PERMITTED DAILY EXPOSURE FOR HYDROCHLOROTHIAZIDE

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 Hydrochlorothiazide 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:

Hydrochlorothiazide (HCTZ or HCT) is a diuretic medication often used to treat high blood pressure and swelling due to fluid buildup. Other uses include diabetes insipidus, renal tubular acidosis, and to decrease the risk of kidney stones in those with a high calcium level in the urine. For high blood pressure it is sometimes considered as a first-line treatment. HCTZ is taken by mouth and may be combined with other blood pressure medications as a single pill to increase effectiveness

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Hydrochlorothiazide is a Benzothiadiazine that is 3, 4-dihydro-2H-1, 2,4-benzothiadiazine 1,1-dioxide substituted by a chloro group at position 6 and a sulfonamide at 7. It is white crystalline powder, very slightly soluble in water.

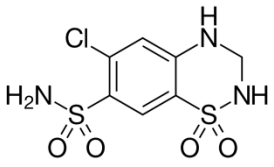
IUPAC name: 6-chloro-1, 1-dioxo-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide

Chemical Abstract Services (CAS) Registry Number: 58-93-5

Molecular Weight: 297.74 g/mol g·mol−1

Chemical Formula: $C_7H_8ClN_3O_4S_2$

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	**Toxicodynamics** Most of the toxicodynamic manifestations are due to electrolyte imbalances including hypochloraemic alkalosis, hyponatraemia, hypokalaemia and hypomagnesaemia. The mechanism of hypercalcaemia and hypophosphataemia are unknown. Clinical studies indicate that depletion of potassium has a role in glucose intolerance, probably by inhibition of insulin secretion (Weiner, 1990). For reasons that are unexplained thiazides increase the concentrations of cholesterol and triglycerides in plasma (Weiner, 1990). Other toxic effects produced by hydrochlorothiazide are due to hypersensitivity reactions. **Pharmacodynamics** Hydrochlorothiazide acts directly on the kidney, increasing the excretion of sodium chloride an potassium and consequently water, mainly in the distal tubule (Ellenhorn & Barceloux, 1988; Weiner, 1990; Reynolds, 1989).
Pharmacokinetics data	**Absorption by route of exposure** Hydrochlorothiazide is variably but fairly rapidly absorbed from the gastrointestinal tract. Bio-availability of hydrochlorothiazide after oral administration is approximately 60 to 80 per cent. Peak plasma level occurs after 1 to 2 hours (Ellenhorn & Barceloux, 1988). **Distribution by route of exposure** Hydrochlorothiazide is widely distributed in body tissue and its volume of distribution following oral administration corresponds to 0.83 L/Kg (Ellenhorn & Barceloux, 1988; Gilman et al., 1990). Protein binding in the plasma is estimated at 58% (Gilman et al., 1990). **Biological half-life by route of exposure** A plasma half-life of about 9.5 hours has been estimated. The red blood cells half-life is 2.7 to 7 hours (Ellenhorn & Barceloux, 1988). **Metabolism** Hydrochlorothiazide is not modified by organic biochemical processes. **Elimination by route of exposure** Elimination of hydrochlorothiazide is mainly due to renal clearance that occurs in about 320 mg/min (Ellenhorn, 1988). It is excreted unchanged in the urine. Hydrochlorothiazide crosses the placental barrier and appears in breast milk (Ellenhorn & Barceloux, 1988; Reynolds, 1989). Total systemic clearance of drug from the plasma is 4.9 mL/min/kg, decreasing in patients with uremia or congestive heart failure. (Gilman et al., 1990)

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SUMMARY OF HAZARD IDENTIFICATION:

Acute Toxicity

Study 1:

Organism	Test type	Route	Dose	Effect
Women	TDLo	Oral	34884 ug/kg/30 (34.884 mg/kg)	Behavioral: changes in motor activity (specific assay); blood: changes in serum composition (e.g., tp, bilirubin, cholesterol)
Man	TDLo	Oral	75 mg/kg/30W-I (75 mg/kg)	Behavioral: Changes In Motor Activity (Specific Assay); Behavioral: Muscle Weakness; Gastrointestinal: Other Changes
Women	TDLo	Oral	500 ug/kg (0.5 mg/kg)	Lungs, thorax, or respiration: acute pulmonary edema; lungs, thorax, or respiration: other changes
Women	TDLo	Oral	500 ug/kg (0.5 mg/kg)	Null
Man	TDLo	Oral	12857 ug/kg/9D (12.85 mg/kg)	Behavioral: convulsions or effect on seizure threshold; gastrointestinal: nausea or vomiting
Women	TDLo	Oral	500 ug/kg (0.5 mg/kg)	Vascular: bp lowering not characterized in autonomic section; lungs, thorax, or respiration: acute pulmonary edema; lungs, thorax, or respiration: cyanosis
Women	TDLo	Oral	2 mg/kg/12H-I (2 mg/kg)	Null
Women	TDLo	Oral	250 ug/kg (0.25 mg/kg)	Cardiac: pulse rate increase without fall in bp; vascular: shock; lungs, thorax, or respiration: acute pulmonary edema
Rat	LD50	Oral	2750 mg/kg (2750 mg/kg)	Null
Rat	LD50	Intraperitoneal	234 mg/kg (234 mg/kg)	Null
Rat	LD50	Subcutaneous	1270 mg/kg (1270 mg/kg)	Null
Rat	LD50	Intravenous	990 mg/kg (990 mg/kg)	Null
Mouse	LD50	Oral	1175 mg/kg (1175 mg/kg)	Null
Mouse	LD50	Intraperitoneal	578 mg/kg (578 mg/kg)	Null
Mouse	LD50	Subcutaneous	1470 mg/kg (1470 mg/kg)	Null
Mouse	LD50	Unreported	1100 mg/kg (1100 mg/kg)	Null
Dog	LD50	Intravenous	250 mg/kg (250 mg/kg)	Null
Rabbit	LD50	Intravenous	461 mg/kg (461 mg/kg)	Null
Women	LDLo	Oral	2500 ug/kg/5D- (2.5 mg/kg)	Behavioral: coma
Women	TDLo	Oral	500 ug/kg (0.5 mg/kg)	Lungs, thorax, or respiration: acute pulmonary edema; gastrointestinal: nausea or vomiting
Mouse	LD50	Intravenous	590 mg/kg (590 mg/kg)	Peripheral nerve and sensation: spastic paralysis with or without sensory change; behavioral: convulsions or effect on seizure threshold; lungs, thorax, or respiration: other changes

Study 2:

Species	Route	End point	Dose (mg/kg)
Rat	Oral	LD50	2750
Mouse	Oral	LD50	2830
Rat	i.v	LD50	990
Dog	i.v	LD50	250

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SUMMARY OF HAZARD IDENTIFICATION:

Repeated Dose Toxicity (Chronic Toxicity)

Study 1:

Duration	Species	Route	Dose (mg/kg/day)	End Point	Target Organ
30 days	Rat	Oral	1000	LOAEL	Blood
13 weeks	Mouse	Oral	12.5	LOAEL	Bladder
9 months	Dog	Oral	50	LOAEL	Endocrine System
1 year	Rat	Oral	2	LOAEL	Kidney
2 year	Rat	Oral	0.25	LOAEL	Kidney

Carcinogenicity

There is limited evidence in humans for the carcinogenicity of Hydrochlorothiazide. Positive associations were observed for squamous cell carcinoma of the skin and lip. There is limited evidence in experimental animals for the carcinogenicity of hydrochlorothiazide. **Overall evaluation:** Hydrochlorothiazide is possibly carcinogenic to humans (Group 2B).

Case Study 1: Two year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice.

Duration	Species	Route	Dose (ppm)	End Point	Effect
2 Year	Rat	Oral	2000	NOAEL	Not Carcinogenic
2 Year	Female Mouse	Oral	5000	NOAEL	Not Carcinogenic
2 Year	Male Mouse	Oral	5000	LOAEL	Malignant Tumors, Liver

IARC: Group 3 (Not Classifiable)

In vivo/In vitro Genotoxicity Studies

Hydrochlorothiazide was not genotoxic in vitro in the Ames mutagenicity assay of Salmonella typhimurium strains TA 98, TA 100, TA 1535, TA 1537 and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations or in vivo in assays using mouse germinal cell chromosomes, Chinese hamster bone marrow chromosomes and the Drosophila sex-linked recessive lethal trait gene. Positive test results were obtained only in the in vitro CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mcg/ml and in the Aspergillus nidulans non-disjunction assay at an unspecified concentration.

