PERMISSIBLE DAILY EXPOSURE (PDE) DETERMINATION STRATEGY FOR MORPHINE SULPHATE SOLUTION FOR INJECTION

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PERMITTED DAILY EXPOSURE FOR MORPHINE SULPHATE SOLUTION FOR INJECTION

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 **Morphine Sulphate Solution** 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:

Morphine is a strong opiate that is found naturally in opium, a dark brown resin produced by drying the latex of opium poppies (Papaver somniferum). It is mainly used as an analgesic (pain medication). There are numerous methods used to administer morphine: oral; sublingual; via inhalation; injection into a muscle, injection under the skin, or injection into the spinal cord area; transdermal; or via rectal suppository. It acts directly on the central nervous system (CNS) to induce analgesia and alter perception and emotional response to pain. Physical and psychological dependence and tolerance may develop with repeated administration. It can be taken for both acute pain and chronic pain and is frequently used for pain from myocardial infarction, kidney stones, and during labor.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Morphine sulfate is a fine white powder. When exposed to air it gradually loses water of hydration, and darkens on prolonged exposure to light. It is soluble in water and ethanol at room temperature.

IUPAC Name: (4R,4aR,7S,7aR,12bS)-3-Methyl-2,3,4,4a,7,7a-hexahydro-1H-4,12-Methano [1]benzofuro[3,2-e]isoquinoline-7,9-diol

Chemical Formula: $C_{17}H_{19}NO_3$

Molecular Weight: 285.34 g/mol

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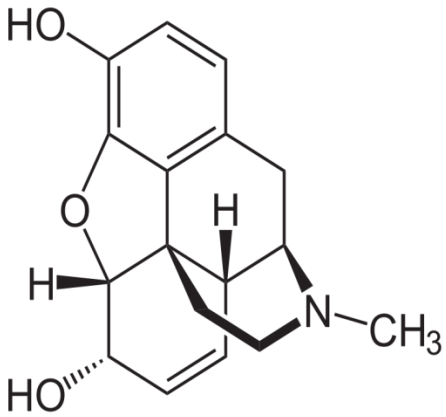
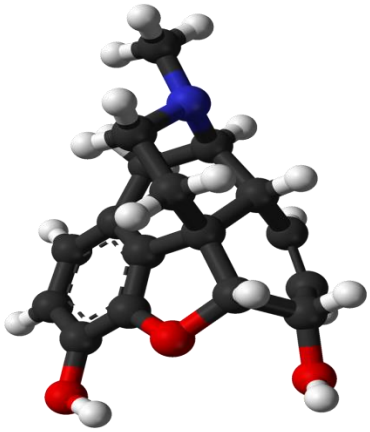
Molecular Structure:



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	Morphine concentrations are not predictive of analgesic response, especially in patients previously treated with opioids. The minimum effective concentration varies widely and is influenced by a variety of factors, including the extent of previous opioid use, age and general medical condition. Effective doses in tolerant patients may be significantly higher than in opioid-naïve patients.
Pharmacokinetic data	**Absorption:** Absorption of morphine sulfate pentahydrate after intramuscular and subcutaneous injection is fairly rapid with peak analgesia occurring 30 to 60 minutes and 50 to 90 minutes after injection via the respective routes. Peak analgesia occurs within 20 minutes after intravenous administration. Distribution Morphine is distributed throughout the body, but particularly to parenchymatous tissue such as kidney, lung, liver and spleen. Lower concentrations are found in skeletal muscle and brain tissue. Morphine diffuses across the placenta and trace amounts are found in sweat and breast milk. About 35% is protein bound, mainly to albumin. **Metabolism:** Morphine is metabolised principally in the liver by conjugation with glucuronic acid. The principal metabolites are morphine-3-glucuronide and morphine-6-glucuronide. Morphine-6- glucuronide is pharmacologically active and has a half-life somewhat longer than morphine. **Elimination**: Elimination half-life from serum is approximately 1.5 to 2 hours in healthy subjects and 90% of the dose is recovered in urine within 24 hours. Approximately 7 to 10% of the dose is recovered in faeces, the majority after conjugation and excretion via bile.
Acute toxicity	A short-term intake of morphine is not linked to any risk of dependence. **Species** — **Route of Administration** — **LD_{50} (mg/kg)** Rat — Oral — 461 Mouse — Oral — 600 Rat — i.p. — 235 Rat — s.c. — 109 Rat — s.c. — 630 Mouse — i.p. — 140 Mouse — s.c. — 220 Mouse — s.c. — 430 Mouse — i.v. — 156
Repeated dose toxicity	**Short Term Study:** Dietary studies in which rats were exposed to 100–200 mg/kg bw morphine for 4–6 weeks showed clear opiate dependence, but no effects on body weight and feed intake. However, a clear decrease in feed intake and body weight was observed when morphine was withdrawn as well as changes in spontaneous locomotor activity

