# PERMISSIBLE DAILY EXPOSURE (PDE) DETERMINATION STRATEGY FOR FENTANYL CITRATE INJECTION USP 0.05 mg/ml

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**PERMITTED DAILY EXPOSURE FOR FENTANYL CITRATE INJECTION USP 0.05 mg/ml**

## 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 **Fentanyl Citrate Injection USP 0.05 mg/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:

Fentanyl is a potent synthetic piperidine opioid drug primarily used as an analgesic. It is 20 to 40 times more potent than heroin and 100 times more potent than morphine;[6] its primary clinical utility is in pain management for cancer patients and those recovering from painful surgeries. Fentanyl is also used as a sedative. Depending on the method of delivery, fentanyl can be very fast acting and ingesting a relatively small quantity can cause overdose. Fentanyl works by activating μ-opioid receptors. Fentanyl is sold under the brand names Actiq, Duragesic and Sublimaze, among others.

## 3. IDENTITY OF THE ACTIVE SUBSTANCE:

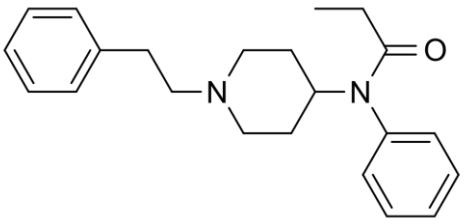
Fentanyl HCl is a white to off-white solid, soluble in water and methanol. As the drug is completely dissolved in the proposed formulation, studies of polymorphism and particle size were not deemed necessary.

**IUPAC Name:** N-phenyl-N-[1-(2-phenylethyl)piperidin-4-yl]propanamide

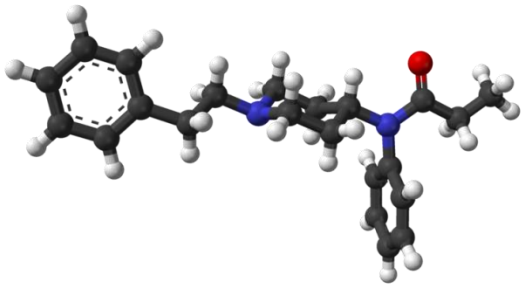
**Chemical Formula**: $C_{22}H_{28}N_2O$

**Molecular Weight:** 336.479 g/mol

**Molecular Structure:**




**2D**



**3D**

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## 4. HAZARDS IDENTIFIED:

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

## 5. SUMMARY OF ASSESSMENT PROCESS:

| HAZARD IDENTIFICATION | |
|---|---|
| **Pharmacodynamics data** | Fentanyl has been extensively described as a potent opioid analgesic and the applicant has provided a summary of the relevant non-clinical literature to establish the applicability of their transdermal product. In vitro studies have demonstrated that fentanyl binds with a higher affinity to μ opioid receptors as compared to κ- or δ-opiate receptors. In vivo pharmacodynamics has been described in mice and rats with clear antinociceptive and analgesic effects, with an increased margin for safety compared to other opioid analgesics such as morphine. Given the well characterised pharmacology of fentanyl, the applicant's review is acceptable. |
| **Pharmacokinetic data** | **Absorption**: Fentanyl is highly lipid soluble, as measured by the octanol-water distribution coefficient (log p of 2.98), and has greater access to the brain and central opioid receptors than morphine (log p of 0.0). Highly lipophilic agents like fentanyl may be rapidly absorbed in neural tissues or through the nasal and buccal mucosa. Opioids in general are readily absorbed from the gastrointestinal tract and act rapidly when administered via intravenous (IV) or intramuscular (IM) injection. The bioavailability of fentanyl after oral and oraltransmucosal administration are 32% and 52%, respectively. Approximately 92% of the fentanyl dose absorbed from a passive transdermal system reaches the systemic circulation as unchanged Fentanyl; therefore, fentanyl biotransformation during passive transdermal penetration appears negligible.<br><br>**Distribution:** Fentanyl is distributed rapidly from plasma to highly vascular tissues (heart, lung, and brain) following an IV bolus. More than 80% of the injected dose leaves plasma in less than 5 minutes and 98.6% within an hour. The large volume of distribution for fentanyl is related to its lipophilic characteristics.<br><br>**Elimination**: Fentanyl is metabolized primarily in the liver. It has a high extraction ratio and clearance ranges from values as low as one-third of hepatic blood flow to those equalling hepatic blood flow. In humans, the drug is metabolized mainly by N-dealkylation to norfentanyl [4-N-(N-propionyl-anilino)-piperidine] and by hydroxylation of both fentanyl and norfentanyl to hydroxypropionyl fentanyl and hydroxypropionyl |