Study Type	Cell Type/Organism	Result
Bacterial Mutagenicity (Ames)	*Salmonella*	Negative
In Vitro sister Chromatid Exchange	Chinese Hamster Ovary (CHO) cells	Positive
Dominant lethal assay	Drosophila	Negative
Mammalian Cell Mutagenicity	Mouse lymphoma	Positive

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SUMMARY OF HAZARD IDENTIFICATION:

Reproductive/Developmental Toxicity

Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein these species were exposed, via their diet, to doses of up to 100 and 4 mg/kg, respectively, prior to conception and throughout gestation.

Pregnancy: Teratogenic Effects. Pregnancy Category B: Studies in which hydrochlorothiazide was orally administered to pregnant mice and rats during their respective periods of major organogenesis at doses up to 3000 and 1000 mg hydrochlorothiazide/kg, respectively, provided no evidence of harm to the fetus. There are, however, no adequate and well controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Non-teratogenic Effects: Thiazides cross the placental barrier and appear in cord blood. There is a risk of fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Nursing Mothers: Thiazides are excreted in breast milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue hydrochlorothiazide, taking into account the importance of the drug to the mother. **Pediatric Use:** There are no well controlled clinical trials in pediatric patients. Information on dosing in this age group is supported by evidence from empiric use in pediatric patients and published literature regarding the treatment of hypertension in such patients.

Study Type	Species	Route	Dose (mg/kg/day)	End Point	Effect
Reproductive & Fertility	Rat	Oral	1000	LOAEL	Maternal Toxicity
Reproductive & Fertility	Mouse	Oral	3000	NOEL	No effect at maximum dose
Embryo/Fetal Development	Rat	Oral	1000	NOEL	Not Teratogenic
Embryo/Fetal Development	Mouse	Oral	3000	NOEL	Not Teratogenic

Highly Sensitizing Potential

Hypersensitivity: Purpura, intravascular immunohaemolysis, pneumonitis, skin rashes, urticaria, eczema, lichen planus-like reactions; photosensitivity, similar to subacute cutaneous lupus erythematosus; vasculitis, Stevens Johnson Syndrome.

IDENTIFICATION OF CRITICAL EFFECTS:

Sensitive Indicator of an adverse effect seen in non-clinical toxicity data

No any adverse effect seen in non-clinical toxicity data.

Clinical therapeutic and adverse effects

Adults

Hypertension

25 to 50 mg daily. Doses of up to 200 mg have been recommended but are rarely necessary. (Ellenhorn & Barceloux, 1988; Reynolds, 1989).

Oedema

50 to 100 mg daily (initial dose), reduced to a dose of 25 to 50 mg daily or intermittently. 200 mg daily have been recommended. (Reynolds, 1989).

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	Renal disorders 50 mg twice daily appeared to be effective in preventing the formation of calcium stones in the urinary tract in a study of 67 patients. (Reynolds, 1989). ***Diabetes insipidus*** 50 mg twice a day. (Randall, 1987). ***Premenstrual tension*** 50 to 100 mg daily. **Children** 2.5 mg/kg body-weight daily in two divided doses. Infants under 6 months may need doses of up to 3.5 mg/kg body-weight daily (Reynolds, 1989).

NOAEL/LOAEL	0.25 mg LOAEL value

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)	1	2 year 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 (Minimum daily dose is selected in mg/kg/day).
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{0.25 (LOAEL) x 50}}{\text{5 x 10 x 1 x 1 x 10}}$ = 0.025 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Hydrochlorothiazide
- https://pubchem.ncbi.nlm.nih.gov/compound/Hydrochlorothiazide#section=Related-Compounds
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/040735s004,040770s003lbl.pdf
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