

GAMMA-BUTYROLACTONE

CAS number: 96-48-0

Synonyms: GBL, oxolan-2-one, 1,4-butanolide, 4-butyrolactone, 1-oxacyclopentane-2-one

Chemical formula: C₄H₆O₂

Structural formula: —

Workplace exposure standard (new)

TWA: —

STEL: —

Peak limitation: —

Notations: Sk.

IDLH: —

Sampling and analysis: —

Recommendation and basis for workplace exposure standard

A TWA is not recommended as a NOAEL for neurotoxicity cannot be determined due to insufficient human toxicological data.

Given the limited data available from the primary sources, it is recommended that a review of additional sources be conducted at the next scheduled review.

Discussion and conclusions

Gamma-butyrolactone (GBL) is used as a solvent, an additive in drilling oils and chemical colour removers, a stabiliser for some pesticides and as a therapeutic sedative.

Critical effects of exposure relate to its neurotoxicity and include euphoria, hallucinations, aggression, analgesia, uncontrolled movement and altered heart and respiratory rates (DFG, 2011; HCOTN, 2008). Chronic oral exposure in animals has shown no evidence of carcinogenic activity (DFG, 2011; IARC, 1999). There is limited substance-specific occupational and sub-chronic or chronic toxicological data in humans.

GBL is rapidly converted to γ-hydroxybutyric acid (GHB) upon absorption with reports of recreational abuse of both compounds common. CNS effects from GHB exposure are reported at approximately 10 mg/kg. By applying a factor of three for the absence of a NOAEL and an additional factor of three for inter-individual differences, the Dutch Expert Committee on Occupational Safety (DECOS) calculated an oral NOAEL of 1 mg/kg for GBL (HCOTN, 2008).

A STEL of 65 mg/m³ was derived by using generic conversion factors using the NOAEL for GBL as the starting point. The TWA of 10 mg/m³ was then calculated after applying a factor of 6.5 to adjust for accumulation and assuming a plasma half-life of 60 minutes (HCOTN, 2008).

The approach presented by the HCOTN is not considered sufficiently robust for the purposes of establishing a health-based workplace exposure standard. Therefore, no recommendation has been

made regarding a TWA or STEL for GBL. It is recommended that a detailed assessment of available inhalational, chronic and dermal exposure data be prioritised at the next scheduled review.

Recommendation for notations

Not classified as a carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Not classified as a skin sensitiser or respiratory sensitiser according to the GHS.

A skin notation is recommended as there is evidence GBL can be absorbed through the skin. However, an assessment of a skin notation has been recommended for priority review based on evidence for systemic toxicity in animals with unknown relevance to exposures in the workplace.

DRAFT

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	NA	NA
ACGIH	NA	NA
No report.		
DFG	2011	Not assigned
<p>Summary of data:</p> <p>MAK not established because a NOAEL for narcotic or pre-narcotic effects cannot be determined due to insufficient detail in human toxicological data. Effects include confusion, euphoria, hallucinations, aggression, analgesia, uncontrolled movement, bradycardia, tachycardia, respiratory depression and unconsciousness.</p> <p>Derivation of a MAK from the lowest reported LOEL of 10 mg/kg for body temperature decrease (rats) by ip injection equates to 17.5 mg/m³ in humans assuming an inhalation rate of 10 m³ per 8 h shift in a 70 kg adult with an interspecies conversion factor of 4 for rats.</p> <p>No indications in human or animal studies for skin or respiratory sensitisation.</p> <p>Human data:</p> <ul style="list-style-type: none"> Onset of acute intoxication observed at 15–20 mg/kg (intravenously) or 20–30 mg/kg (intramuscularly) after 0.5–3 h Volunteers given 2.5 g orally fell asleep within 20 min and exhibited ECG profiles comparable to sleep under pentobarbital Skin penetration rate of 0.11±0.01 mg/cm²/h <i>in vitro</i> <ul style="list-style-type: none"> 1 h exposure of 2,000 cm² skin in saturated aqueous solution ≅2.9 mg/kg Accidental poisoning common due to recreational abuse (unknown concentrations) Chronic oral intake associated with anxiety, depression, tremor and sleep disorder 60 mg/kg required for surgical anaesthesia Accidental near-fatal poisoning at 570 mg/kg in 44 yr old man Analgesic effects in laboratory worker's skin exposed to unspecified large amount No sensitisation in occlusive application of pure substance to skin (unspecified amount) for 5 d followed by 2 d exposure after 3 wk No increased incidences of non-Hodgkin's lymphoma and soft-tissue sarcoma reported in 2 case studies of workers with mixed exposure to herbicides A skin notation is assigned due to evidence for appreciable skin penetration from an <i>in vitro</i> permeability study with human skin. <p>Animal data:</p> <ul style="list-style-type: none"> In rats, γ-butyrolactone (GBL) is rapidly and completely absorbed from the GIT and metabolised to γ-hydroxybutyric acid (GHB) LC50: 2,680–5,100 mg/m³ (rats, 4 h) Dermal LD50: >5,640 mg/kg (rabbits); 7% (un-depilated) and 11% (depilated) skin absorption (rats) NOEL: 11 mg/kg for locomotive effects (mice; ip); "extended climbing time" 		