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## HAZARD IDENTIFICATION

| | |
|---|---|
| | norfentanyl, respectively. Fentanyl amide hydrolysis to despropionylfentanyl and alkyl hydroxylation to hydroxyfentanyl are comparatively minor pathways, and hydroxyfentanyl is subsequently N-dealkylated to hydroxynorfentanyl, another minor metabolite. The elimination of Fentanyl from the body is governed by its reuptake from storage sites and its metabolism in the liver. The serum Fentanyl concentration profile is often best described by a three-compartment model. The half-life of Fentanyl is approximately 4–8 hours following IV administration and renal elimination is low in humans. |
| **Acute toxicity** | **Single dose toxicity:** For acute toxicity a number of legacy studies have been reported with Fentanyl using a variety of routes of administration, including subcutaneous. The main findings relate to excessive opioid-like effects – CNS effects, decreased activity, convulsions, tremors, loss of righting reflex, sedation and respiratory depression. The applicant also completed two GLP compliant studies in mice and rats using the intravenous route, confirming the effects already established with Fentanyl. These studies determined lethal dose in 50 percent of animals to be 12.3 mg/kg in mice and 2.3 mg/kg in rats.<br>**Species Route End Point Dose**<br>Rat Oral $LD_{50}$ 18 mg/kg<br>Rat Para-periosteal $LD_{50}$ 990 µg/kg<br>Rat Intraperitoneal $LD_{50}$ 2070 µg/kg<br>Mouse Oral $LD_{50}$ 368 mg/kg<br>Mouse Intravenous $LD_{50}$ 10100 µg/kg |
| **Repeated dose toxicity** | Repeat dose toxicity studies were presented from a variety of routes of administration, and species. Dermal toxicity has been presented in the mouse and rabbit. Further studies are also provided in the rat (SC, IM and IV) and dog (IV) to provide added support for systemic exposure with fentanyl. Concerning the dermal repeat dose toxicity studies, findings were related to pharmacological effects of opioids, with weight loss and CNS effects prevalent in the mouse and in the rabbit the adverse effects were limited to skin changes hyperkeratosis, acanthosis and sub-acute dermatitis indicating more of an irritation potential. |
| **Carcinogenicity** | The applicant has provided a long term carcinogenicity study with fentanyl in rats using daily SC administration up to 100 µg/kg/day. Although findings of pituitary adenomas (males and females), and mammary gland fibroadenomas and carcinomas (females) were observed, these appeared in all dose groups at comparable levels so was not considered to be related to treatment. To further support the rat study a 26 week dermal alternative bioassay in Tg.AC transgenic mice has been reported. No evidence of increased neoplastic risk was identified, and so it is agreed that fentanyl shows no carcinogenic potential, and the risks of short term treatment with the IONSYS product would in any case be negligible given the low dose and treatment duration (up to 72 hrs). |

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**Genotoxicity studies**

Genotoxicity was examined in a range of GLP in vitro and a single in vivo micronucleus study. A variation was observed in the mouse lymphoma study in the presence of S9, however once repeated the increase concern for increased mutation could not be replicated to the same extent. Results from the Ames and chromosome aberration studies and the micronucleus test indicate that fentanyl is not mutagenic. This is supported.

