PERMISSIBLE DAILY EXPOSURE (PDE) DETERMINATION STRATEGY FOR PETHIDINE INJECTION BP 75 mg/1.5 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 **Pethidine Injection BP 75 mg/1.5 ml** for Injection 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:

Pethidine, also known as meperidine is a fully synthetic opioid pain medication of the phenylpiperidine class, its analgesic properties. Pethidine is the prototype of a large family of analgesics including the pethidine 4-phenylpiperidines (piminodine, anileridine and others), the prodines (alphaprodine, MPPP, etc.), bemidones (ketobemidone, etc.) and others more distant, including diphenoxylate and analogues.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

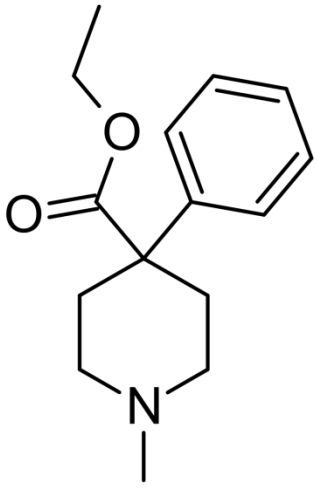
Meperidine hydrochloride is a white crystalline substance with a melting point of 186° C to 189° C. It is readily soluble in water and has a neutral reaction and a slightly bitter taste. The solution is not decomposed by a short period of boiling.

IUPAC Name: Ethyl 1-methyl-4-phenylpiperidine-4-carboxylate

Chemical Formula: $C_{15}H_{21}NO_2$

Molecular Weight: 247.338 g/mol

Molecular Structure:



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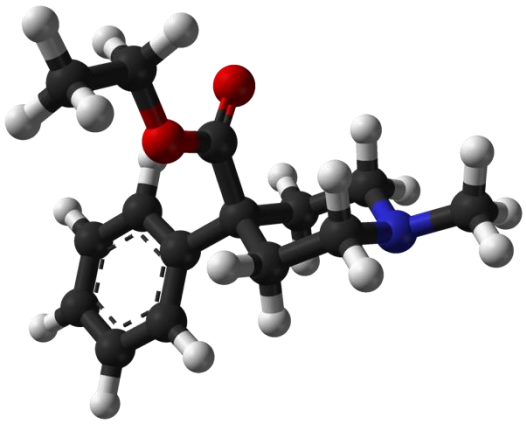

3D

4. HAZARDS IDENTIFIED:

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

5. SUMMARY OF ASSESSMENT PROCESS:

HAZARD IDENTIFICATION	
Pharmacodynamics data	Pethidine is a synthetic opiate agonist belonging to the phenylpiperidine class. Pethidine may produce less smooth muscle spasm, constipation, and depression of the cough reflex than equivalent doses of morphine. The onset of action is lightly more rapid than with morphine, and the duration of action is slightly shorter. The chemical structure of Pethidine is similar to local anesthetics. Pethidine is recommended for relief of moderate to severe acute pain and has the unique ability to interrupt postoperative shivering and shaking chills induced by amphotericin B. Pethidine has also been used for intravenous regional anesthesia, peripheral nerve blocks and intraarticular, epidural and spinal analgesia. Pethidine is considered a second-line agent for the treatment of acute pain. Pethidine is primarily a kappa-opiate receptor agonist and also has local anesthetic effects. Pethidine has more affinity for the kappa-receptor than morphine. Opiate receptors are coupled with G-protein receptors and function as both positive and negative regulators of synaptic transmission via G-proteins that activate effector proteins. Binding of the opiate stimulates the exchange of GTP for GDP on the G-protein complex. As the effector system is adenylate cyclase and cAMP located at the inner surface of the plasma membrane, opioids decrease intracellular cAMP by inhibiting adenylate cyclase. Subsequently, the release of nociceptive neurotransmitters such as substance P, GABA, dopamine, acetylcholine and noradrenaline is inhibited. Opioids also inhibit the release of vasopressin, somatostatin, insulin and glucagon. Opioids close N-type voltage-operated calcium channels (OP2-receptor agonist) and open calcium-dependent inwardly rectifying potassium channels (OP3 and OP1 receptor agonist). This results in hyperpolarization and reduced neuronal excitability
Pharmacokinetic data	**Absorption:** The oral bioavailability of Pethidine in patients with normal hepatic function is 50-60% due to extensive first-pass metabolism. Bioavailability increases to 80-90% in patients with hepatic impairment (e.g. liver cirrhosis). Pethidine is less than half as effective when administered orally compared to parenteral administration. One study reported that 80-85% of the drug administered intramuscularly was absorbed within 6 hours of intragluteal injection in health adults; however, inter-individual variation and patient-specific variable appear to cause considerable variations in absorption upon IM injection. **Volume of Distribution:** Pethidine crosses the placenta and is distributed into breast milk. **Protein Binding:** 60-80% bound to plasma proteins, primarily albumin and α_1-acid glycoprotein. The presence of cirrhosis or active viral hepatitis does not appear to affect the extent of protein binding. **Metabolism:** Pethidine is metabolized in the liver by hydrolysis to Pethidine acid

