PERMITTED DAILY EXPOSURE FOR FOLIC 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 Folic 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:

The term folate is used generically to describe the various derivatives of pteroylglutamic acid (PGA, folic acid), the common pharmaceutical and most stable form of the folate vitamins group, which is composed of three major subunits – pteridine, *p*-aminobenzoic acid, and glutamic acid. Folic acid (PGA) per se is not present in significant quantities in foods or in the human body. The derivatives of PGA which are predominantly present in the human body, and in plant- and animalderived foods, are reduced folates, mostly 5,6,7,8-tetrahydrofolates (THF), and also 7,8-dihydrofolate (DHF). Other modifications also occur.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

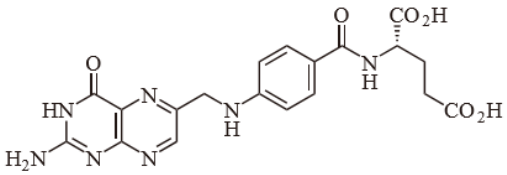
IUPAC name: (2S)-2-[[4-[(2-Amino-4-oxo-1H-pteridin-6-yl) methylamino] benzoyl] amino] pentanedioic acid

Chemical Abstract Services (CAS) Registry Number: 59-30-3

Molecular Weight: 441.404 g·mol−1

Chemical Formula: $C_{19}H_{19}N_7O_6$

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	Folic acid is transformed into different coenzymes that are responsible for various reactions of intracellular metabolism mainly conversion of homocysteine to methionine, conversion of serine to glycine, synthesis of thymidylate, histidine metabolism, synthesis of purines and utilization or generation of formate. In man, nucleoprotein synthesis and the maintenance of normal erythropoiesis requires exogenous folate. Folic acid is the precursor of tetrahydrofolic acid which is active and acts as a co-factor for 1-carbon transfer reactions in the biosynthesis of purines and thymidylates of nucleic acids.
Pharmacokinetics data	Folic acid is rapidly absorbed from the proximal part of the gastrointestinal tract following oral administration. It is mainly absorbed in the proximal portion of the small intestine. The naturally occurring folate polyglutamate is enzymatically hydrolyzed to monoglutamate forms in the gastrointestinal tract prior to absorption. The peak folate activity in blood after oral administration is within 30 to 60 minutes (McEvoy, 1990). Enterohepatic circulation of folate has been demonstrated.
Acute Toxicity	**Non-Clinical Studies:** The administration of Folic acid to adult (not pregnant) mice by intra-peritoneal injection showed large differences between various strains and a fairly low LD50 value (85 6 10 mg/kg) in some murine strains (Parchure et al., ’85). Hyperkinesis, ataxia, and convulsions suggested neural involvement and the most common cause of death was renal tubular necrosis in mature mice receiving the high doses. **Clinical Studies:** Folic acid has been described as generally not toxic for man (Gilman et al., ’80). However, the higher, so-called pharmacological doses (1 mg) can mask the neurological manifestation of pernicious anemia, may reduce the efficacy of anticonvulsant medication (Ero¨s et al., ’98), and may have some other hazards (Czeizel, ’95). In Hungary, suicide attempts by self-poisoning have been used as a human model for the study of mutagenic (Czeizel, ’94) and teratogenic (Czeizel et al., ’97) effects of large doses of chemicals. Databases include 4 pregnant women and 15 nonpregnant individuals (12 women and 3 men) who attempted suicide by drugs, including folic acid. The results of the follow-up study of the 4 pregnant women are summarized here. Between 1985–1993, a sensitive serum pregnancy test was performed in all admitted women aged between 15–50 years and pregnant women were followed up till the end of pregnancy. Of 22,969 admitted women, 645 had a positive pregnancy test (Czeizel et al., ’97). Of 559 women ingesting drugs, one used folic acid alone and three used folic acid plus other drugs for self-poisoning. No acute adverse effects of high doses (120– 150 mg) of folic acid during pregnancy or long-term consequences were detected at the birth of their newborn infants. The goal of the follow-up study was to obtain case histories of mothers and children and to make a general medical checkup, including specific nephrological, hematological, neurological, and EEG examinations in mothers. Of four mother-children pairs, three had the follow-up study, and no particular disease connected with previous self-poisoning was found. In conclusion, acute and long-term adverse effects of self-poisoning by ingesting folic acid during pregnancy could not be detected.
Repeated Dose Toxicity	**Non-Clinical Trials:**

