PERMITTED DAILY EXPOSURE FOR DICLOFENAC SODIUM

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 Diclofenac Sodium 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:

Diclofenac is a phenylacetic acid derivative and non-steroidal anti-inflammatory drug (NSAID). Label NSAID's inhibit cyclooxygenase (COX)-1 and-2 which are the enzyme responsible for producing prostaglandins (PG's). PG's contribute to inflammation and pain signalling. Diclofenac, like other NSAIDs, is often used as first line therapy for acute and chronic pain and inflammation from a variety of causes. Diclofenac was the product of rational drug design based on the structures of phenylbutazone, mefenamic acid, and indomethacin.12 The addition of two chlorine groups in the ortho position of the phenyl ring locks the ring in maximal torsion which appears to be related to increased potency. It is often used in combination with misoprostol to prevent NSAID-induced gastric ulcers.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Diclofenac Sodium is Off-White Crystalline Solid powder, slightly soluble in water.

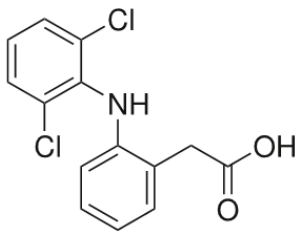
IUPAC name: Sodium 2-{2-[(2, 6-dichlorophenyl) amino] phenyl} acetate.

Chemical Abstract Services (CAS) Registry Number: 15307-79-6

Molecular Weight: 318.1 g/mol

Chemical Formula: $C_{14}H_{10}Cl_2NNaO_2$

Molecular Structure:



4. HAZARDS IDENTIFIED:

CATEGORIZATION:			
TOXICITY	**YES**	**NO**	**UNKNOWN**
Genotoxicant	-	√	-
Carcinogen	-	√	-
Reproductive/Developmental Toxicant	-	√	-
Highly Sensitizing potential	√	-	-

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SUMMARY OF HAZARD IDENTIFICATION:	
Pharmacodynamics data	The primary mechanism responsible for its anti-inflammatory, antipyretic, and analgesic action is thought to be inhibition of prostaglandin synthesis by inhibition of the transiently expressed prostaglandin-endoperoxide synthase-2 (PGES-2) also known as cycloxygenase-2 (COX-2). It also appears to exhibit bacteriostatic activity by inhibiting bacterial DNA synthesis. Research and an updated reveal of mechanism of action of Diclofenac shows, that its action is as with all NSAIDs by inhibition of prostaglandin synthesis. Important is that Diclofenac inhibits COX-1 and COX-2 with relative equipotency. The action of one single dose is much longer (6 to 8 hr) than the very short 1.2–2 hr half-life of the drug would indicate. This could be partly because it persists for over 11 hours in synovial fluids. Diclofenac may also be a unique member of the NSAIDs. Some evidence indicates it inhibits the lipoxygenase pathways, thus reducing formation of the leukotrienes (also pro-inflammatory autacoids). It also may inhibit phospholipase A2 as part of its mechanism of action. These additional actions may explain its high potency - it is the most potent NSAID on a broad basis. Marked differences exist among NSAIDs in their selective inhibition of the two subtypes of cyclooxygenase, COX-1 and COX-2. Much pharmaceutical drug design has attempted to focus on selective COX-2 inhibition as a way to minimize the gastrointestinal side effects of NSAIDs such as aspirin. In practice, use of some COX-2 inhibitors with their adverse effects has led to massive numbers of patient family lawsuits alleging wrongful death by heart attack, yet other significantly COX-selective NSAIDs, such as Diclofenac, have been well tolerated by most of the population.[1] Besides the COX-inhibition, a number of other molecular targets of Diclofenac possibly contributing to its pain-relieving actions have recently been identified. These include: • Blockage of voltage-dependent sodium channels (after activation of the channel, Diclofenac inhibits its reactivation also known as phase inhibition)[1] • Blockage of acid-sensing ion channels (ASICs) • Positive allosteric modulation of KCNQ- and BK-potassium channels (Diclofenac opens these channels, leading to hyperpolarization of the cell membrane)

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SUMMARY OF HAZARD IDENTIFICATION:

Acute Toxicity

Case 1:

Species	Route	End point (mg/kg/day)	Dose
Mouse	P.O.	LD50	389
	I.V.	LD50	133
Rat	P.O.	LD50	173
	I.V.	LD50	106
Guinea Pig	P.O.	LD50	1110
	I.V.	LD50	127
Rabbit	P.O.	LD50	194

The symptoms included bradycardia and convulsions. The most frequent autopsy findings in animals that died were gastric irritation, perforation and their sequel.