Source	Year set	Standard
<ul style="list-style-type: none"> • LOEL: 10 mg/kg for body temperature decrease (rats; ip); 0.7 °C decrease • Oral NOAEL: 131 mg/kg/d for sedative effects in repeat gavage study (mice) <ul style="list-style-type: none"> ○ treatment range: 0–1,050 mg/kg/d (mice, n=10/sex, 10 wk) ○ 3 males and 1 female died in highest dose group ○ symptoms of inactivity in 525 mg/kg/d group decreased after 3–4 wk suggesting habituation ○ NOAEL of 112 mg/kg/d in similar 13 wk study with rats • Oral NOAEL ≈280 mg/kg/d for body or organ weight change, clinical parameters and histopathological parameters in repeat feeding study (dogs, 90 d) <ul style="list-style-type: none"> ○ no LOAEL determined • No maternal toxicity at 500 mg/kg/d (rats, 9 d) or 5,000 mg/m³ (rabbits, 6 h/d, 12 d) in repeat dose reproductive study • Negative genotoxicity results for several in vivo mammalian and <i>Drosophila melanogaster</i> and in vitro mutagenicity studies. • Long-term (2 yr) in vivo studies, e.g. feeding and dermal application studies, show no increase in tumour incidences in mice • LOAEL of 262 mg/kg/d for bw change in repeat gavage study <ul style="list-style-type: none"> ○ treatment range: 0–525 mg/kg/d (mice, n=50/sex/group, 2 yr) ○ bw was 6% (males) and 14–17% (females) lower than controls at end of experiment ○ partial sedation and lethargy observed after each dose • Based on negative results in animal studies, the substance is not classified as a carcinogen. 		
SCOEL	NA	NA
No report.		
OARS/AIHA	NA	NA
No report.		
HCOTN	2008	TWA: 10 mg/m³; STEL; 65 mg/m³
<p>TWA and STEL recommended to protect for depression of the CNS leading to symptoms including epileptic seizures, loss of consciousness, hallucinations, confusion and euphoria.</p> <p>Summary of additional data:</p> <p>Occupational exposure thresholds based on combination of human oral data for both GBL and GHB due to rapid conversion of GBL to GHB upon absorption. A factor of 10 is applied to the lowest reported GHB dose at which neurological effects are reported (10 mg/kg) to estimate a NOAEL of 1 mg/kg.</p> <p>The systemic bioavailability of an absorbed oral dose of GHB is 27%, which is also assumed for GBL, affords a systemic concentration of 0.27 mg/kg at the calculated NOAEL. In the absence of inhalational data for either GBL or GHB, 100% absorption following inhalation is assumed; a 15 min exposure at the NOAEL (corresponding to 0.3 m³ inhaled air in a 70 kg worker, i.e. [0.27 mg/kg×70 kg]/0.3 m³) ≅65 mg/m³, which is the basis of the STEL. Taken together with the longest reported plasma half-life of GHB (60 min) in humans, this equates to an internal exposure 6.5 times higher than the NOAEL after an 8 h shift due to systemic accumulation of the substance, hence the TWA of 10 mg/m³ is derived by division of the STEL by this factor.</p> <p>Human data:</p> <ul style="list-style-type: none"> • Plasma half-life of GHB between 30–60 min 		

