	132.16 1 ppm = 5.44 mg/m^3
Key data / database			
Key study, author(s), year	9	Critical study with lowest relevant effect level	ECHA, 2018 (13-week oral study)
Read across compound	10	Where applicable	
Species	11	Rat, human, etc.	Rats
Route/type of study	12	Inhalation, oral feed, etc.	Oral
Study length	13	Days, subchronic, chronic	Subchronic
Exposure duration	14	Hrs/day, days/week	13 weeks
Critical endpoint	15	Effect(s), site of	Nephrotoxicity
Point of departure (POD)	16	LOAEC*L, NOAEC*L, NOEC*L, Benchmark dose, etc.	NOAEL
POD value	17	[mg/m^3] or [ppm] or [mg/kg$_{BW}$×d]	100 mg/kg bw/day
Assessment factors (AF)	**18**		
Adjustment for exposure duration	19	Study exposure hrs/day, days/week	1
Study length	20	sa→ sc→ c *(R8-5)*	2
Route-to-route extrapolation factor	21	Oral-to-inhalation	1.15
Dose-response	22 a	Reliability of dose-response, LOAEL → NOAEL	1
	22 b	Severity of effect *(R 8-6d)*	1
Interspecies differences	23 a	Allometric Metabolic rate *(R8-3)*	1[1]
	23 b	Kinetic + dynamic	2.5
Intraspecies differences	24	Kinetic + dynamic Worker - general population	10

[1] Allometric scaling is already included in line 21

AF (sensitive population)	25	Children or other sensitive groups	1
Other adjustment factors Quality of whole database	26	Completeness and consistency Reliability of alternative data *(R8-6 d,e)*	1
Result			
Summary of assessment factors	27	Total Assessment Factor (TAF)	50
POD/TAF	28	Calculated value (µg/m³ and ppb)	869.6 µg/m³ and 159.8 ppb
Molar adjustment factor	29	Used in read-across	
Rounded value	30	[µg/m³]	900
Additional comments	31		
Rationale section	32		

The data compiled and evaluated for butyl glycolate are based on a project funded by the European Commission and carried out by Ramboll Environment & Health GmbH.

Only limited data was available on the toxicity of butyl glycolate (also known as hydroxyacetic acid butyl ester or butyl 2-hydroxyacetate). There was one assessment report identified in the public domain on butyl glycolate, which was published by the German MAK Commission (MAK, 2012). The MAK Commission concluded that the MAK value for butyl glycolate could not be established because the toxicity studies available yielded insufficient information to derive the value (DFG, 2017). A targeted literature search using PubMed, TOXNET and Google Scholar was also carried out with the aim of identifying other relevant literature on the toxicity of butyl glycolate but it identified no relevant references.

A REACH registration dossier on butyl glycolate is available (tonnage band of 1000-10000 tonnes per annum), which includes some toxicity data on butyl glycolate such as developmental toxicity and repeated dose oral studies (ECHA, 2019). Data from the MAK report and REACH registration dossier were evaluated and taken into account to calculate the EU-LCI derivation for butyl glycolate.

There is no human or experimental data available on the toxicokinetics of butyl glycolate, but information for the inhalation route can be extrapolated from existing toxicity data on butyl glycolate and on its physicochemical properties. Butyl glycolate is an ester of n-butyl alcohol and glycolic acid, and upon contact with nasal mucosa, it is expected that butyl glycolate will be rapidly hydrolysed via esterases to yield n-butyl alcohol and glycolic acid. These metabolites will be readily bioavailable and widely distributed in the body. This assessment is supported by observations of kidney and urinary bladder effects from 28- and 90-day repeated oral exposure studies (described further below).

Glycolic acid has been reported to trigger respiratory irritation effects, and this may be substantiated by an acute (4-h) inhalation study in rats of butyl glycolate, as described in the REACH registration dossier and MAK assessment report. Male Sprague-Dawley rats (n = 5) were exposed nose-only to 0, 400, 3000, 4300 or 6200 mg/m³ (0, 73.5, 551, 790 or 1140 ppm, respectively) of butyl glycolate (vapour only for 400 mg/m³ and a mixture of aerosol and vapour starting at 3000 mg/m³) for 4 hours and sacrificed 24 hours after exposure for histopathological evaluation of the respiratory system. From 3000 mg/m³ onwards, rats exhibited signs of respiratory irritation. For example, the olfactory epithelium showed necrosis and degeneration and regeneration of the respiratory epithelium was observed. It is believed that these effects are similar to those caused by glycolic acid. Rats exposed to 400 mg/m³ exhibited no respiratory irritation effects, and no effects in the lungs were found in any of the exposed rats (DuPont, 2000; ECHA, 2019; MAK, 2012).

