PERMISSIBLE DAILY EXPOSURE (PDE) DETERMINATION STRATEGY FOR MICONAZOLE NITRATE CREAM BP 2%w/v

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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 **Miconazole Nitrate BP 2% w/v** for Cream 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:

Miconazole is used to treat skin infections such as athlete's foot, jock itch, ringworm, and other fungal skin infections (candidiasis). This medication is also used to treat a skin condition known as pityriasis (tinea versicolor), a fungal infection that causes a lightening or darkening of the skin of the neck, chest, arms, or legs. Miconazole is an azole antifungal that works by preventing the growth of fungus.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

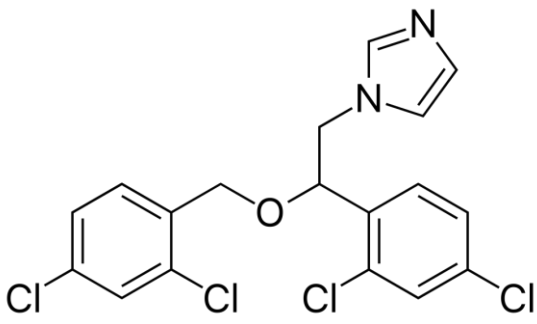
Miconazole nitrate is a white, crystalline powder. It is very slightly soluble in water (0.03%), and very slightly to slightly soluble in most common organic solvents and diluted solutions of inorganic acids

IUPAC Name: (RS)-1-(2-(2,4-Dichlorobenzyloxy)-2-(2,4-dichlorophenyl)ethyl)-1H-imidazole

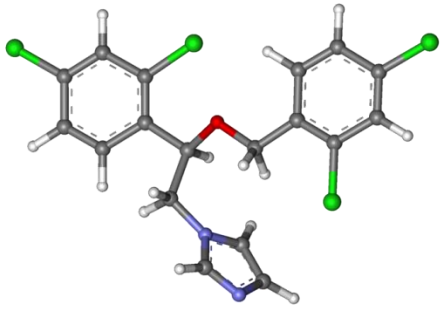
Chemical Formula: $C_{18}H_{14}C_{l4}N_2O$

Molecular Weight: 416.12 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	Tissue and Whole Animal The agonist activity of miconazole on the guinea pig ileum, rabbit duodenum, rabbit spleen and rat stomach fundus tissue preparations is limited to a slight initial tonus increase observed with the rabbit duodenum preparation at concentrations of 2.5 - 10 mg/I. This compound is observed to antagonize the spasmogenic effects of bradykinin, serotonin, nicotine, eledoisin, angiotensin and histamine, but is devoid of anticholinergic (rabbit duodenum), antiserotoninergic (rat stomach fundus) anti-a-adrenergic (rabbit spleen) and β-adrenergic blocking (fowl rectal caecum) activity. Miconazole given to mice in a single dose of 40 mg/kg had no influence on the licking reflex or other gross behavioural characteristics. In addition, rats treated with this regimen showed no autonomic or CNS induced effects. As well, no morphine-like properties, anticonvulsant effects or change in body temperature was recorded in this species. After repeated administration at this dose level (40 mg/kg/day for 7 consecutive days) no significant changes were again observed in behavioural characteristics and gross overall condition of pathological examination at autopsy.
Pharmacokinetic data	Studies were conducted using miconazole labelled with tritium at C-2 of the imidazole ring or the β-carbon of the ethylside chain. It was noted that the tritium label at C-2 of the imidazole ring was labile. Rats (miconazole tritium labelled at C-2 of the imidazole ring). Five male Wistar rats were each given an oral dose of 40 mg/kg miconazole in PEG-200. During the four days in which urine and faeces were collected, 66% of the total radioactivity administered was collected (62% after 48 hours). In the urine collected, more than 37% of the radioactivity recovered was in the form of tritiated water. At autopsy (day 4) blood, liver and brain tissues contained 1.9% of the administered radioactivity. Examination of the excreta by the inverse isotope dilution method revealed that 18% of the administered dose was excreted unchanged, 19%as α-(2,4-dichlorophenyl) imidazole-1- ethanol or its parent ketone and traces as imidazole. Dogs and Rabbits (miconazole tritium labelled at C-2 of the imidazole ring). In separate