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HAZARD IDENTIFICATION

(EFSA CONTAM Panel, 2011). The data in rats and mice clearly show the dose dependency with marginal effects in rats at a serum concentration of 200 ng/mL, resulting from an oral dose of 60 mg/kg bw (Van der Laan et al., 1988).

Long Term Study: Long-term feeding toxicity studies in rats and mice showed no evidence of carcinogenic activity. Exposure-related decreased body weight was noted in treated animals.

In rats, at 2 years, there was an exposure-related decrease in the incidences of adrenal medulla hyperplasia in both sexes, of benign pheochromocytomas in males and of mammary gland fibroadenomas and fibroadenomas or adenocarcinomas (combined).

In mice, at 2 years, there was a significant increased incidence of thyroid gland follicular cell hyperplasia. The incidence of hepatocellular adenomas and adenomas or carcinomas (combined) were significantly lower at 400 mg/kg bw per day than in controls. The lower incidence of tumours in high-dose animals of both species compared with control was considered to be related to the suppression of body weight gain at this level.

Duration	Species	Route	Dose	End Point	Target Organ
18 Weeks	Rat	Oral	60 g/kg	LOAEL	Lungs
15 Days	Rat	Subcutaneous	3144 mg/kg	LOAEL	Kidney, Urethra, Bladder
9 Weeks	Rat	Subcutaneous	3150 mg/kg	LOAEL	--

Carcinogenicity

No carcinogenicity study is available on morphine. However, based on the lack of carcinogenicity in mice or rats of codeine, which is metabolised to morphine, the CONTAM Panel concluded that morphine is unlikely to be carcinogenic (EFSA CONTAM Panel, 2011). Tumour promotion effects were reported with s.c. administration of morphine in a transgenic mice model with breast cancer (female transgenic mice carrying a rat C3(1) simian virus 40 large tumour antigen fusion gene (called C3TAG mice) which causes highly invasive breast tumours) (Gupta et al., 2002; Farooqui et al., 2007; Nguyen et al., 2014). Gach et al. (2011) observed both growth-promoting and growth-inhibiting effects. The CONTAM Panel considered the data to be too limited to be further considered in this Scientific Opinion.

Genotoxicity studies

No formal studies to assess the mutagenic potential of morphine have been conducted. In the published literature, morphine was found to be mutagenic in vitro increasing DNA fragmentation in human T-cells. Morphine was also reported to be mutagenic in the in vivo mouse micronucleus assay and positive for the induction of chromosomal aberrations in mouse spermatids and murine lymphocytes. Mechanistic studies suggest that the in vivo clastogenic effects reported with morphine in mice may be related to increases in glucocorticoid levels produced by morphine in these species. In contrast to the above positive findings, in vitro studies in the literature have also shown that morphine did not induce chromosomal aberrations in human leukocytes or translocations or lethal mutations in Drosophila