**Reproductive/Developmental Toxicity**

Two study reports are provided evaluating fertility and early embryonic development in rats following continuous intravenous infusion with Fentanyl in both sexes. There are no adverse effects for fertility for either male or female rats. NOAEL in male rats is 0.4 mg/kg, and in females this is 0.025 mg/kg for maternal effects and 0.4 mg/kg for developmental effects. In addition to these two studies, two published references are provided to further describe the in vitro effects of Fentanyl on fertilisation and subsequent cell division in sea urchin eggs and an in vivo study in rats using SC continuous infusion using implanted osmotic minipumps. Five study reports are provided evaluating embryo-fetal development in rats (IV, SC) and in rabbits (IV infusion).

No teratogenic effects were detected in any of the five studies completed in rats or in rabbits. The most relevant finding is that of loss of maternal weight gain (rats and rabbits) and decreased pup weight (rats).

In a pre- and post-natal developmental toxicity study all animals survived. At dosages of 0.025 and 0.1 mg/kg/day, neither maternal toxicity nor adverse effects on the litter were demonstrated. at 0.4 mg/kg, slight maternal toxicity was evidenced by a marginal decrease in body weight. NOAEL's are 0.1 mg/kg for the F0 and F1 generation and 0.4 mg/kg for the F2 generation. Margins of safety for the high dose 0.4 mg/kg/day; Cmax 6.2 ng/mL), is at least 3 fold the human plasma level (2 ng/mL), although this is less than one for the 0.1 mg/kg level (Cmax 1.5 ng/mL).

| Study Type | Species | Route | Dose | End Point | Effect |
|---|---|---|---|---|---|
| Reproductive & Fertility | Rat | Subcutaneous | 1.25 mg/kg | LOAEL | Fertility |
| Reproductive & Fertility | Rat | Intravenous | 30 µg/kg | LOAEL | Fertility |
| Reproductive & Fertility | Rat | Subcutaneous | 160 µg/kg | LOAEL | Fertility |
| Embryo/Fetal Development | Rat | Oral | 500 µg/kg | NOAEL | Not Teratogenic |

**Highly sensitizing potential**

A number of skin irritation studies have now been completed to assess the potential of the hydrogel formulation to sensitise the skin. Studies were completed in the rabbit and on hairless guinea pigs using a variety of formulations. Most importantly the final clinical product was used on hairless guinea pigs, and rabbits in this study in which the hydrogel was detected to be a mild irritant in both species. It was also established that use of a polymeric buffer – polacrilin – did not increase the skin irritation potential to any great extent. Animals were treated with placebo hydrogel, Fentanyl hydrogel and Fentanyl hydrogel with an electrical current and were then topically induced. All three preparations demonstrated mild irritation, and there was no increased discomfort in groups given

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| **HAZARD IDENTIFICATION** | |
|---|---|
| | electrically-assisted delivery of Fentanyl. |
| **Hazard Identification Symbol** |  Acute Toxicity |
| **IDENTIFICATION OF CRITICAL EFFECTS** | |
| **Clinical therapeutic and Adverse effects** | **Therapeutic Effects:** Fentanyl is used to treat acute (short term), severe pain caused by major trauma or surgery, as well as for chronic pain caused by cancer.<br>**Adverse Effects:** Pharmaceutical Fentanyl's adverse effects are identical to those of other narcotic opioids, including addiction, confusion , respiratory depression (which, if extensive and untreated, may lead to arrest), drowsiness, nausea, visual disturbances, dyskinesia, hallucinations , delirium, a subset of the latter known as "narcotic delirium", analgesia, narcotic ileus, muscle rigidity, constipation, loss of consciousness, hypotension, coma, and death. |

| | |
|---|---|
| **NOAEL/LOAEL/NOEL/LOEL** | Rat Intravenous 30 µg/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 (Reproductive Cycle) 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:**

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

$$= \frac{0.03 \times 50}{5 \times 10 \times 10 \times 1 \times 10}$$

= **0.0003 mg/day**

## 6. REFERENCES:


- https://www.ema.europa.eu/en/documents/assessment-report/ionsys-epar-public-assessment-report_en.pdf
- https://www.pharmacopoeia.com/Catalogue/Preview?uri=%2Fcontent%2Ffile%2Fproducts%2Fhealthandsafety%2FCat_683_GB.pdf
- https://cdn.pfizer.com/pfizercom/products/material_safety_data/PZ00161.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 substanceby 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 substanceby 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.