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HAZARD IDENTIFICATION

excretion and absorption studies involving 2 animals per study, miconazole was administered intravaginally in carbowax 1000 and wecobee FS and M (7:3) vehicles to beagle bitches (1 mlof 1% formulation) and New Zealand white rabbit doe (0.5mL of 1%formulation). In the excretion studies urine and faeces were collected for 12 days from the dogs and urine only from rabbits.

In both species, the major percentage of the recovered radioactivity was obtained during the 3 days after dosing. In dogs, greater than 60% of the radioactivity was in the urine where the carbowax vehicle was used whereas less than 50% was recovered in the urine of dogs given miconazole in the wecobee vehicle. This observation was made with rabbits as well. In the absorption studies blood samples were obtained at 2, 4, 7 and 25 hours. Peak levels in dogs occurred 4-7 hours after dosing whereas in rabbits blood levels peaked at 2 hours. The highest level in dogs (0.06 µg/mL) was found with the carbowax vehicle as was the case with rabbits (0.17 - 10.8µg/mL). At autopsy (25 hours) the vaginas were dissected and washed. Only 0.08% of the administered dose to dogs and 0.456% to rabbits was found in the tissues and washings.

Rabbits (miconazole tritium labelled in the β-carbon of the ethvl side chain). Vaginal suppositories (2% miconazole) were administered to 2 New Zealand White rabbits. Urine and faeces were collected daily and blood at 3, 6, 24, 72, 96,144 and 168 hours. Most of the administered radioactivity (90% in one animal and 70% in the other) was excreted in eight days. Fifty percent of the tritium excreted is recovered in 2-3 days and found in the faeces. Maximum blood levels of tritium occured 6 hours after dosing (0.95 µg/mL).

Human: The absorption, metabolism and excretion of orally, intravaginally and topically administered labelled miconazole nitrate was observed in healthy normals. Blood, urine and faecal samples were taken. The study indicated that the absorption and excretion of miconazole administered orally was unrelated to dosage and duration of treatment. lntravaginal and topical administration indicated low absorption. Eight hours after topical examination, 90% of the drug was recovered from the skin.

Acute toxicity

Organism	Test Type	Route	Dose
Rat	LD_{50}	Oral	920 mg/kg
Rat	LD_{50}	Intraperitoneal	1060 mg/kg
Rat	LD_{50}	Subcutaneous	>5 g/kg
Rat	LD_{50}	Intravenous	14700 µ/kg
Mouse	LD_{50}	Oral	578 mg/kg
Mouse	LD_{50}	Intraperitoneal	480 mg/kg
Mouse	LD_{50}	Subcutaneous	>5 g/kg
Mouse	LD_{50}	Intravenous	28 mg/kg
Dog	LD_{50}	Oral	>160 mg/kg
Guinea Pig	LD_{50}	Oral	276 mg/kg

