PERMISSIBLE DAILY EXPOSURE (PDE) DETERMINATION STRATEGY FOR CHLORPHENIRAMINE MALEATE ORAL SOLUTION USP 2 mg/5 ml

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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 **Chlorpheniramine Maleate** 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:

Chlorpheniramine (klor fen IR a meen) is an antihistamine. It is used to treat sneezing, runny nose, and itchy or watery eyes from allergies or a cold. It is also used to treat the symptoms of an allergic reaction. It is taken orally (by mouth). The medication takes effect within two hours and lasts for about 4-6 hours

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Chlorpheniramine Maleate appears as odorless white crystalline solid or white powder with a bitter taste.

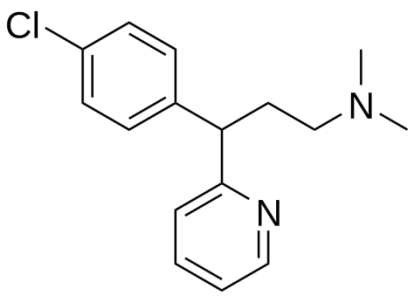
IUPAC Name: 3-(4-Chlorophenyl)-N, N-dimethyl-3-(pyridin-2-yl)-propan-1-amine.

Chemical Abstract Services (CAS) Registry Number: 132-22-9

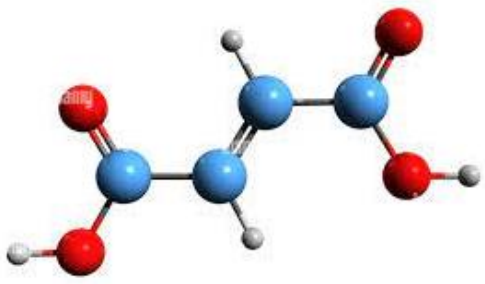
Molecular Weight: 274.79 g·mol−1

Chemical Formula: $C_{16}H_{19}ClN_2$

Molecular Structure:



2D



3D

4. HAZARDS IDENTIFIED:

CATEGORIZATION:			
Toxicity	**Yes**	**No**	**Unknown**
Genotoxicant	-	√	-
Carcinogen	-	√	-
Reproductive/Developmentaltoxicity	-	√	-
Highly sensitizingpotential	-	√	-

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5. SUMMARY OF ASSESSMENT PROCESS:

HAZARD IDENTIFICATION	
Pharmacodynamics data	In allergic reactions an allergen interacts with and cross-links surface IgE antibodies on mast cells and basophils. Once the mast cell-antibody-antigen complex is formed, a complex series of events occurs that eventually leads to cell-degranulation and the release of histamine (and other chemical mediators) from the mast cell or basophil. Once released, histamine can react with local or widespread tissues through histamine receptors. Histamine, acting on H_1-receptors, produces pruritis, vasodilatation, hypotension, flushing, headache, tachycardia, and bronchoconstriction. Histamine also increases vascular permeability and potentiates pain. Chlorpheniramine, is a histamine H1 antagonist (or more correctly, an inverse histamine agonist) of the alkylamine class. It competes with histamine for the normal H_1-receptor sites on effector cells of the gastrointestinal tract, blood vessels and respiratory tract. It provides effective, temporary relief of sneezing, watery and itchy eyes, and runny nose due to hay fever and other upper respiratory allergies.
Pharmacokinetic data	**Mechanism of action:** Chlorpheniramine binds to the histamine H1 receptor. This block the action of endogenous histamine, which subsequently leads to temporary relief of the negative symptoms brought on by histamine. **Absorption:** Well absorbed in the gastrointestinal tract. **Volume of Distribution:** Not Available **Protein Binding:** 72% **Route of Elimination:** Not Available
Acute toxicity	**Species** — **Route of Administration** — **LD_{50}** — **Duration** Rat — Oral — 680 mg/kg — 29 days Mouse — Oral — 121 mg/kg — 29 days Guinea Pig — Oral — 186 mg/kg — 29 days
Repeated dose toxicity	Although repeated dose toxicity tests were performed in rats (3-generation study), dogs (6-month toxicity study) and monkeys (7-week study), it was not possible establish NOELs due to the poor quality of the documentation provided. 6. A 13-week study was conducted in rats treated 5 days per week with chorphenamine doses of 0, 3.75, 7.5, 15, 30 and 60 mg/kg bw/day. All rats survived to the end of the study. Lower final bodyweights were observed in the male rat 15 mg/kg bw group. A NOEL of 7.5 mg/kg bw/day was established based on the decreased bodyweight in males.
Carcinogenicity	A 2-year oncogenicity study of chlorpheniramine maleate was conducted in which groups of 50 male and 50female CD albino rats were fed diets containing SCH 190 (Chlor-trimeton') for 103 weeks (Schering-Plough Research Division, 1978, unpublished). The doses (approximately 2, 10, or 20 mg/kg per day) were formulated based on group mean values for body weight and feed consumption. There were no reported increases in the incidences of neoplastic lesions attributed

