PERMITTED DAILY EXPOSURE FOR VALPROIC ACID

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 Valproic acid 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:

Valproate (VPA), and its valproic acid, sodium valproate, and valproate semisodium forms, are medications primarily used to treat epilepsy and bipolar disorder and to prevent migraine headaches. They are useful for the prevention of seizures in those with absence seizures, partial seizures, and generalized seizures. They can be given intravenously or by mouth.

Common side effects include nausea, vomiting, sleepiness, and dry mouth. Serious side effects can include liver problems and regular monitoring of liver function tests is therefore recommended. Other serious risks include pancreatitis and an increased suicide risk. The drug is known to cause serious abnormalities in babies if taken during pregnancy. Because of this it is not typically recommended in women of childbearing age who have migraines.

It is unclear exactly how valproate works. Proposed mechanisms include affecting GABA levels, blocking voltage-gated sodium channels, and inhibiting histone deacetylases. Valproic acid is a branched short-chain fatty acid (SCFA) made from valeric acid.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

It is Colourless to pale yellow & slightly soluble in water (1.2 mg/ml) fully soluble in acetone, chloroform, ether and methyl alcohol.

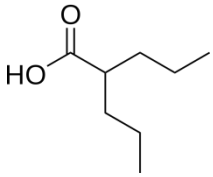
IUPAC name: 2-propylpentanoic acid

Chemical Abstract Services (CAS) Registry Number:

Molecular Weight: 144.211 g·mol−1

Chemical Formula: $C_8H_{16}O_2$

Molecular Structure:



PERMITTED DAILY EXPOSURE FOR VALPROIC ACID

4. HAZARDS IDENTIFIED:

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

SUMMARY OF HAZARD IDENTIFICATION:	
Pharmacodynamics data	Valproate has been shown to reduce the incidence of complex partial seizures and migraine headaches. It also improves symptom control in bipolar mania. Although the exact mechanisms responsible are unknown, it is thought that valproate produces increased cortical inhibition to contribute to control of neural synchrony. It is also thought that valproate exerts a neuroprotective effect preventing damage and neural degeneration in epilepsy, migraines, and bipolar disorder. Valproate is hepatotoxic and teratogenic. The reasons for this are unclear but have been attributed to the genomic effects of the drug.[1] A small proof-of concept study found that valproate increases clearance of human immunodeficiency virus (HIV) when combined with highly active antiretroviral therapy (HAART) by reactivating the virus to allow clearance, however, a larger multicentre trial failed to show a significant effect on HIV reservoirs when added to HAART. The FDA labeling contains a warning regarding HIV reactivation during valproate use.
Pharmacokinetics data	Absorption/Bioavailability Equivalent oral doses of Divalproex sodium products Valproic acid capsules deliver equivalent quantities of valproate ion systemically. Although the rate of valproate ion absorption may vary with the formulation administered (liquid, solid, or sprinkle), conditions of use (e.g., fasting or postprandial) and the method of administration (e.g., whether the contents of the capsule are sprinkled on food or the capsule is taken intact), these differences should be of minor clinical importance under the steady state conditions achieved in chronic use in the treatment of epilepsy. However, it is possible that differences among the various valproate products in Tmax and Cmax could be important upon initiation of treatment. For example, in single dose studies, the effect of feeding had a greater influence on the rate of absorption of the tablet (increase in Tmax from 4 to 8 hours) than on the absorption of the capsules (increase in Tmax from 3.3 to 4.8 hours). While the absorption rate from the G.I. tract and fluctuation in valproate plasma concentrations vary with dosing regimen and formulation, the efficacy of valproate as an anticonvulsant in chronic use is unlikely to be affected. Experience employing dosing regimens from once-a-day to four-times-a-day, as well as studies in primate epilepsy models involving constant rate infusion, indicate that total daily systemic bioavailability (extent of absorption) is the primary determinant of seizure control and that differences in the ratios of plasma peak to trough concentrations between valproate formulations are inconsequential from a practical clinical standpoint. Co-administration of oral valproate products