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HAZARD IDENTIFICATION

	Acute Acute oral toxicity of miconazole (7-day mortality) was assessed in male white mice, male Wistar rats, female ginea pigs and male and female mongrel dogs. The compound was administered in a micronized aqueous suspension. The following values were obtained: **Species** — **LD_{50}(95% Confidence Limits) mg/kg** Mice — 578 (324.4 - 1030) Rats — >640 Guinea Pigs — 276 (201.2 - 378.3) Dogs — >160 The Intraperitoneal LD_{50} in male Swiss Webster mice was 670 mg/kg ± 0.36
Repeated dose toxicity	**Subacute**: Rats Adult Wistar Rats (10 males and 10 females per dose group) were given miconazole at 80, 20 and 5 mg/kg/day in their diet for 13 weeks. All animals survived the test. Comparing the dose levels to control, urine specific gravity was increased in the high dose group, urine pH was lowered in the intermediate and high dose groups, and small changes in liver, thymus, spleen and kidney were noted in the high dose group after histopathological examination. From the results the no-effect dose is calculated to be less than 80 mg/kg, but greater than 20 mg/kg. **Dogs**: Adult Beagle dogs (3 males and 5 females per dose group) were given miconazole at 40, 10 and 2.5 mg/kg/day orally by capsule, 6 days a week, for 13 weeks. All animals survived the test. The following changes were noted: haematocrit and haemoglobin values were lowered in the high dose group; serum calcium and cholesterol and sulfhydryl groups decreased in the intermediate and high dose groups; alkaline phosphatase was elevated in the high dose group and the odd animal in the high dose group salivated and would vomit subsequent to drug administration. At autopsy slight liver changes were noted in the high dose group animals. From these results the no-effect dose is calculated to be less than 40 mg/kg but greater than 10 mg/kg. **Chronic**: **Rats Adult Wistar** rats (30 males and 30 females per dose group) were given miconazole at 160, 40 and 10 mg/kg/day in their diet. Interim sacrifices of 20 animals (10 males and 10 females) per dose level were made at 6 and 12 months, the remaining animals being sacrificed at the termination of the study (18 months). Histopathology showed some slight liver changes which appeared to be more pronounced in the males. However, this finding did not progress with time. No other significant findings were reported and miconazole was well tolerated up to 160 mg/kg over the study period. **Dogs**: **Adult Beagle dogs** (3 males and 3 females per dose group) were given oral doses by capsule of miconazole at 20, 5 and 1.25 mg/kg/day, 6 days a week for 52 weeks. All animals survived the study period. Persistent increased alkaline phosphatase levels and slightly increased SGPT values were noted with the high dose group; however, all other measured parameters were normal. At autopsy no significant histopathological changes were evident.

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HAZARD IDENTIFICATION

Group A 20 males - drug given 60 days premating
20 females - no drug

Group B 20 males - no drug
20 females - drug 14 days premating plus 21 days gestation

Females were sacrificed at day 22 of gestation. There was no difference between dose levels or groups A or B in pregnancy rate, but the number of dead foetuses and resorbed foetuses was increased in the high dose level. No abnormalities were noted among pups born to dosed females with the exception of two animals with rib deformities born to a high dose female. Based on the study findings, miconazole had no effect on the fertility of dosed males or Females.

Peri-and Postnatal Studies in Rats In one study, pregnant rats (20 animals per dose group) were given miconazole at 320, 160 and 80 mg/kg in their diet from day 16 of gestation through the 3 week lactation period. The gestation period was increased one day for the intermediate and high dose groups. In the test animals, litter size and the number of live foetuses at birth were slightly lower when compared to controls. As well, body weight gains in the intermediate and high dose groups for the surviving pups were lower, whereas the birth weights of pups in the various groups had not differed.

In a second study pregnant Long-Evans derived rats (20 animals per dose group) were given miconazole, suspended in carboxymethylcellulose at 80, 40 and 20 mg/kg by gastric gavage from day 14 of gestation through to day 21 post partum. In the high dose group a prolonged gestation period associated with an increase in the number of still born pups was noted. Performance of the other dose groups was comparable to controls.

Teratology

Rats

Pregnant rats (20 animals per dose group) were given miconazole at 160 and 80 mg/kg in their diet from day 6 to day 15 of gestation. On day 22 of gestation, foetuses were delivered by caesarean section. No abnormalities were noted in this study either in the offspring or the reproductive performance of the dams.

