PERMITTED DAILY EXPOSURE FOR ACETYLCYSTEINE

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 the 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 Acetylcysteine 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:

Acetylcysteine (also known as N-Acetylcysteine or N-acetyl-L-cysteine or NAC) is primarily used as a mucolytic agent and in the management of Acetaminophen (Paracetamol) poisoning. It is a derivative of cysteine with an acetyl group attached to the amino group of cysteine. NAC is essentially a pro-drug that is converted to cysteine (in the intestine by the enzyme aminoacylase 1) and absorbed in the intestine into the blood stream.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Acetylcysteine is a white crystalline powder that is freely soluble in water, alcohol, practically insoluble in chloroform and in ether.

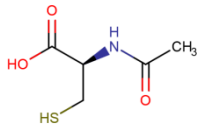
IUPAC NAME: (2R)-2-acetamido-3-sulfanylpropanoic acid

Chemical Abstract Services (CAS) Registry Number: 616-91-1

Molecular Weight: 163.195 $g \cdot mol^{-1}$

Chemical Formula: $C_5H_9NO_3S$

Molecular Structure:



4. HAZARDS IDENTIFIED:

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

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

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SUMMARY OF HAZARD IDENTIFICATION:

Pharmacodynamics data

Acetylcysteine has been shown to reduce the extent of liver injury following Acetaminophen overdose. It is most effective when given early, with benefit seen principally in patients treated within 8-10 hours of the overdose. Acetylcysteine likely protects the liver by maintaining or restoring the glutathione levels, or by acting as an alternate substrate for conjugation with, and thus detoxification of, the reactive metabolite.

Pharmacokinetic data

Absorption: After administration of a single oral dose of 11 grams of Acetylcysteine tablets (dissolved in 300 ml of water) to 29 healthy adult subjects, the mean Cmax (CV%) was 26.5 (29) mcg/mL and mean (CV) AUC_{inf} was 186 (29) hr•mcg/ml. The median (range) time to reach Cmax (Tmax) was 2 (1 to 3.5) hours.

Distribution: The steady-state volume of distribution (V_d) following administration of an intravenous dose of Acetylcysteine was 0.47 liter/kg. The protein binding for Acetylcysteine ranges from 66% to 87 %.

Metabolism: Acetylcysteine (i.e., N-Acetylcysteine) undergoes extensive first pass metabolism and is postulated to form cysteine and disulfides (N, N-diacetylcysteine and N-Acetylcysteine). Cysteine is further metabolized to form glutathione and other metabolites. Excretion After a single oral dose of [35S]-Acetylcysteine 100 mg, between 13 to 38% of the total radioactivity administered was recovered in urine within 24 hours. In a separate study, renal clearance was estimated to be approximately 30% of total body clearance. In healthy subjects given a single oral dose of 11 grams of Acetylcysteine tablets, the mean (CV%) terminal plasma half-life (T1/2) was 18.1 (22%) hours.

Acute Toxicity

Species	Route	End Point	Dose (mg/kg)
Rat	Oral	LD_{50}	>6000
Rat	Intravenous	LD_{50}	1140
Mouse	Oral	LD_{50}	>3000
Mouse	Intravenous	LD_{50}	3800
Mouse	Intraperitoneal	LD_{50}	400

Repeated Dose Toxicity (Chronic Toxicity)

Dosing and route of administration of N-acetylcysteine (NAC) for protection against cisplatin (CDDP) nephrotoxicity was investigated in rats.

Two models of toxicity were tested:

(i). A Single High Dose of CDDP: 10 mg/kg intraperitoneally (IP) and multiple low dose treatments (1 mg/kg IP twice a day for 4 days, 10 days' rest, then repeated). NAC (50-1, 200 mg/kg) was given to the rats by IP, oral (PO), intravenous (IV) and intra-arterial (IA) routes. Renal toxicity was determined by blood urea nitrogen (BUN) and creatinine (CR) levels 3 days after treatment. Blood collected 15 min after NAC was analyzed for total NAC. Both models of CDDP administration produced renal toxicity. In the single dose CDDP model, NAC 400 mg/kg given IP and PO produced no renal protection as measured by BUN (131.8 +/- 8.2 and 123.3 +/- 8.2, respectively) or CR (2.3 +/- 0.38 and 1.77 +/- 0.21, respectively). IV NAC reduced nephrotoxicity, (BUN 26.3 +/- 6.8, CR 0.47 +/- 0.15). NAC 50 mg/kg IA gave better protection than IV.