Case 2:

Species	Route	End point (mg/kg/day)	Dose
Rat	Oral	LD50	53-77 mg/kg

Repeated Dose Toxicity (Chronic Toxicity)

Case 1:

Species	Duration	Daily Dose (mg/kg/day) p.o.		
		No signs of intoxication	Reversible signs of toxicity, mainly GI Tract	Minimum lethal dose
Rat	**3 months**	2	-	6
	6 months	1	2	4
	98 weeks	0.25	-	1
Dog	**3 months**	-	0.5	2
Rhesus Monkey	**6 months**	-	5-15	75
Baboon	**12 months**	-	5	10

Diclofenac sodium was given orally to male and female rats in doses of 0.25 1.0 and 2.0 mg/kg/day from 59 weeks (high-dose groups) to 98 weeks (low- and intermediate-dose groups). High dose-related mortality rates resulted in termination of the high-dose administration after 59 weeks; the high mortality rate was caused by severe dose-dependent ulceration of the gastrointestinal tract, with perforated ulcers leading to peritonitis and sequelae. Body-weight gains and feed consumption of the treated groups were close to the controls. Hematologic patterns showing neutrophilic leucocytosis and anemia were seen in the high- and intermediate-dose groups, particularly females at weeks 52 and 98, respectively. Female animals tended to develop enlarged adrenals and eventually experienced depressed glucose and elevated alkaline phosphatase levels. Histology studies carried out on the tissues of the control, low- and intermediate-dose groups showed drug-related changes including mucosal ulceration of the small intestine, lymphangiectasis, lymphoid hypoplasia, and plasma cell hypoplasia of the mesenteric lymph nodes, foci of hepatocytic hyperplasia, adrenal cortical atrophy and prostatitis. No increase in tumour incidence was observed in the drug-treated groups as compared to the control group. Diclofenac sodium was administered orally in gelatin capsules once daily to baboons (Papio spp.) at dose levels of 0, 5, 15 (reduced to 10 on day 254) and 50 (reduced to 30 on day 38) mg/kg/day for up to 52 weeks. At all dose

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SUMMARY OF HAZARD IDENTIFICATION:

levels studied, Diclofenac caused ulceration of the gastrointestinal tract. Ulceration was confined to the colon in the low-dose group but was present in the stomach and small intestine also in the other two groups. Body weights were below controls. Constipation, with occasional episodes of diarrhea, was a marked feature. In all treated groups, there was a dose-related fall in serum albumin levels. Anemia and an increased ESR were observed in the high-dose group. In the recovery groups (control, low, and intermediate), no intestinal lesions were present. Food consumption and body-weight gains were within normal limits. Hematology parameters were comparable to controls and serum albumin levels returned towards normal values.

Case 2:

Duration	Species	Route	Dose (mg/kg)	End point (mg/kg/day)	Target Organ
30 days	Rat	Oral	14	LOAEL	None identified
5 Weeks	Mouse	Oral	9	LOAEL	Lungs, Spleen
26 Weeks	Rat	Oral	50	LOAEL	Blood, Gastrointestinal system

Carcinogenicity

Case 1: Long-term carcinogenicity studies in rats given Diclofenac Sodium up to 2 mg/kg/day have revealed **no significant increases in tumor incidence**. There was a positive dose-related trend with respect to adrenal medullary hyperplasia, mammary fibroadenomas and subcutaneous tissue fibromas in females, as well as of C-cell adenomas of the thyroid in males. The differences in the incidence between the various groups, including control, were small and were considered to reflect the variation in the spontaneous occurrence of these incidental lesions, common in old laboratory rats. In a 2-year mouse study, only controls and animals at the two lower daily doses of 0.1 and 0.3 mg/kg showed survival sufficient for assessment of carcinogenic potential. The two higher Page 33 of 41 daily doses of 1 and 2 mg/kg resulted in a shortening of lifespan, particularly in males, as a consequence of ulceration and/or perforation of the small intestine and therefore prevented evaluation. The known susceptibility of rodents to non-steroidal anti-inflammatory drugs, resulting in high mortality at dose levels close to the therapeutic dose, is considered to be a rodent-specific effect. **Diclofenac sodium was not carcinogenic to mice under the conditions of this study.**

Case 2:

Duration	Species	Route	Dose	End Point	Effects
Not specified	Rat	Oral	2 mg/kg/day	NOEL	Not Carcinogenic

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SUMMARY OF HAZARD IDENTIFICATION:

In vivo/In vitro Genotoxicity Studies

Case 1: Mutagenicity studies were carried out in vitro using bacteria with, and without microsomal activation, and in mammalian cells. Studies in vivo were also performed. **Diclofenac sodium was not mutagenic** in any of these test systems.

