PERMITTED DAILY EXPOSURE FOR BACLOFEN

1. OBJECTIVE & SEARCH STRATEGY:

Determination of Health based exposure limits for a residual active substance through the derivation of a safe threshold value like Permitted daily exposure (PDE) or threshold of toxicological concern are used to determine the risk of the active pharmaceutical substance. For determination of PDE, all the available pharmacological and toxicological data including both non-clinical and clinical data should be evaluated. This involves hazard identification by reviewing all relevant data, identification of critical effects, determination of NOAEL of the findings that are considered to be critical effects.

In this document, brief summary of pharmacological, pharmacokinetics and toxicity data of Baclofen have been presented based on the published data. The data were extracted from PubMed, PubChem, TOXLINE, Drugdex, RTECS (Registry of Toxic effects of Chemical Substances), National Toxicology Program (NTP) and FDA.

2. INTRODUCTION:

Baclofen is a synthetic Chlorophenyl-butanoic acid derivative used to treat spasms due to spinal cord damage & multiple sclerosis, it may also be used for hiccups and muscle spasms near the end of life. It is taken by mouth or by delivery into the spinal canal.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

IUPAC NAME: β-(4-chlorophenyl)-γ-aminobutyric acid (β-(4-chlorophenyl)-GABA)

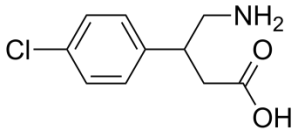
Chemical Abstract Services (CAS) Registry Number: 1134-47-0

Molecular Weight: 213.661 g/mol

Chemical Formula: $C_{10}H_{12}ClNO_2$

Description: Baclofen is a white to off-white, odorless or practically odorless crystalline powder. It is slightly soluble in water, very slightly soluble in methanol and insoluble in chloroform.

Molecular Structure:



4. HAZARDS IDENTIFIED:

CATEGORIZATION:			
TOXICITY	**YES**	**NO**	**UNKNOWN**
Genotoxicant	-	√	-
Carcinogen	-	√	-
Reproductive/Developmental Toxicant	-	√	-
Highly Sensitizing potential	-	√	-

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SUMMARY OF HAZARD IDENTIFICATION:

Pharmacodynamics data

Baclofen is capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by hyperpolarization of afferent terminals, although actions at supraspinal sites may also occur and contribute to its clinical effect. Although Baclofen is an analog of the putative inhibitory neurotransmitter gamma-amino butyric acid (GABA), there is no conclusive evidence that actions on GABA systems are involved in the production of its clinical effects. In studies with animals, Baclofen has been shown to have general CNS depressant properties as indicated by the production of sedation with tolerance, somnolence, ataxia, and respiratory and cardiovascular depression. Baclofen is rapidly and extensively absorbed and eliminated. Absorption may be dose-dependent, being reduced with increasing doses. Baclofen is excreted primarily by the kidney in unchanged form and there is relatively large inter subject variation in absorption and/or elimination.

Acute Toxicity

Case Study 1:

Species	Route	LD50 mg/kg
Mouse	Intravenous	26
Mouse	Oral (P.O.)	75
Rat	Intravenous	112
Rat	Oral (P.O.)	150
Rat	Sub-cutaneous	137

Case Study 2:

ORGANISM	TEST TYPE	ROUTE	DOSE (Baclofen)	EFFECT	REFERENCE
Women	TDLo	Oral	9 mg/kg (9 mg/kg)	Behavioral: convulsions or effect on seizure threshold; behavioral: coma; lungs, thorax, or respiration: other changes	Postgraduate Medical Journal., 56(865), 1980 [PMID:7267501]
Women	TDLo	Oral	8 mg/kg (8 mg/kg)	Cardiac: pulse rate; lungs, thorax, or respiration: respiratory depression	Postgraduate Medical Journal., 57(580), 1981 [PMID:7329897]
Man	TDLo	Oral	571 ug/kg	Lungs, thorax, or respiration: dyspnea	Annals of Pharmacotherapy., 27(883), 1993 [PMID:8364269]
Man	TDLo	Oral	14 mg/kg (14 mg/kg)	Behavioral: muscle weakness; behavioral: coma	Journal of Toxicology, Clinical Toxicology., 20(59), 1983 [PMID:6887300]
Man	TDLo	Oral	4286 ug/kg	Behavioral: coma; cardiac: pulse rate; vascular: bp lowering not characterized in autonomic section	American Journal of Emergency Medicine., 4(552), 1986 [PMID:3778604]

