PERMISSIBLE DAILY EXPOSURE (PDE) DETERMINATION STRATEGY FOR DEXAMETHASONE SODIUM PHOSPHATE INJECTION

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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 **Dexamethasone Sodium Phosphate** 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:

Dexamethasone Sodium Phosphate Injection belongs to a group of medicines called steroids. It is used in the treatment of various diseases and conditions such as inflammatory and autoimmune conditions. It provides relief from swelling, redness, and pain, by preventing the release of substances that cause inflammation.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

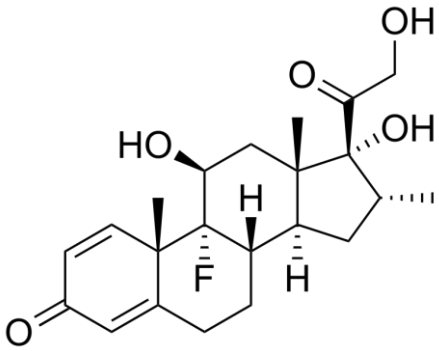
Dexamethasone Sodium Phosphate is a white to off-white crystalline powder.

IUPAC Name: (8S,9R,10S,11S,13S,14S,16R,17R)-9-Fluoro-11,17-dihydroxy-17-(2-hydroxyacetyl)-10,13,16-trimethyl-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta[a]phenanthren-3-one

Chemical Formula: $C_{22}H_{29}FO_5$

Molecular Weight: 392.467 g/mol

Molecular Structure:



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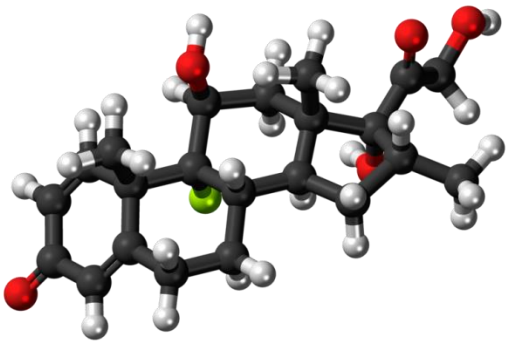

3D

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	Dexamethasone has been shown to induce multiple myeloma cell death (apoptosis) via a down-regulation of Nuclear Factor-κB activity (NF κB)and an activation of caspase -9 through an apoptosis promoting factor.
Pharmacokinetic data	**Absorption:** After oral administration of dexamethasone, dexamethasone peak plasma levels are reached at a median of three hours. Bioavailability of Dexamethasone is approximately 80%. **Distribution:** Dexamethasone is bound by plasma proteins, principally Albumin, up to about 80%, depending on the administered dose. **Metabolism:** A minor part of administered dexamethasone is excreted unchanged by the kidney. The major part is hydrogenated or hydroxylated in humans, the major metabolites being hydroxy-6-dexamethasone and dihydro-20-dexamethasone. **Excretion:** The plasma half-life of dexamethasone is approximately 250 minutes.
Acute toxicity	Acute toxicity studies have been conducted in mice by various routes. The LD_{50} (mg/kg) value was found to be 550 (i.p.), 932 (i.v.) & >1800 (p.o.).

Species	**Route**	**LD_{50} (mg/kg)**
Mice	Intraperitoneal (i.p.)	550
	Intravenous (i.v.)	932
	Oral (p.o.)	>1800

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Repeated dose toxicity	Long term toxicity studies have been performed in rats, rabbits and dogs. Decrease in the thymus and adrenal weights were reported.	
	Toxicity study in rats	
	Dose: 0.0005, 0.001, 0.0015, 0.002 and 0.004 mg/kg/day **Route:** Oral(p.o.) **Duration:** 7-days	**Clinical findings: i.** Corticosterone levels werereduced at the highest dose. **No-observed-adverse-effect-level (NOAEL):** 0.0015mg/kg/day.
	Dose: 0, 0.0003, 0.001, 0.003, 0.01, 0.03 and 0.1 mg/kg/day **Route:** Oral (p.o.) **Number:** 20/sex/group. **Duration:** 90-days	**Clinical findings:** **i.** Thymus involution and morphological changes was observed in adrenal gland at the dose of 0.1 mg/kg/day. **ii.** Reduction in the corticosteroid level in theplasma and hepatic glycogen was reported. **No-observed-adverse-effect-level (NOAEL):** 0.003 mg/kg/day.
	Dose: 0.5 ml **Route:** Subcutaneous **Number:** 15 **Duration:** 6 weeks	**Clinical findings:** Decreased body-weight gain,adrenal weights were observed.
	Dose: 0, 0.125, 0.25 and 0.4 mg/kg/day **Route:** Oral (p.o.) **Number:** 15/sex/group. **Duration:** 181-185 days (~6 months)	**Clinical findings: i.** Treatment (dose) related deaths were reported [(4/30: low dose), (14/30: mid dose) and (26/30: high dose)]. **ii.** Decrease in the body weight and relative adrenaland thymus weight was reported at all dose levels. **Low-observed-adverse-effect-level (LOAEL):** 0.125 mg/kg/day.