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HAZARD IDENTIFICATION	
	to dosing with chlorpheniramine maleate; however, the tissues examined microscopically were limited to gross lesions, liver, spleen, lung, urinary bladder, mammary tissue (in females), and kidney. The tumor incidence data were based on the evaluations of two pathologists.
Genotoxicity studies	Chlorpheniramine maleate was not mutagenic to Salmonella typhimurium strains TA98, TA100, TA1535, or TA1537 in the presence or absence of S9 metabolic activation systems prepared from the livers of Aroclor 1254-treated male Sprague-Dawley rats or male Syrian hamsters (Andrews et al., 1980; Mortelmans et al., 1986; Appendix G, Table Gl). Since chlorpheniramine is a tertiary amine that could potentially react with nitrite to form nitrosamines in vivo, it was treated with sodium nitrite in acetic acid, and the products of this reaction were tested for mutagenicity in the Ames Salmonelldmammalian-microsomemutagenicity test (Andrews et al., 1980). Nitrosation of chlorpheniramine did not produce a mutagenic response in Salmonella; however, nitrosation of methapyrilene, a carcinogenic antihistaminic drug, did yield mutagenic products. Chlorpheniramine maleate was not mutagenic when tested by the NTP in the mouse lymphoma L5178Yfl'K''- forward mutation assay with or without metabolic activation from Aroclor 1254- induced F344 male rat liver S9.
Reproductive/Developmentaltoxicity	In a reproduction study CD rats received by gavage 0, 5, 10 and 20 mg/kg bw chlorphenamine maleate. Males were dosed daily for 63 weeks, plus a 3-week mating period. Females were treated 21 days before mating, until sacrifice at either 14 days of gestation or 21 days after parturition. A NOEL of 5 mg/kg bw of chlorphenamine maleate (3.5 mg/kg bw of chlorphenamine) was established based on post natal survival of the pups.
Highly Sensitizing Potential	Allergic responses to chlorpheniramine in skin prick, intradermal, and oral provocation tests points to IgE-mediated type I hypersensitivity as the mechanism of chlorpheniramine hypersensitivity reaction in this case.
Hazard Identification	 Acute Toxic

IDENTIFICATION OF CRITICAL EFFECTS	
Clinical therapeutic and adverse effects	**Therapeutic Effect:** Chlorpheniramine relieves red, itchy, watery eyes; sneezing; itchy nose or throat; and runny nose caused by allergies, hay fever, and the common cold. Chlorpheniramine helps control the symptoms of cold or allergies but will not treat the cause of the symptoms or speed recovery. **Adverse Effect:** Common side effects include feeling sick (nausea), sleepy

	or dizzy. You may also have difficulty concentrating, a dry mouth, headaches or blurred vision. Wait a minimum of 4 hours between taking doses. Do not drink alcohol while you're taking chlorphenamine.

NOAEL/NOEL/LOEL/ LOAEL	**Species:** Rat **Application Route:** Oral **Exposure time:** 2 Years **NOAEL:** 30 - 60 mg/kg body weight **Result:** Negative **Species:** Mouse **Application Route:** Oral **Exposure time:** 2 Years **NOAEL:** 20 - 50 mg/kg body weight **Result:** Negative

APPLICATION OF ADJUSTMENT FACTORS- PDE calculation		
F1: Extrapolation between species	5	Based on the selection of toxicity study of rats.
F2: Inter-individual variability	10	Conventionally used to allow for differences betweenindividuals in the human population
F3: Duration of toxicity	1	Long Term Study (2 Year) toxicity study in rats
F4: Severe toxicity (1-10)	1	No any toxicity
F5: NOAEL/NOEL/LOAEL/LOEL	1	Selection of NOAEL dose.
PK correction		For PDE calculation, no factor is applied.