Source	Year set	Standard
		<ul style="list-style-type: none"> Intravenous and oral LOEL: 10 mg/kg GHB for neurotoxic effects in single dose study Additional to neurotoxic effects, other adverse effects include nausea and vomiting, diaphoresis, and urinary and faecal incontinence (unknown dose levels). <p>Animal data:</p> <ul style="list-style-type: none"> Insufficient evidence for classification as carcinogenic in animals based on long-term exposure studies Not classified as toxic to reproduction due to inadequacies (non-standard studies) in available data: <ul style="list-style-type: none"> reduced ovulation observed at the lowest-tested single intraperitoneal dose of 62.5 mg/kg (rats) reduced foetal weights reported at 50 mg/kg (rats) reduced testes weight with doses in tap water at >550 mg/kg (young male rats) Weak skin and eye irritant (rabbits) <ul style="list-style-type: none"> data on skin sensitisation are too limited to assign a notation NOAEL: 25 mg/kg for central nervous effects in single dose study (mice; ip) <ul style="list-style-type: none"> treatment range: 0–150 mg/kg (mice) 50 mg/kg had depressing locomotor effect within 20 min followed by stimulation for next 20 min higher doses caused severe locomotor and body temperature depression for 1 h Non-mutagenic based on <i>in vitro</i> and <i>in vivo</i> studies. However, chromosomal aberrations and sister chromatid exchanges observed <i>in vitro</i> in Chinese hamster ovary cells.

Secondary source reports relied upon

Source	Year	Additional information
IARC	✓ 1999	<ul style="list-style-type: none"> Inadequate evidence of carcinogenicity in humans; evidence suggesting lack of carcinogenicity in experimental animals Not classifiable as carcinogenic in humans.
Nordic Council	✓ 2004	<ul style="list-style-type: none"> Not evaluated as a carcinogen based on studies with mice and rats; supported by <i>in silico</i> modelling based on structure and short-term genotoxicity tests, which predict no genotoxic- and unlikely non-genotoxic carcinogenicity Non-mutagenic based on <i>in vivo</i> results; some positive <i>in vitro</i> results are presented but relevance is questioned due to low predictive reliability.

Carcinogenicity — non-threshold based genotoxic carcinogens

Is the chemical mutagenic?

No

The chemical is not a non-threshold based genotoxic carcinogen.

Notations

Source	Notations
SWA	NA
HCIS	NA
NICNAS	NA
EU Annex	NA
ECHA	NA
ACGIH	NA
DFG	H (skin)
SCOEL	NA
HCOTN	Skin
IARC	Carcinogenicity – Group 3
US NIOSH	NA

NA = not applicable (a recommendation has not been made by this Agency); — = the Agency has assessed available data for this chemical but has not recommended any notations

Skin notation assessment

Calculation	
Adverse effects in human case study:	no
Dermal LD ₅₀ ≤ 1000 mg/kg:	no
Dermal repeat-dose NOAEL ≤ 200 mg/kg:	
Dermal LD ₅₀ /Inhalation LD ₅₀ < 10:	
<i>In vivo</i> dermal absorption rate > 10%:	yes
Estimated dermal exposure at WES > 10%:	yes
consider assigning a skin notation	

IDLH

Is there a suitable IDLH value available?

No

Additional information

Molecular weight:	86.09
Conversion factors at 25°C and 101.3 kPa:	1 ppm = Number mg/m ³ ; 1 mg/m ³ = Number ppm
This chemical is used as a pesticide:	✓
This chemical is a biological product:	✓
This chemical is a by-product of a process:	<input type="checkbox"/>
A biological exposure index has been recommended by these agencies:	<input type="checkbox"/> ACGIH <input type="checkbox"/> DFG <input type="checkbox"/> SCOEL

Workplace exposure standard history

Year	Standard
Click here to enter year	

References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7th Edition Documentation, CD-ROM, Single User Version. Copyright 2018. Reprinted with permission. See the [TLVs® and BEIs® Guidelines section](#) on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2011) gamma-Butyrolacton – MAK value documentation German language edition.

Health Council of the Netherlands (HCOTN) (2008) Gamma-Butyrolactone. Health-based recommended occupational exposure limit. The Hague: Health Council of the Netherlands; publication no. 2008/13OSH.

International Agency for Research on Cancer (IARC) (1999) Volume 71 re-evaluation of some organic chemicals, hydrazine and hydrogen peroxide. IARC Monographs on the evaluation of the carcinogenic risk to humans.

Nordic Expert Group for Criteria Documentation of Health Risks of Chemicals (2004) 135. γ-Butyrolactone (GBL). NR 2004;7.