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SUMMARY OF HAZARD IDENTIFICATION:	
(Chronic Toxicity)	**Study 1:** Folic acid is relatively non-toxic. Toxicity studies in mice showed that folic acid could cause convulsions, ataxia and weakness. Histopathological studies in some strains of mice showed that toxic doses may also cause acute renal tubular necrosis. A possible relationship between folic acid neurotoxicity and cholinergic receptors in the pyriform cortex and amygdala has been shown (McGeer et al, 1983). **Study 2:** Toxicity in different strains of mice showed that toxic doses of folic acid may lead to convulsions, ataxia and weakness (Parchure et al., 1985). Histopathological studies in some strains of mice showed acute renal tubular necrosis. **Study 3:** **Relevant in vitro data:** Cytomorphological effects of folic acid were studied using in-vitro establishment human oral epithelium. A concentration twice that used clinically (200 mcg/ml of folic acid) did not induce marked cytotoxic reaction in cultured cells. The most pronounced changes were cultures which showed degenerating cells showing oedema, increased translucency of the cytoplasm, flattened cells and atypical filaments (Jainkittivong et al., 1989). **Clinical Trials:** **Adults** There is little data available on folic acid toxicity in humans. A case of 2 patients who showed exacerbation of psychotic behaviour during treatment with folic acid has been reported (Prakash et al., 1982). The significance of this finding is uncertain since other authors have suggested that folic acid has antipsychotic properties. Adverse gastrointestinal and central nervous system effects have been reported rarely in patients receiving 15 mg of folic acid daily for **one month**. However, other studies have failed to confirm these findings (McEvoy, 1990).
Carcinogenicity	There are limited data to suggest that folic acid supplementation, in comparison to deficiency, may be associated with the promotion of tumors in animals that develop spontaneous tumors or are exposed to chemical carcinogens. However, this may be related to the role of folic acid in supporting cell replication.
In vivo/In vitro Genotoxicity Studies	Data from *in vitro* and *in vivo* studies indicate that folic acid is not genotoxic.
Reproductive/Developmental Toxicity	In a study of the synergistic effects of folic acid and the anti-malarial drug, pyrimethamine (an inhibitor of dihydrofolate reductase), groups of 10 pregnant female rats were supplemented with combinations of the anti-malarial drug, pyrimethamine, and/or folic or folinic acid, from days 7–17 of gestation, by gavage. Folic acid treatment (50 mg/kg bw/day) alone showed no significant maternal or embryo toxicity, as compared with vehicle-only treatment.
Highly Sensitizing Potential	No any sensitivity to skin recorded.

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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	**Adults** **Folate deficient megoblastic anaemia** ***Therapeutic dose*** 5 mg daily orally for 4 months; up to 15 mg daily may be required in malabsorption states.(UK) 250 mcg to 1.0 mg orally daily (USA) ***Prophylactic dose*** 200 to 500 mcg orally daily (UK) 400 mcg orally daily (USA) **Adverse effects:** Allergic reactions to folic acid have been rarely reported including erythema, rash, itching, general malaise and bronchospasm. Adverse gastrointestinal and central nervous system effects have been reported in patients receiving 15 mg of folic acid daily for one month.

NOAEL/LOAEL	A supplemental dose of 1 mg/day (equivalent to 0.014 mg/kg bw/day in a 50 kg adult) would not be expected to cause adverse effects.

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)	10	Short duration study in rodent (1 month).
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	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{0.014 \text{ (NOAEL)} \times 50}{5 \times 10 \times 10 \times 1 \times 5}$ = 0.00028 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Folate
- http://www.inchem.org/documents/pims/pharm/folicaci.htm#SectionTitle:7.2%20Toxicity
- https://cot.food.gov.uk/sites/default/files/vitmin2003.pdf
- https://www.ncbi.nlm.nih.gov/pubmed/10413330