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PDE CALCULATION:

$$\text{PDE (mg/day)} = \frac{\text{NOAEL (mg/day)} \times \text{Body weight (kg)}}{F1 \times F2 \times F3 \times F4 \times F5}$$

$$= \frac{30 \times 50}{5 \times 10 \times 1 \times 1 \times 1}$$

= **30 mg/day**

6. REFERENCES:

- https://go.drugbank.com/drugs/DB01114https://pubmed.ncbi.nlm.nih.gov/26705515/
- Toxicology & Carcinogenesis studies of Chlorpheniramine Maleate.
- https://www.ema.europa.eu/en/documents/mrl-report/chlorphenamine-summary-report-committee-veterinary-medicinal-products_en.pdf
- https://www.msd.com/docs/product/safety-data-sheets/ah-sds/Dexamethasone%20and%20Chlorphenamine%20Hydrogen%20Maleate%20Formulation_AH_NZ_6N.pdf

7. GLOSSARY:

PDE: Permitted daily exposure
AUC: Area under the curve **GRAS:**
Generally regarded as safe**GLP:** Good
laboratory practice
GMP: Good manufacturing practice
LD: Lethal dose
LED: Lowest-effective dose
TDLo (Toxic Dose Low): Lowest published toxic dose
LOAEL: Lowest-observed-adverse-effect level **LOEL:**
Lowest-observed-effect level
MSDS: Material safety data sheet
MTD: Maximum tolerable dose
MPDD: Maximum permissible daily dose
MTEL: Maximum tolerable exposure level**NEL:**
No-effect level
NOAEL: No-observed-adverse-effect level
NOEL: No-observed-effect level
OEL: Occupational exposure limit
QSAR: Quantitative structure–activity relationship
SDS: Safety data sheet
ADI: Acceptable daily intake. Estimate by JECFA; the amount of a food additive, expressed on a body weight basis that can be ingested daily over a lifetime without appreciable health risk.

Area under the curve (AUC): Area between a curve and the abscissa (horizontal axis), i.e., the area underneath the graph of a function; often, the area under the tissue (plasma) concentration curve of a substance expressed as a function of time.

Bioaccumulation: progressive increase in the amount of a substance in an organism or partof an organism that occurs because the rate of intake exceeds the organism's ability to remove the substance from the body.

Bioavailability: biological and physiological availability. Extent of absorption of a substance by a living organism compared to a standard system.

Biological half-life: for a substance, the time required for the amount of that substance in a biological system to be reduced to one-half of its value by biological processes, when the rate of removal is approximately exponential.

Carcinogen: agent (chemical, physical, or biological) that is capable of increasing the incidence of malignant neoplasms, thus causing cancer.

Clastogen: agent causing chromosome breakage and (or) consequent gain, loss, or rearrangement of pieces of chromosomes.

Clearance: volume of blood or plasma or mass of an organ effectively cleared of a substance by elimination (metabolism and excretion) divided by time of elimination.

Cmax: used in pharmacokinetics referring to the maximum (or peak) serum concentrationthat a drug achieves in a specified compartment or test area after the drug has been administrated and before the administration of a second dose.

Critical dose: dose of a substance at and above which adverse functional changes, reversible or irreversible, occur in a cell or an organ.

Critical effect: for deterministic effects, the first adverse effect that appears when the threshold (critical) concentration or dose is reached in the critical organ:

Adverse effects with no defined threshold concentration are regarded as critical. Dose (of a substance): total amount of a substance administered to, taken up, or absorbed by an organism, organ, or tissue.

Draize test: evaluation of materials for their potential to cause dermal or ocular irritation and corrosion following local exposure; generally using the rabbit model (almost exclusively the New Zealand White) although other animal species have been used.

Elimination (in toxicology): disappearance of a substance from an organism or a partthereof, by processes of metabolism, secretion, or excretion.

Embryotoxicity: production by a substance of toxic effects in progeny in the first period of pregnancy between conception and the fetal stage.

Fetotoxicity: production by a substance of toxic effects in progeny in the second period of pregnancy between fetal stage and delivery.

First-pass effect: biotransformation and, in some cases, elimination of a substance in theliver after absorption from the intestine and before it reaches the systemic circulation.