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HAZARD IDENTIFICATION	
	followed by partial conjugation with glucuronic acid. Pethidine also undergoes N-demethylation to normeperidine, which then undergoes hydrolysis and partial conjugation. Normeperidine is about half as potent as Pethidine, but it has twice the CNS stimulation effects. **Route of Elimination:** Excreted in the urine. The proportion of drug that is excreted unchanged or as metabolites is dependent on pH. When urine pH is uncontrolled, 5-30% of the Pethidine dose is excreted as normeperidine and approximately 5% is excreted unchanged. Pethidine and normeperidine are found in acidic urine, while the free and conjugated forms of Pethidine c and normperidinic acids are found in alkaline urine.
Acute toxicity	**Species** **Route** **End Point** **Dose** Rat, Oral, LD_{50} 170 mg/kg Mouse, Oral, LD_{50} 178 mg/kg
Repeated dose toxicity	Long-term exposure to the product is not thought to produce chronic effects adverse to the health (as classified by EC Directives using animal models); nevertheless exposure by all routes should be minimised as a matter of course. Chronic morphine poisoning or addiction causes pin-point pupils, rapid mood changes and poor social adaptation. As dependence and tolerance occurs, there is an overwhelming need to continue taking the drug or similar drugs and to increase the dose. Long-term exposure to methanol vapour, at concentrations exceeding 3000 ppm, may produce cumulative effects characterised by gastrointestinal disturbances (nausea, vomiting), headache, ringing in the ears, insomnia, trembling, unsteady gait, vertigo, conjunctivitis and clouded or double vision. Liver and/or kidney injury may also result.
Carcinogenicity	No any information available related to Carcinogenicity of Pethidine.
Genotoxicity studies	**Germ Cell Mutagenicity - Assessment:** The substance is not considered to be Genotoxic.
Reproductive/Developmental Toxicity	Some evidence of adverse effects on development, based on animal experiments., Studies in animals have shown that high doses produce embryo/foetotoxic effects
Highly sensitizing potential	May cause eye irritation.
Hazard Identification Symbol	 Health Hazard  Irritant

IDENTIFICATION OF CRITICAL EFFECTS

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Clinical therapeutic andadverse effects	**Therapeutic Effects:** Like other opioids, pethidine binds to opioid receptors and exerts its principal pharmacological actions on the central nervous system where its analgesic and sedative effects are of particular therapeutic value. **Adverse Effects:** The severe or irreversible adverse effects of Pethidine (HCl), which give rise to further complications include Myoclonus, GI symptoms, Dizziness, Vertigo, Hallucinations, Hypertension, Convulsions, Tachycardia, Hypotension, Skin rashes.

NOAEL/LOAEL/NOEL/LOEL	No adequate data for the intravenous or intramuscular route for Pethidine is available in the literature so, the minimum human dose of 50 mg/day is used as LOAEL based on the adverse effects associated with clinical use.

APPLICATION OF ADJUSTMENT FACTORS- PDE calculation		
F1: Extrapolation between species	1	A factor of 1 is selected since human dose is used for PDE calculation.
F2: Inter-individual variability	10	Conventionally used to allow for differences betweenindividuals in the human population
F3: Duration of toxicity	1	A factor of 1 is used as the human dose is used.
F4: Severe toxicity (1-10)	1	No any toxicity
F5: LOAEL	10	A factor of 10 is used as the human dose is used as LOAEL.

PDE CALCULATION:

$$\text{PDE (mg/day)} = \frac{\text{Human Dose}}{\text{F1x F2 x F3 x F4 x F5}}$$

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

= **0.5 mg/day**

6. REFERENCES:

- https://en.wikipedia.org/wiki/Pethidine.
- https://www.druginfosys.com//drug.aspx?drugCode=557&type=1
- https://www.astrazeneca.com.au/content/dam/az-au/Material%20Safety%20Data/Pethidine-Solution.pdf
- https://www.astrazeneca.com.au/content/dam/az-au/Material%20Safety%20Data/2018/MSDS_Pethidine%20solution_SDS20461_01.18_v2.0.pdf
- https://cdn.pfizer.com/pfizercom/products/material_safety_data/Meperidine_HCl_Inj_16-Jul-2018.pdf
- https://pubchem.ncbi.nlm.nih.gov/compound/Meperidine#section=Human-Toxicity-Values
- https://dl.novachem.com.au/sds/assets/novachem.sds.M-035.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 OECD guidelines 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 onmorphology, 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 whosepenetration 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 alterationof 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.

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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.