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	Women	TDLo	Parenteral	25 ug/kg/2D-I (0.025 mg/kg)	Sense organs and special senses: mydriasis (pupillary dilation): eye; behavioral: coma	International Journal of Clinical Pharmacology, Therapy and Toxicology., 29(274), 1991
	Man	TDLo	Unreported	857 ug/kg/2D-I	Brain and coverings: changes in surface eeg; behavioral: somnolence (general depressed activity); behavioral: hallucinations, distorted perceptions	Italian Journal of Neurological Sciences., 12(323), 1991 [PMID:1874611]
	Rat	LD50	Oral	145 mg/kg (145 mg/kg)	Null	Drugs in Japan, 6(576), 1982
	Rat	LD50	Subcutaneous	115 mg/kg (115 mg/kg)	Null	Iyakuhin Kenkyu. Study of Medical Supplies., 11(181), 1980
	Rat	LD50	Intravenous	78 mg/kg (78 mg/kg)	Null	Iyakuhin Kenkyu. Study of Medical Supplies., 11(181), 1980
	Mouse	LD50	Oral	200 mg/kg (200 mg/kg)	Null	Drugs in Japan, 6(576), 1982
	Mouse	LD50	Subcutaneous	103 mg/kg (103 mg/kg)	Null	Iyakuhin Kenkyu. Study of Medical Supplies., 11(181), 1980
	Mouse	LD50	Intravenous	31 mg/kg (31 mg/kg)	Behavioral: altered sleep time (including change in righting reflex); behavioral: ataxia; lungs, thorax, or respiration: respiratory depression	Gekkan Yakuji. Pharmaceuticals Monthly., 21(2069), 1979
	Man	TDLo	Oral	3429 mg/kg (3429 mg/kg)	Behavioral: coma; cardiac: pulse rate increase without fall in bp; lungs, thorax, or respiration: respiratory obstruction	Journal of Toxicology, Clinical Toxicology., 32(291), 1994 [PMID:8007036]
	Women	TDLo	Oral	18 mg/kg (18 mg/kg)	Behavioral: coma; lungs, thorax, or respiration: respiratory depression	Journal of Toxicology, Clinical Toxicology., 22(11), 1984 [PMID:6492227]

Repeated Dose Toxicity (Chronic Toxicity)

Case Study 1:

Species	Sex (M/F)	No. of Groups	Dose mg/kg/day	Route	Duration of Study	Toxic Effects
Rat	20 each	4	0,5,10; 20-80 (weekly increase of 10 mg/kg/day)	P.O.	30 Days	Slight adrenal enlargement
Rat	10 each	5	Baclofen + Diazepam: 0 + 0, 4 + 2, 20 + 10, 0 + 10, 20 + 0	P.O.	30 Days	None

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SUMMARY OF HAZARD IDENTIFICATION:

Dog	8 each	4	0,1,2,4-8 (Doubled in last week)	P.O.	30 Days	Emesis at all dose levels, anorexia, salivation, ataxia, sedation, weight loss
Rat	80 each	4	0,5,20-160,40-500	P.O.	1 Year	Weight loss, mild alopecia, 20F 40-500 urinary incontinence at intermediate and high doses. Elevated mean neutrophil/ lymphocyte ratios and SGPT at intermediate and high doses.
Rat	280 each	1 & 3	0,5,25-50,50-100	P.O.	1 Year	Reduced weight gain. Dose related urinary frequency. Dose-related increase in incidence of ovarian cysts.
Dog	12 each	4	0,2-4,3-8,4-12	P.O.	1 Year	Transient emesis, sedation, 3F 4-12 convulsions and cardiovascular collapse (single animal), possible slight adrenal enlargement, hind limb weakness or paralysis.