Rabbits

Pregnant New Zealand white rabbits were given miconazole in carboxymethylcellulose (CMC) at 80 (17 animals), 40 (15 animals) and 20 (15animals) mg/kg by gavage from day 7 to day 19 of gestation. On day 30 of gestation, the animals were sacrificed. No adverse effect was noted at the low or intermediate dose levels upon maternal mortality, pregnancy rate or early parturition or on foetal resorption, size, sex ratio or malformation. At the high dose level there was evidence of maternal and foetal toxicity as indicated by maternal weight loss during gestation, increased parturition and significant foetal resorption. However, at the high dose there was no indication of teratogenicity.

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HAZARD IDENTIFICATION	
Carcinogenicity	No indication of carcinogenicity to humans (not listed by IARC).
Genotoxicity studies	Miconazole nitrate was not genotoxic when tested in vitro in a bacterial reverse mutation (Ames) assay or in an in vivo mouse bone marrow micronucleus test. Intraperitoneal injections of miconazole to mice induced chromosomal aberrations in spermatocytes and bone marrow cells, and morphologic abnormalities in sperm at doses similar to or below clinical doses.
Reproductive/Developmental Toxicity	However, no impairment of fertility was observed in intravenous studies with miconazole at 40 mg/kg/day in rats or 20 mg/kg/day in rabbits, which are approximately 8 times higher than the dose a patient would receive if she swallowed a Miconazole buccal tablet, based on body surface area comparisons.
Highly sensitizing potential	Dermal and ocular studies on rabbits ranging from 24 hours to 1 month in duration have revealed little irritation when miconazole was utilized in the 2% cream formulation. Dose levels of miconazole in these studies were as high as 50 mg/kg/day. In addition, no evidence of systemic toxicity has been apparent in these studies.
Hazard Identification Symbol	 Irritant
IDENTIFICATION OF CRITICAL EFFECTS	
Clinical therapeutic and Adverse effects	**Therapeutic Effect:** This medication is used to treat vaginal yeast infections. Miconazole reduces vaginal burning, itching, and discharge that may occur with this condition. This medication is an azole antifungal. It works by stopping the growth of yeast (fungus) that causes the infection. **Adverse Effect:** On rare occasions it has been reported that patients treated with Micatin® experience mild pruritus, irritation and burning at the site of application.

NOAEL/LOAEL/NOEL/LOEL	Embryo-foetal development - Intravenous Result: Foetal NOAEL = 20 mg/kgday Species: Rabbit Embryo-foetal development - Intravenous Result: Foetal NOAEL = 40 mg/kg/day Species: Rat Embryo-foetal development - Oral Result: Foetal LOAEL = 80 mg/kg/day; evidence of foetal toxicity including increased resorptions Species: Rabbit Embryo-foetal development - Oral Result: Foetal LOAEL = 80 mg/kg/day; evidence of foetal toxicity including increased resorptions, prolonged gestation and dystocia Species: Rat Fertility, Literature data Result: NOAEL (intravenous) / fertility = 20 mg/kg/day (maximum dose) Species: Rabbit

	Fertility, Literature data Result: NOAEL (intravenous) / fertility = 40 mg/kg/day (maximum dose) Species: Rat As no any conversion factor is available hence smallest therapeutic dose is selected as LOAEL i.e. 1% or 10 mg

APPLICATION OF ADJUSTMENT FACTORS- PDE calculation		
F1: Extrapolation between species	1	Human therapeutic dose is selected.
F2: Inter-individual variability	10	Conventionally used to allow for differences betweenindividuals in the human population
F3: Duration of toxicity	1	Human therapeutic dose is selected.
F4: Severe toxicity (1-10)	10	For observed adverse effects and boxed warning in humans.
F5: NOAEL Vs LOAEL (10 if LOAEL)	10	Human therapeutic dose is selected and considered as LOAEL.

PDE CALCULATION:

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

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

= **0.01 mg/day**

6. REFERENCES:

- https://pdf.hres.ca/dpd_pm/00056596.PDF
- https://pubchem.ncbi.nlm.nih.gov/compound/Miconazole#section=FDA-Orange-Book
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022404s003lbl.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.