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SUMMARY OF HAZARD IDENTIFICATION:

(ii). In the Repeated Dose CDDP model: Nephrotoxicity was blocked by 800 mg/kg NAC given IV but not IP. Blood concentrations of total NAC showed a dose response after IV NAC, but high dose NAC (1,200 mg/kg) by the PO route gave very low levels of NAC. Thus the protective properties of NAC are affected by the dose and route of administration.

Carcinogenicity

Duration	Species	Route	Dose (mg/kg/day)	End Point	Effect (s)
18 months	Rat	Oral	1000	NOAEL	Not Carcinogenic

Carcinogenicity studies in laboratory animals have not been performed with Acetylcysteine.

In vivo/In vitro Genotoxicity Studies

Study type	Cell type/Organism	Result
Bacterial Mutagenicity (Ames)	Salmonella , E. coli	Negative

Acetylcysteine was negative in the Ames test.

Reproductive/Developmental Toxicity

Study Type	Species	Route	Dose (mg/kg/day)	End Point	Effect
Reproductive & Fertility	Rat	Oral	1000	NOAEL	Fertility
Embryo / Fetal Development	Rabbit	Oral	500	NOAEL	Not Teratogenic

Impairment of Fertility: In a fertility study of Acetylcysteine in rats, intravenous administration of 1000 mg/kg/day (0.3 times the recommended human oral dose based on body surface area) caused a profound reduction of fertility in females, which was correlated with morphological changes in oocytes and severe impairment of implantation (18 of 20 mated females had no implantations). The reversibility of this effect was not evaluated. No effects on fertility were observed in female rats at intravenous doses up to 300 mg/kg/day (0.1 times the recommended human oral dose based on body surface area), or in male rats at intravenous doses up to 1000 mg/kg/day. Mating was unaffected in this study. In a reproduction study of Acetylcysteine, male rats were treated orally for 15 weeks prior to mating and during the mating period. A slight non-dose related reduction in fertility was observed at oral doses of 500 and 1000 mg/kg/day (0.1 and 0.3 times the recommended human dose, respectively, based on body surface area).

No teratogenic effects were observed in embryo-fetal development studies in rats at oral doses up to 2000 mg/kg/day (0.6 times the maximum recommended human dose based on body surface area) or in rabbits at oral doses up to 1000 mg/kg/day (0.6 times the maximum recommended human dose based on body surface area) administered during organogenesis.

Highly Sensitizing Potential

Hypersensitivity reactions, including generalized urticaria may occur.

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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	**Clinical therapeutic effects:** Acetylcysteine, also known as N-Acetylcysteine (NAC), is a medication that is used to treat paracetamol (acetaminophen) overdose, and to loosen thick mucus in individuals with cystic fibrosis or chronic obstructive pulmonary disease. It can be taken intravenously, by mouth, or inhaled as a mist. Some people use it as a dietary supplement. **Adverse effects:** Nausea, vomiting, or stomach pain may occur.

NOAEL/LOAEL	NOAEL selected 500 mg/kg for Reproductive toxicity.

APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	2.5	For extrapolation from rabbit to humans.
F2: Inter Individual Variability	10	Used for differences between individuals in the human population.
F3: Duration of Toxicity (Repeat Dose Toxicity)	10	Short duration study in Rabbit.
F4: Severe Toxicity (1-10)	1	No any toxicity (Genotoxicity/Reproductive toxicity/ Carcinogenicity) observed
F5: NOAEL or LOAEL (10 if LOAEL)	5	NOAEL value is selected
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION:	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{500 (NOAEL) x 50}}{\text{2.5 x 10 x 10 x 1 x 5}}$ = 20 mg/day

5. REFERENCES:

- https://www.drugbank.ca/drugs/DB06151.
- https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/207916s003lbl.pdf.
- https://pfe-pfizercom-d8-prod.s3.amazonaws.com/products/material_safety_data/PZ00221.pdf.
- https://pubmed.ncbi.nlm.nih.gov/17909806/.
- https://en.wikipedia.org/wiki/Acetylcysteine.