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SUMMARY OF HAZARD IDENTIFICATION:	
	Case Study 2: The study was performed on 30 healthy adult male albino rats divided into four groups with 5 rats in each control group, and 10 rats in either experimental groups (two experimental and two control groups). Five rats (negative control) were kept in a quite non-stressful environment, provided with food ad libitum and free access to water. Normal saline (1 ml) was given orally as placebo in the positive control group (n = 5). Experimental group III, baclofen acute toxicity group (10 rats): Each animal received a single dose of lethal dose (LD_{50}) of baclofen orally by gavage. It equals 145 mg/kg body weight. The rats were observed for acute toxicity manifestations as well as for LD_{50} deaths. Group IV, (baclofen-dependent group, 10 rats): Each animal received baclofen (1/10th LD_{50}) in gradually increasing doses for 1 month.
Carcinogenicity	An apparently dose related increase in the incidence of ovarian cysts and of enlarged and/or haemorrhagic adrenals at the maximum dose used (50 to 100 mg/kg) were observed in female rats treated with baclofen for two years. The clinical relevance of these findings is not known.
In vivo/In vitro Genotoxicity Studies	Baclofen was negative for mutagenic and genotoxic potential in tests in bacteria, mammalian cells, yeast, and Chinese hamsters. A 2-year rat study (oral administration of baclofen) found no evidence of carcinogenesis.
Reproductive/Developmental Toxicity	Reproductive toxicity Oral baclofen showed no significant adverse effects on fertility or postnatal development at non-maternally toxic dose levels in rats (approximately 2.1-times the maximum oral mg/kg dose in adults). At maternally toxic dose levels (8.3-times the maximum oral mg/kg dose in adults), baclofen increased the incidence of omphalocoeles (ventral hernias) in rats, an effect not seen in mice or rabbits. Delayed fetal growth (ossification of bones) in the fetuses of rats and rabbits was also observed at maternotoxic doses. Rat: Doses of 4.4-5 and 17.7-21.3 mg/kg/day were administered orally to two groups of female rats during pre-mating, mating, gestation, and lactation. The only significant effect was a reduction in litter size and survivability of offspring (possibly due to agalactia) in the high-dose group. In another rat study, doses of 5 and 10 mg/kg/day were administered by gavage during the last trimester of pregnancy and throughout the lactation period. Five of 31 dams in the high-dose group showed severe weight loss from days 15-21 of gestation as well as agalactia and the entire litter of each of these dams died by day 2 post-partum. In a third study, baclofen doses of 30 mg/kg/day produced symptoms of ataxia and drowsiness in dams and the death of 4 of 24 dams dosed from gestation Days 1 to 12. At this high dose level, there was a slight increase in the resorption rate; however, the number and size of the fetuses remained normal and no malformations were reported. Rat and Mouse: Doses of 5 and 20 mg/kg/day were administered by gavage to two groups of pregnant rats on days 6-15 of gestation. The only significant finding was the presence of abdominal hernias in 4/160 fetuses in the high-dose group. In a second similar study, 1/229 control fetuses and 6/293 fetuses from dams receiving 20 mg/kg/day had abdominal hernias. Comparable lesions did not occur in a similar mouse study. The average number of stillbirths or viable newborns did not differ significantly between control and medicated groups. The average weight of neonates from the high-dose group was significantly reduced. Rabbit: Doses of 1, 5, and 10 mg/kg/day were administered by gavage to groups of rabbits from the 6th to 18th day of gestation. There was an increased incidence of unossified phalangeal nuclei of forelimbs and hind-limbs in the fetuses from the high-dose group. In another study, a slight increase in resorption rates and the number of rabbits that were non-gravid was observed

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SUMMARY OF HAZARD IDENTIFICATION:	
	in 27 rabbits receiving 10 and 15 mg/kg/day of oral baclofen.
Highly Sensitizing Potential	No any serious allergic reaction in Baclofen reported.
IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	The FDA requires a black box warning for Baclofen. Abrupt withdrawal of intrathecal baclofen may occur in patients using the drug over 2 months and may result in a hypermetabolic state with hyperpyrexia, impaired mental status, muscle rigidity, and severe rebound spasticity which may advance to rhabdomyolysis and multi-organ system failure.
Clinical therapeutic and adverse effects	The recommended oral dose of Baclofen is 15-80 mg daily. **Common adverse effects of Baclofen:** • Drowsiness • weakness • dizziness • tiredness • headache • seizures • nausea • vomiting • low blood pressure • constipation • confusion • respiratory depression • Trouble sleeping (insomnia), and increased urinary frequency or urinary retention.
NOAEL/LOAEL	Minimum therapeutic dose has been taken as NOAEL.

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APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	**5**	For extrapolation from rat to humans
F2: Inter Individual Variability	**10**	Used for differences between individuals in the human population
F3: Duration of Toxicity	**1**	For 1 year study in rats in repeat dose toxicity
F4: Severe Toxicity (1-10)	**1**	No any toxicity (Genotoxicity/Reproductive toxicity/ Carcinogenicity) observed
F5: NOAEL or LOAEL (10 if LOAEL)	**5**	NOAEL value is selected
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{0.30 (NOAEL) x 50}}{\text{5 x 10 x 1 x 1 x 5}}$ = 0.06 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Baclofen.
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4229966/.
- https://www.researchgate.net/publication/326183587_Baclofen_systemic_toxicity_Experimental_histopathological_and_biochemical_study.
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- https://www.drugbank.ca/drugs/DB00181.
- https://www.drugs.com/dosage/baclofen.html.
- https://pubchem.ncbi.nlm.nih.gov/compound/Baclofen#section=Acute-Effects.
- https://journals.sagepub.com/doi/abs/10.1177/0960327117712369.
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