The REACH registration dossier identified only repeated exposure studies of butyl glycolate via the oral route, also described in the MAK assessment report. In a subacute GLP-compliant study performed according to OECD test guideline 407 ("Repeated Dose 28-Day Oral Toxicity in Rodents"), Wistar rats of both sexes were exposed to 0, 8, 40, 200 or 1000 mg/kg bw/day of butyl glycolate (Polysolvan O®) by daily gavage over a period of 29 days (28 applications). This study showed only isolated minor and reversible changes in clinical chemistry (e.g. a slight increase in inorganic phosphor and a slight decrease

in protein) in both male and female Wistar rats at 1000 mg/kg bw/day. Changes in urinalysis (e.g. slight increase of erythrocytes in urine) were also observed in both sexes at a dose starting at 1000 mg/kg bw/day. Based on the findings of this study, a No-Observed-Adverse-Effect-Level (NOAEL) for butyl glycolate of 200 mg/kg bw/day could be established (ECHA, 2019; Hoechst AG, 1990; MAK, 2012).

In a subchronic GLP-compliant study performed according to OECD test guideline 408 ("Repeated Dose 90-Day Oral Toxicity in Rodents"), Wistar rats were exposed for 13 weeks via a daily oral gavage of 0, 100, 300 or 1000 mg/kg bw/day of butyl glycolate (Polysolvan O®). One male at 1000 mg/kg bw/day was sacrificed on day 33, showing clinical signs of toxicity (abdominal swelling and dehydration) and histopathological findings in the pituitary gland and kidney. Surviving males at 1000 mg/kg bw/day showed lower body weight (gain) and food intake during the last several weeks of treatment. There was no change in body weight (gain) in females of all groups. There were changes in multiple haematological, clinical chemistry and urinary parameters starting at 300 mg/kg bw/day, with males displaying more effects than females. Males at 1000 mg/kg bw/day also showed higher absolute and relative kidney weights compared to the control weight. The most sensitive treatment-related adverse effects were observed in the kidneys and urinary bladder/urethra of Wistar rats at a concentration starting at 300 mg/kg bw/day. The primary histopathological findings were reported in the kidneys of males treated at 300 and 1000 mg/kg bw/day and females treated at 1000 mg/kg bw/day. They consisted of obstructive nephropathy (i.e. accumulation of crystals in the tubules of the kidneys). The kidneys of all affected animals showed crystals in the tubules of the cortex, medulla and/or papilla, combined with other peripheral effects (e.g. inflammation, fibrosis) in the surrounding areas. Based on the findings of this study, a NOAEL for butyl glycolate of 100 mg/kg bw/day could be established (ECHA, 2018).

A prenatal developmental toxicity study (conducted according to OECD Test Guideline 414 ("Prenatal Developmental Toxicity Study"); GLP-compliant) investigated pregnant female Wistar rats. Pregnant females (n = 20) were exposed to 0, 62.5, 250 or 1250 mg/kg bw/day orally by gavage from gestation day 7 to 16. Maternal and developmental effects from butyl glycolate exposure were only observed at the highest dose of 1250 mg/kg bw/day, and therefore the NOAEL for maternal toxicity and for developmental toxicity was set at 250 mg/kg bw/day (ECHA, 2019; MAK, 2012).

There is no evidence of the genotoxic potential of butyl glycolate shown as a result of several *in vitro* tests, and no data was identified on the carcinogenic potential of butyl glycolate.

Rationale for key study

No repeated inhalation toxicity studies were identified in the public domain on butyl glycolate in either experimental animals or humans. The derivation of the EU-LCI for butyl glycolate is based on the kidney and urinary bladder/urethra effects observed from a 13-week oral gavage rat study, as described in detail in the REACH registration dossier for butyl glycolate (ECHA, 2018). The NOAEL of this 13-week study of 100 mg/kg bw/day was then selected as the point of departure (POD).