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Dose: 0,40 or 79 mcg/kg bw/day **Route:** Subcutaneous **Number:** 20 (male & female); 5 (male&female) **Duration:** 13 weeks; 7-week recoveryperiod	**Clinical findings: i.** Elevation in ALAT activity, total cholesterol concentrations, lipid levels, adrenal glycogen levels in males were reported. **ii.** Decreased plasma corticosteroid levels, hepaticglycogen, body weight and organ weight. **iii.** Marked changes in the thymus and adrenalglands were observed. **iv.** Due to loss of regular structuring of the cells,adrenal cortex was narrowed. **v.** No significant changes were observed after therecovery period.

Toxicity study in rabbits	
Dose: 513, 684, 1368 mcg **Route:** Intraocular injection	**Clinical findings:** No effects were observed.

Toxicity study in dogs	
Species: Mongrel **Number:** 3 male and 2 female/group. **Dose:** 0, 0.125 mg/kg/day **Route:** Oral (p.o.) **Duration:** 6-weeks	**Clinical findings: i.** Relative adrenal weights were decreased. **ii.** No treatment related effects were reported on clinical signs, body weight, liver and renalparameters.

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	Species: Beagle dogs **Number:** 3 (male & female); additional2 groups of 3 (males &females) **Dose:** 0,40 or 79 mcg/kg bw **Route:** Subcutaneous **Duration:** 13 weeks; 4 weeks recovery period	**Clinical findings: i.** Decreased body weight gain and reversible hepatic effects were seen. **ii.** Elevated ALAT (alanine aminotransferase) activity which regressed to normal after the recovery period was observed at both 40 and 79 mcg/kg/bw. **iii.** Reversible increased total lipid level and increased triglyceride levels in the adrenal and liver glycogen were seen. **iv.** Animals receiving a dose of 79 mcg/kg bw/day experienced reversible reduction in plasma corticoid levels. **No-observed-adverse-effect-level (NOAEL):** 40 mcg/kg because of reversibility of toxic effects.
	Species: Beagle **Number:** 4 female dogs **Dose:** 2 and 8 mg/kg/day.**Route:** Oral (p.o.) **Duration:** 26-weeks	**Clinical findings: i.** Alopecia was reported in 1dog in each dose group. **ii.** Atrophy of the lymphatic organs were reportedin all dogs. **iii.** Decreased adrenal weight was reported.
Carcinogenicity	Long term carcinogenicity studies of dexamethasone sodium phosphate have not beenconducted to evaluate the carcinogenic potential.	
Genotoxicity studies	Battery of tests such as Ames test (10-1000 µg/plate), mouse lymphoma assay (12.5-400 µg/ml) and mouse micronucleus test (5 mg/kg) revealed the negative genotoxic and mutagenic potential of dexamethasone. **a. In-vivo/ in-vitro genotoxicity studies** **Table no. 3:** In-vivo/in-vitro genotoxicity studies of dexamethasone **(4).**	

o.	**Test type**	**Dose/concentration**	**Resul**

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	A.	**In-Vitro tests**		
	1.	Ames test: *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537). *Escherichia coli* (WP2*uvr*A)	10-1000 µg/plate	Negative
	2.	Fluctuation assay: mouse lymphoma L5178Y cells	12.5-400 µg/ml (-)	Negative
	B.	**In-vivo assay**		
	3.	Micronucleus test: NMRI mice	5 mg/kg (intravenous)	Negative
	(-): without metabolic activation			

Reproductive/Developmentaltoxicity	Reproductive and developmental toxicity studiesof dexamethasone in rats, mice, rabbits and monkeys revealed fetotoxic effects.	
	Teratology study in rats	
	Dose: 0.01-1.25 mg/kg/day	**Clinical findings: i.** Maternal toxicity was reported at the dose of ≥ 0.05 mg/kg/day. **ii.** Structural malformations such as hydrops fetalis, cleft palate) was reported at the dose of ≥ 1mg/kg/day. **iii.** Thymus involution and decrease in body weight was reported in fetuses. **NOAEL (for embryotoxicity):** 0.01 mg/kg/day.
	Species: SPF-FW 49 Biberach rats **Route:** Subcutaneous **Dose:** 0, 20, 40 or 79 mcg/kg bw/day **Number:** 20 **Duration:** Gestation day 6-15	**Clinical findings: i.** Lower food consumptio andlitter weight was observed. **ii.** Implantation rates and resorption rates were higher. **iii.** Retarded ossification of the sternebrae andhydronephrosis was seen.
	Species: Holtzmann **Route:** Subcutaneous **Dose:** 0.05, 0.2 or 0.8 mg/day **Duration:** Days 12-15 post-c onception	**Clinical findings: i.** High rate of cleft palat wasobserved in the high dose group.