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HAZARD IDENTIFICATION	
Reproductive/Developmental Toxicity	Depressed sexual activity was observed in male rats treated with morphine. This effect is reversible and results from lowering serum luteinising hormone and testosterone. Reduced testicular function and spermatogenesis has been reported after prenatal administration of morphine. It was also shown that morphine disrupted ovarian cyclicity, decrease pregnancy rate and increase still births (EFSA CONTAM Panel, 2011). More recently, Ghosian Moghaddam et al. (2013) reported that oral morphine exposure for 21 days of adult male rats results in significantly lower luteinising hormone level, testosterone level, oestrogen level and progesterone level than the control group and a higher follicle-stimulating hormone level. Developmental toxicity studies in experimental animal species are not conclusive. Subcutaneous injection of high doses of morphine to hamster dams has been reported to cause CNS defects in the fetuses. **Teratogenic Effects (Pregnancy Category C):** No formal studies to assess the teratogenic effects of morphine in animals have been conducted. It is also not known whether morphine can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Morphine should be given to a pregnant woman only if clearly needed. In humans, the frequency of congenital anomalies have been reported to be no greater than expected among the children of 70 women who were treated with morphine during the first four months of pregnancy or in 448 women treated with morphine anytime during pregnancy. Furthermore, no malformations were observed in the infant of a woman who attempted suicide by taking an overdose of morphine and other medication during the first trimester of pregnancy. Several literature reports indicate that morphine administered subcutaneously during the early gestational period in mice and hamsters produced neurological, soft tissue and skeletal abnormalities. With one exception, the effects that have been reported were following doses that were maternally toxic and the abnormalities noted were characteristic of those observed when maternal toxicity is present. In one study, following subcutaneous infusion of doses greater than or equal to 0.15 mg/kg to mice, exencephaly, hydronephrosis, intestinal hemorrhage, split supraoccipital, malformed sternebrae, and malformed xiphoid were noted in the absence of material toxicity. In the hamster, morphine sulfate given subcutaneously on gestation day 8 produced exencephaly and cranioschisis. In rats treated with subcutaneous infusions of morphine during the period of organogenesis, no teratogenicity was observed.
Highly sensitizing potential	No any sensitivity to skin or eyes
Hazard Identification Symbol	 Health Hazard

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IDENTIFICATION OF CRITICAL EFFECTS	
Clinical therapeutic and adverse effects	**Therapeutic Effects:** In general, morphine is used for the treatment of severe pain and dyspnoea. **Adverse Effects:** The most serious adverse reactions encountered are respiratory depression, apnea, circulatory depression, respiratory arrest, shock, and cardiac arrest. Other common frequently observed adverse reactions include: sedation, lightheadedness, dizziness, nausea, vomiting, constipation, and diaphoresis.

NOAEL/LOAEL/NOEL/LOEL	15 Days/Rat/Subcutaneous/3144 mg/kg/LOAEL

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	10	Short Term (15 days) toxicity study in rats
F4: Severe toxicity (1-10)	1	No any toxicity
F5: NOAEL Vs LOAEL (10 if LOAEL)	10	Selection of LOAEL dose.

PDE CALCULATION:

$$\text{PDE (mg/day)} = \frac{\text{NOAEL (mg/day) x Body weight (kg)}}{\text{F1x F2 x F3 x F4 x F5 x } \alpha}$$

$$= \frac{3144 \text{ x } 50}{5 \text{ x } 10 \text{ x } 10 \text{ x } 1 \text{ x } 10}$$

= **31.44 mg/day**

6. REFERENCES:

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- https://en.wikipedia.org/wiki/Morphine
- https://www.medsafe.govt.nz/profs/datasheet/d/dblmorphinesulphbpinj.pdf
- https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5243
- https://efsa.onlinelibrary.wiley.com/doi/pdf/10.2903/j.efsa.2018.5243
- https://cdn.pfizer.com/pfizercom/products/material_safety_data/morphine_sulfate_preservative-free_(Hospira)1-Apr-2017.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 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.