Case 2:

Study Type	Cell type/Organism	Result
Bacterial Mutagenicity (Ames)	Salmonella	Negative

Reproductive/Developmental Toxicity

Case 1: Rats: Doses of 2 and 4 mg/kg/day were given orally to male and female rats with no noticeable effect on fertility. Dosing was carried out during premating, mating, gestation, and lactation periods. At the higher dose, prolonged gestation and dystocia were observed. Embryo toxicity (low birth weight, failure to survive) was observed at both doses but it was minimal at 2 mg/kg/day. Post-natal survival and growth of pups from drug-treated animals were comparable to those of controls except for slightly retarded growth at the higher dose.

Mice and Rats: Teratology studies at oral doses of 2, 3, 10, and 20 mg/kg/day showed **no Teratogenic effects on fetuses**. At the higher doses, pronounced gastrointestinal effects were observed in the dams and a marked toxic effect noted in fetuses (reduced birth weights and increased fetal deaths).

Rabbits: Pregnant females treated with oral doses of 5 or 10 mg/animal/day throughout the gestation period showed a dose-dependent increase in resorption rates, diminished fetus weights, and abnormal skeletal findings. Definite embryo toxicity was observed at the highest dose although there **was no evidence to suggest teratogenicity**. Administration of NSAIDs (including Diclofenac) inhibited ovulation in the rabbit and implantation and placentation in the rat, and led to premature closure of the ductus arteriosus in the pregnant rat. Maternally toxic doses of Diclofenac were associated with dystocia, prolonged gestation, decreased fetal survival, and intrauterine growth retardation in rats. The slight effects of Diclofenac on reproduction parameters and delivery as well as constriction of the ductus arteriosus in utero are pharmacologic consequences of this class of prostaglandin synthesis inhibitors.

Case 2:

Study Type	Species	Route	Dose (mg/kg/day)	End point	Effect
Embryo/Fetal Development	Rat	Oral	24	LOAEL	Maternal Toxicity & Fetotoxicity
Embryo/Fetal Development	Rat	No route specified	1	LOAEL	Developmental Toxicity
Embryo/Fetal Development	Rat	No route specified	20	NOEL	Not Teratogenic
Embryo/Fetal Development	Rabbit	No route specified	10	NOEL	Not Teratogenic

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SUMMARY OF HAZARD IDENTIFICATION:	
Highly Sensitizing Potential	**Skin Irritation:** Positive **Eye Irritation:** Positive

IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	NSAID's hypersensitivity has a spectral manifestation varying from simple isolated urticaria to severe anaphylaxis which could be life threatening. These reactions are more common in patients with a known allergic reaction or autoimmune disorders which should be considered as the population at risk. It is therefore important that this thought be kept in mind while prescribing the 'commonly used NSAIDs' and any history of allergic reaction be evaluated in detail and the patient counseled for the nature of illness and subsequent precautions the patient has to follow.
Clinical therapeutic and adverse effects	Diclofenac consumption has been associated with significantly increased vascular and coronary risk in a study including Coxib, Diclofenac, ibuprofen and naproxen. Upper gastrointestinal complications were also reported. Major adverse cardiovascular events (MACE) were increased by about a third by Diclofenac, chiefly due to an increase in major coronary events. Compared with placebo, of 1000 patients allocated to Diclofenac for a year, three more had major vascular events, one of which was fatal. Vascular death was increased significantly by Diclofenac.

NOAEL/LOAEL	9 mg/kg/day (LOAEL value selected for PDE evaluation).

APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	5	For extrapolation from rats to humans.
F2: Inter Individual Variability	10	Used for differences between individuals in the human population.
F3: Duration of Toxicity (Repeat Dose Toxicity)	2	6 months duration study in rodent.
F4: Severe Toxicity (1-10)	1	No any toxicity (Genotoxicity/Reproductive toxicity/ Carcinogenicity) observed
F5: NOAEL or LOAEL (10 if LOAEL)	10	LOAEL value is selected.
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{9 (LOAEL) x 50}}{\text{5 x 10 x 2 x 1 x 10}}$ = 0.45 mg/day

5. REFERENCES:

- https://www.novartis.ca/sites/www.novartis.ca/files/voltaren_scrip_e.
- https://pfe-pfizercom-prod.s3.amazonaws.com/products/material_safety_data/PZ00318.

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- https://en.wikipedia.org/wiki/Diclofenac.
- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4529582/.
- https://www.drugbank.ca/salts/DBSALT000466.