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	Species: Morini Wistar **Route:** Subcutaneous **Dose:** 0, 40 or 79 mcg/kg bw/day **Duration:** Gestation day 6-15	**Clinical findings: i.** Decrease in body-weight gain, fetal weights and food consumption and elevated resorption rate was seen. **ii.** At the dose of 40 and 90 mcg/kg, hydronephrosis was reported.
	Species: SPF, SD-JCL strain **Route:** Subcutaneous **Dose:** 0, 20, 40 or 80 mcg/kg bw/day **Duration:** Gestation day 6-15	**Clinical findings: i.** Decrease in maternal body weight and elevated pre- and post-implantationlosses was reported. **ii.** In one fetus, cleft palate was observed. **iii.** At the dose of 20 mcg/kg bw/day, one fetus observed thoracoschisis and sternum deformitywas reported in one rat.
	Teratology study in mice	
6	**Species:** A/J mice **Route:** Subcutaneous **Dose:** mg/kg bw/day **Duration:** Days 11-14 post conception	**Clinical findings:** High incidence of cleft palatewas observed.
	Species: NMRI mice **Route:** Intramuscular **Dose:** 10 or 50 mg/kg bw/day **Duration:** Gestation day 13	**Clinical findings:** Resorptions and cleft palatewere observed.
	Teratology study in rabbits	
	Route: Intramuscular **Dose:** 25-1000 mcg/kg bw/day**Duration:** Days 13.5-16.5 post-conception	**Clinical findings: i.** At 700 and 1000 mcg/kg bw/day, litter resorptions were observed. **ii.** Cleft palate was observed at and higher doses of62 mcg/kg. **iii.** No effects on cleft palate or resorption wereobserved at 25 mcg/kg.
	Species: SPF Himalyan/Biberach **Route:** Subcutaneous **Dose:** 0, 20, 40 or 79 mcg/kg bw/ day **Duration:** Gestation day 6-18	**Clinical findings: i.** Increase in resorption rate, incidence of forefeet, malformations and number of runts were observed. **ii.** Decrease in fetal weights were reported.

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	Species: New Zealand white rabbits **Route:** Subcutaneous **Dose:** 0, 40 or 79 mcg/kg bw/day **Duration:** Gestation day 6-18	**Clinical findings:** Increase in resorption rate anddecrease in body weight was reported.
	Teratology study in monkeys	
	Species: Rhesus macaques **Route:** Intramuscular **Dose:** 1.0 or 10.0 mg/kg **Duration:** Gestation day 23 and 49	**Clinical findings: i.** Reduction in the brain weightand the diameter of the cranial fossa was reported.
Highly sensitizing potential	Data regarding the sensitizing potential of dexamethasone in animals and humans is notavailable.	

IDENTIFICATION OF CRITICAL EFFECTS	
Clinical therapeutic and adverse effects	Dexamethasone is used to treat many different inflammatory conditions such as allergic disorders, skin conditions and is also used totreat ulcerative colitis, arthritis, lupus, psoriasis,and breathing disorders. Common adverse effectsassociated with dexamethasone are anxiety, blurred vision, headache, mental depression and mood changes..

NOAEL	0.0015 mg/kg/day from rats toxicity study

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 between individuals in the human population
F3: Duration of toxicity	10	Short term (6-Month) toxicity study in rats
F4: Severe toxicity (1-10)	1	No any toxicity
F5: NOAEL Vs LOAEL (10 if LOAEL)	5	Selection of NOAEL dose.
PK correction	PDE	For PDE calculation, correction factor of 1.25 (80% oral bioavailability) (injectable/ oral bioavailability ratio) is applied because the intended route is injectable and oral toxicity studyis taken for PDE calculation.

PDE CALCULATION:

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

$$= \frac{0.0015 \times 50}{5 \times 10 \times 10 \times 1 \times 1 \times 1.25}$$

= **0.00012 mg/day**

6. REFERENCES:

- https://pubchem.ncbi.nlm.nih.gov/compound/Dexamethasone-sodium-phosphate
- https://www.ema.europa.eu/en/documents/mrl-report/dexamethasone-extrapolation-goats-summary-report-3-committee-veterinary-medicinal-products_en.pdf
- https://www.drugs.com/dexamethasone.html
- https://www.sin-nl.org/wp-content/uploads/2016/10/Rapport-dexamethasone-201615_.pdf
- https://www.waitematadhb.govt.nz/assets/Documents/health-professionals/palliative-care/Dexamethasone-PalliativeCareJul16.pdf
- https://www.ncbi.nlm.nih.gov/pubmed/15022581

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.

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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.