PERMITTED DAILY EXPOSURE FOR VALPROIC ACID

SUMMARY OF HAZARD IDENTIFICATION:	
	with food should cause no clinical problems in the management of patients with epilepsy. Nonetheless, any changes in dosage administration, or the addition or discontinuance of concomitant drugs should ordinarily be accompanied by close monitoring of clinical status and valproate plasma concentrations. Distribution Protein Binding The plasma protein binding of valproate is concentration dependent and the free fraction increases from approximately 10% at 40 mcg/ml to 18.5% at 130 mcg/ml. Protein binding of valproate is reduced in the elderly, in patients with chronic hepatic diseases, in patients with renal impairment, and in the presence of other drugs (e.g., aspirin). Conversely, valproate may displace certain protein-bound drugs (e.g., phenytoin, carbamazepine, warfarin, and tolbutamide). (See Drug Interactions (7.2) for more detailed information on the pharmacokinetic interactions of valproate with other drugs.) CNS Distribution Valproate concentrations in cerebrospinal fluid (CSF) approximate unbound concentrations in plasma (about 10% of total concentration). Metabolism Valproate is metabolized almost entirely by the liver. In adult patients on monotherapy, 30-50% of an administered dose appears in urine as a glucuronide conjugate. Mitochondrial β-oxidation is the other major metabolic pathway, typically accounting for over 40% of the dose. Usually, less than 15-20% of the dose is eliminated by other oxidative mechanisms. Less than 3% of an administered dose is excreted unchanged in urine. The relationship between dose and total valproate concentration is nonlinear; concentration does not increase proportionally with the dose, but rather, increases to a lesser extent due to saturable plasma protein binding. The kinetics of unbound drug are linear. Elimination Mean plasma clearance and volume of distribution for total valproate are 0.56 L/hr/1.73 m2 and 11 L/1.73 m^2 , respectively. Mean plasma clearance and volume of distribution for free valproate are 4.6 L/hr/1.73 m^2 and 92 L/1.73 m^2. Mean terminal half-life for valproate mono therapy ranged from 9 to 16 hours following oral dosing regimens of 250 to 1000 mg. The estimates cited apply primarily to patients who are not taking drugs that affect hepatic metabolizing enzyme systems. For example, patients taking enzyme-inducing antiepileptic drugs (carbamazepine, phenytoin, and phenobarbital) will clear valproate more rapidly. Because of these changes in valproate clearance, monitoring of antiepileptic concentrations should be intensified whenever concomitant anti-epileptics are introduced or withdrawn.
Acute Toxicity	**Study 1:** Acute hepatoxicity that may terminate fatally, usually seen in children and adolescents during the first six months of therapy. Its frequency is 1 in 5,000 children. Hepatic failure has been observed displaying a Reye's syndrome like illness (Ellenhorn & Barceloux, 1988). **Study 2:** Acute Valproic acid poisoning is observed relatively infrequently compared to other anticonvulsants. Reports have shown that in most patients the poisoning follows a benign course. Death is rare but if it occurs it results from cardio-pulmonary arrest secondary to hepatic failure.
Repeated Dose Toxicity (Chronic Toxicity)	In 2-year rat and chronic mouse studies using dosages of 80 to 170 mg/kg/day, an increased incidence of subcutaneous fibrosarcoma occurred in male rats at the higher dosage level and a dose-related trend for an increased incidence of benign pulmonary adenomas was observed in male mice. The importance of these findings to humans is

PERMITTED DAILY EXPOSURE FOR VALPROIC ACID

SUMMARY OF HAZARD IDENTIFICATION:	
	not known (McEvoy, 1991).
Carcinogenicity	Valproate was administered orally to rats and mice at doses of 80 and 170 mg/kg/day (less than the maximum recommended human dose on a mg/m^2 basis) for two years. The primary findings were an increase in the incidence of subcutaneous fibrosarcomas in high-dose male rats receiving valproate and a dose-related trend for benign pulmonary adenomas in male mice receiving valproate. The significance of these findings for humans is unknown.
In vivo/In vitro Genotoxicity Studies	Valproate was not mutagenic in an in vitro bacterial assay (Ames test), did not produce dominant lethal effects in mice, and did not increase chromosome aberration frequency in an in vivo cytogenetic study in rats. Increased frequencies of sister chromatid exchange (SCE) have been reported in a study of epileptic children taking valproate, but this association was not observed in another study conducted in adults. There is some evidence that increased SCE frequencies may be associated with epilepsy. The biological significance of an increase in SCE frequency is not known.
Reproductive/Developmental Toxicity	Chronic toxicity studies of valproate in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at oral doses of 400 mg/kg/day or greater in rats (approximately equivalent to or greater than the maximum recommended human dose (MRHD) on a mg/m^2 basis) and 150 mg/kg/day or greater in dogs (approximately 1.4 times the MRHD or greater on a mg/m^2 basis). Fertility studies in rats have shown no effect on fertility at oral doses of valproate up to 350 mg/kg/day (approximately equal to the MRHD on a mg/m^2 basis) for 60 days. The effect of valproate on testicular development and on sperm production and fertility in humans is unknown. **Teratogenicity:** Safe use of Valproic acid during pregnancy has not been established. Adverse foetal effects have been observed in reproduction studies in rats and mice. Although several reports suggest an association between the use of Valproic acid in pregnant epileptic women and an increased incidence of birth defects (particularly neural tube defects) in children born to these women, a causal relationship remains to be established (McEvoy, 1991).
Highly Sensitizing Potential	Cutaneous eruptions are one of the most common type of drug-related adverse reactions and accounted for 2-3% in hospital-based series. About 10% of patients receiving antiepileptic drug therapy develop **skin allergy**. Among the AEDs, **Sodium Valproate** is relatively free from **skin allergy**.

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 dose:** Initially 600 mg daily, increased by 200 mg daily at three-day intervals

PERMITTED DAILY EXPOSURE FOR VALPROIC ACID

	Daily doses generally within the range 1,000 to 2,000 mg/day (20 to 30 mg/kg/day) Maximum 30 to 60 mg/kg/day **Adverse effect:** Congenital anomalies, infection, abdominal pain, asthenia, drowsiness, nausea, tremor, vomiting, alopecia, diarrhea, dizziness, flu-like symptoms, thrombocytopenia, and anorexia.

NOAEL/LOAEL	Minimum daily dose of 20 mg/kg/day is considered as NOAEL

APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	1	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 study available for rodent.
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 (Minimum daily dose is selected in mg/kg/day).
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

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

5. REFERENCES:

- https://en.wikipedia.org/wiki/Valproate
- http://www.inchem.org/documents/pims/pharm/pim551.htm