Since the key study is a repeated oral study, a route-to-route extrapolation approach was carried out to derive a corresponding inhalation concentration of butyl glycolate. To do this, understanding of the toxicokinetics of butyl glycolate is needed. Although no information was identified on the toxicokinetics of butyl glycolate, it is understood that inhaled or ingested butyl glycolate will be rapidly hydrolysed via esterases to yield n-butyl alcohol and glycolic acid. Both the respiratory tract and the liver have the capacity to readily metabolise esters such as butyl glycolate due to the widespread presence and abundance of esterases found in the body (Dahl & Hadley, 1991; Dahl et al., 1987). Therefore, it is expected that inhalation and oral exposure to butyl glycolate will both result in rapid hydrolysis and subsequent systemic bioavailability. In line with the ECHA Guidance on information requirements R.8 (V2.1) ECHA (2012b), in the absence of route-specific absorption data for both routes, worst case assumptions have to be made. In this context, the worst case is obtained by assuming limited absorption (of the compound or its metabolites) for the starting route, leading to a low (conservative) internal NOAEL. To achieve a conservative external NOAEL a maximum absorption should thereafter be assumed for the end route, leading to a low external NOAEL. Therefore it is proposed to include a default factor of 2 (i.e. the absorption percentage for the starting route is half that of the end route) in the case of oral-to-inhalation extrapolation. Inclusion of this factor 2 means that 50% (instead of 100%) absorption is assumed for oral absorption, and 100% for inhalation.

With this considered, the route-to-route extrapolation from oral to inhalation exposure was carried out with the assumption of 100% and 50% absorption of butyl glycolate following inhalation and oral exposure, respectively. The NOAEL from the 90-day repeated dose toxicity oral study in rats was then converted to the corresponding inhalation concentration in humans as shown below:

$NOAEC_{human}$: oral NOAEL x 1/sRVrat x (Absorption oral-rat/Absorption inhal-human)
100 mg/kg bw /day ÷ 1.15 m^3/kg bw x 50/100 = 43.48 mg/m^3

Assessment factors

Standard default assessment factors for the length of study, interspecies and intraspecies differences were applied:

- Study length: 2
- Interspecies differences: 2.5 (kinetics + dynamics)
- Intraspecies differences: 10

The total assessment factor is 50.

This resulted in a calculated value of 869.6 µg/m^3 (159.85 ppb) and a derived EU-LCI for butyl glycolate of 900 µg/m^3. No information on the odour threshold of butyl glycolate was available in the public domain.

Appendix: Local respiratory irritation of butyl glycolate

A 4-h acute inhalation study in rats showed irritation effects in the upper respiratory tract, which is most likely attributable to the formation of glycolic acid due to the rapid hydrolysis of butyl glycolate in the nasal mucosa. In this study, the NOAEC for respiratory irritation was 400 mg/m^3. Selecting this as the key study and the NOAEC as point of departure would result in a total assessment factor of 25 (no assessment factor applied for exposure duration due to local irritation, 2.5 for interspecies difference and 10 for intraspecies difference) and a subsequent calculated EU-LCI value of 16 mg/m^3. Therefore, the EU-LCI value of 900 µg/m^3 derived from the 90-day repeated oral toxicity study will protect against local respiratory irritation observed in the acute inhalation rat study.

References

Dahl AR and Hadley WM, 1991. Nasal cavity enzymes involved in xenobiotic metabolism: effects on the toxicity of inhalants. Critical reviews in toxicology, 21, 345-372.

Dahl AR, Miller SC and Petridou-Fischer J, 1987. Carboxylesterases in the respiratory tracts of rabbits, rats and Syrian hamsters. Toxicology letters, 36, 129-136.

DFG 2017. List of MAK and BAT Values 2017 - Report 53. Retrieved from https://onlinelibrary.wiley.com/doi/pdf/10.1002/9783527812127.oth (last accessed on 9.02.2021).

DuPont, 2000. E. I. du Pont de Nemours and Company. H-24386: Inhalation approximate lethal concentration (ALC) in rats. Report number DuPont-4242, Newark, Delaware, USA.

ECHA 2019. Butyl glycollate. Retrieved from https://echa.europa.eu/fr/registration-dossier/-/registered-dossier/23612/1 (last accessed on 9.02.2021).

Hoechst AG, 1990. Polysolvan O, Subakute orale Toxizität (28 Applikationen in 29 Tagen) an SPF-Wistar-Ratten. Bericht No. 89.0972, Hoechst AG, Frankfurt/Main.

MAK, 2012. Hydroxyessigsäurebutylester [MAK Value Documentation in German language, 2006]. The MAK-Collection for Occupational Health and Safety.

PubChem 2019. Butyl glycolate. Retrieved from https://pubchem.ncbi.nlm.nih.gov/compound/Butyl-glycolate (last accessed on 9.02.2021).