Gavage: administration of materials directly into the stomach by esophageal intubation.

Generally regarded as safe (GRAS): phrase used to describe the USFDA philosophy that justifies approval of food additives that may not meet the usual test criteria for safety but have been used extensively and have not demonstrated that they cause any harm to consumers.

Genotoxic: capable of causing a change to the structure of the genome.

Good laboratory practice (GLP) principles: fundamental rules incorporated in OECDguidelines and national regulations concerned with the process of effective organization and the conditions under which laboratory studies are properly planned, performed, monitored, recorded, and reported.

Hazard identification: determination of substances of concern, their adverse effects, target

populations, and conditions of exposure, taking into account toxicity data and knowledge of effects on human health, other organisms, and their environment.

Hypersensitivity: state in which an individual reacts with allergic effects following exposure to a certain substance (allergen) after having been exposed previously to the same substance.

In silico: phrase applied to data generated and analyzed using computer modeling and information technology.

In vitro: in glass, referring to a study in the laboratory usually involving isolated organ, tissue, cell, or biochemical systems.

In vivo: In the living body, referring to a study performed on a living organism.

Lethal dose (LD): amount of a substance or physical agent (e.g., radiation) that causes death when taken into the body.

Lowest-effective dose (LED): lowest dose of a chemical inducing a specified effect in a specified fraction of exposed individuals.

Lowest published toxic dose (Toxic Dose Low, TDLo): the lowest dosage per unit of bodyweight (typically stated in milligrams per kilogram) of a substance known to have produced signs of toxicity in a particular animal species.

Lowest-observed-adverse-effect level (LOAEL): lowest concentration or amount of a substance (dose), found by experiment or observation, that causes an adverse effect on morphology, functional capacity, growth, development, or life span of a target organism distinguishable from normal (control) organisms of the same species and strain under defined conditions of exposure.

Lowest-observed-effect level (LOEL): lowest concentration or amount of a substance (dose), found by experiment or observation, that causes any alteration in morphology, functional capacity, growth, development, or life span of target organisms distinguishable from normal (control) organisms of the same species and strain under the same defined conditions of exposure.

Material safety data sheet (MSDS): compilation of information required under the U.S. OSHA Hazard Communication Standard on the identity of hazardous substances, health and physical hazards, exposure limits, and precautions.

Maximum permissible daily dose (MPDD): maximum daily dose of substance whose penetration into a human body during a lifetime will not cause diseases or health hazards that can be detected by current investigation methods and will not adversely affect future generations.

Maximum tolerable dose (MTD): highest amount of a substance that, when introduced into the body, does not kill test animals (denoted by LD0).

Maximum tolerable exposure level (MTEL): maximum amount (dose) or concentration of a substance to which an organism can be exposed without leading to an adverse effect after prolonged exposure time. Maximum tolerated dose (MTD): high dose used in chronic toxicity testing that is expected on the basis of an adequate sub-chronic study to produce limited toxicity when

administered for the duration of the test period.

Median lethal dose (LD50): statistically derived median dose of a chemical or physical agent (radiation) expected to kill 50 % of organisms in a given population under a defined set of conditions.

Mutagenicity: ability of a physical, chemical, or biological agent to induce (or generate) heritable changes (mutations) in the genotype in a cell as a consequence of alterations or loss of genes or chromosomes (or parts thereof).

No-effect level (NEL): maximum dose (of a substance) that produces no detectable changes under defined conditions of exposure.

No-observed-adverse-effect level (NOAEL): greatest concentration or amount of a substance, found by experiment or observation, which causes no detectable adverse alteration of morphology, functional capacity, growth, development, or life span of the target organism under defined conditions of exposure.

No-observed-effect level (NOEL): greatest concentration or amount of a substance, found by experiment or observation, that causes no alterations of morphology, functional capacity, growth, development, or life span of target organisms distinguishable from those observed in normal (control) organisms of the same species and strain under the same defined conditions of exposure.

Quantitative structure–activity relationship (QSAR): quantitative structure–biological activity model derived using regression analysis and containing as parameters physicochemical constants, indicator variables, or theoretically calculated values.

Safety data sheet (SDS): single page giving toxicological and other safety advice, usually associated with a particular preparation, substance, or process.

Target (in biology): any organism, organ, tissue, cell or cell constituent that is subject to the action of an agent.