PERMITTED DAILY EXPOSURE FOR DICYCLOMINE HCL

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 Dicyclomine Hcl 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:

Dicycloverine, also known as dicyclomine, is a medication that is used to treat spasms of the intestines such as occur in irritable bowel syndrome. Common side effects include dry mouth, blurry vision, weakness, sleepiness, and lightheadedness. Serious side effects may include psychosis and breathing problems in babies. Use in pregnancy appears to be safe while use during breastfeeding is not recommended.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

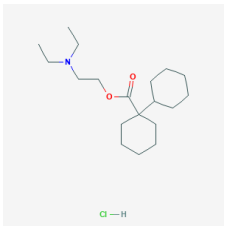
IUPAC name: 2-(diethyl amino) ethyl 1-cyclohexylcyclohexane-1-carboxylate; hydrochloride

Chemical Abstract Services (CAS) Registry Number: 67-92-5

Molecular Weight:

Chemical Formula: $C_{19}H_{36}ClNO_2$

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

Dicyclomine is an anticholinergic drug used to relax the smooth muscles of the intestines. It's duration of action is not especially long as it is usually taken 4 times daily with individual doses of 20-40 mg orally or 10-20 mg by intramuscular injection.

Acute Toxicity

Organism	Test type	Route	Dose (mg/kg)	Effect	Reference
Infant	TDLo	Oral	1000	Behavioral: Regidity; Lungs, Thorax, Or Respiration: Dyspnea; Lungs, Thorax, Or Respiration: Cyanosis	British Medical Journal., 288(901), 1984
Rat	LD50	Oral	1290	Behavioral: convulsions or effect on seizure threshold; behavioral: muscle weakness; lungs, thorax, or respiration: dyspnea	Kiso to Rinsho. Clinical Report., 8(1954), 1974
Mouse	LD50	Oral	625	Behavioral: somnolence (general depressed activity); behavioral: convulsions or effect on seizure threshold	Journal of the American Pharmaceutical Association, Scientific Edition., 39(305), 1950
Mouse	LD50	Subcutaneous	1.9	NULL	Farmaco. Scienza e Tecnica., 7(448), 1952
Mouse	LD50	Intravenous	31.5	Autonomic nervous system: smooth muscle relaxant (mechanism undefined, spasmolytic)	Arzneimittel-Forschung. Drug Research., 11(1119), 1961 [PMID:13893481]
Rabbit	LD50	Intravenous	35	Behavioral: Convulsions Or Effect On Seizure Threshold; Kidney, Ureter, And Bladder: Hematuria	Journal of the American Pharmaceutical Association, Scientific Edition., 39(305), 1950

Repeated Dose Toxicity (Chronic Toxicity)

No data available.

Carcinogenicity

There are no known human data on long-term potential for carcinogenicity or mutagenicity. Long-term studies in animals to determine carcinogenic potential are not known to have been conducted. In studies in rats at doses of up to 100 mg/kg/day, Dicyclomine Hcl produced no deleterious effects on breeding, conception, or parturition.

In vivo/In vitro Genotoxicity Studies

No mutagenicity observed.

Reproductive/Developmental Toxicity

Teratogenic Effects: Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at doses up to 33 times the maximum recommended human dose based on 160 mg/day (3 mg/kg) and have revealed no evidence of impaired fertility or harm to the fetus due to dicyclomine. Epidemiologic studies in pregnant women with products containing dicyclomine hydrochloride (at doses up to 40 mg/day) have not shown that dicyclomine increases the risk of fetal abnormalities if administered during the first trimester of pregnancy. There are, however, no adequate and well-controlled studies in pregnant women at the recommended doses (80-160 mg/day). Because animal reproduction studies are not always predictive of human response, Dicyclomine Hcl as indicated for functional bowel/irritable bowel

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SUMMARY OF HAZARD IDENTIFICATION:	
	syndrome should be used during pregnancy only if clearly needed.
Highly Sensitizing Potential	A Skin Rash, an Abnormally fast heartbeat; fainting; hallucinations; hives; increased pressure in the eye; inflammation of the skin due to an allergy may observed.

IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	No any adverse effect seen in non-clinical toxicity data.
Clinical therapeutic and adverse effects	**Clinical Therapeutic Dose** **Initial Dose:** 10 mg/day **Maintenance Dose:** 40 mg/day **Maximum Dose:** 160 mg/day **Adverse effects:** Include nausea, vomiting, dilated pupils, weakness or loss of movement in any part of your body, trouble swallowing, fainting, or seizure (convulsions). This medication may cause blurred vision and may impair your thinking or reactions.

NOAEL/LOAEL	0.2 mg/kg/day considered as NOAEL value (Smallest Therapeutic Dose)

APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	1	For extrapolation from rats to humans.
F2: Inter Individual Variability	10	Used for differences between individuals in the human population.
F3: Duration of Toxicity (Repeat Dose Toxicity)	10	Chronic toxicity data not available.
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 (Minimum daily dose is selected in mg/kg/day).
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{0.2 (NOAEL) x 50}}{\text{1 x 10 x 10 x 1 x 5}}$ = 0.02 mg/day

5. REFERENCES:

- https://pubchem.ncbi.nlm.nih.gov/compound/Dicyclomine-hydrochloride#section=Safety-and-Hazards