PERMITTED DAILY EXPOSURE FOR DOXYLAMINE SUCCINATE

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 Doxylamine Succinate 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:

Doxylamine is a first-generation antihistamine used as a short-term sedative and hypnotic (sleep aid) or in combination formulations to provide night-time allergy and cold relief.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Doxylamine succinate appears as white or creamy white powder. pH (1% aqueous solution) between 4.9 and 5.1. NTP, 1992). Doxylamine succinate is an organic molecular entity.

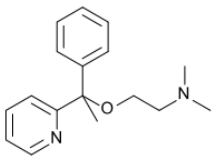
IUPAC name: butanedioic acid; N, N-dimethyl-2-(1-phenyl-1-pyridin-2-ylethoxy) ethanamine

Chemical Abstract Services (CAS) Registry Number: 469-21-6

Molecular Weight: 270.369 $g \cdot mol^{-1}$

Chemical Formula: $C_{17}H_{22}N_2O$

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

Doxylamine acts primarily as an antagonist or inverse agonist of the histamine H1 receptor. This action is responsible for its antihistamine and sedative properties. To a lesser extent, Doxylamine acts as an antagonist of the muscarinic acetylcholine receptors, an action responsible for its minor hypnotic, anticholinergic and (at high doses) deliriant effects.

Pharmacokinetic data

The bioavailability of Doxylamine is 24.7% for oral administration and 70.8% for intranasal administration. The Tmax of Doxylamine is 1.5 to 2.5 hours. Its elimination half-life is 10 to 12 hours. Doxylamine is metabolized in the liver primarily by the cytochrome P450 enzymes P450 enzymes CYP2D6, CYP1A2, and CYP2C9. The main metabolites are N-desmethyldoxylamine, N, N-didesmethyldoxylamine, and Doxylamine N-oxide. Doxylamine is eliminated 60% in the urine and 40% in feces.

Acute Toxicity

Species	End Point (mg/kg/day)	Route	Dose (mg/kg)	Effect	Reference
Rat	LDL_0	Oral	600	Behavioral: convulsions or effect on seizure threshold; behavioral: food intake (animal)	Journal of the American Pharmaceutical Association, Scientific Edition., 37(311), 1948
Rat	LD50	Subcutaneous	440	-	Journal of Laboratory and Clinical Medicine., 33(325), 1948
Mouse	LD50	Oral	470	behavioral: convulsions or effect on seizure threshold	Journal of Laboratory and Clinical Medicine., 33(325), 1948
Mouse	LD50	Subcutaneous	460	-	Journal of Laboratory and Clinical Medicine., 33(325), 1948
Mouse	LD50	intravenous	62	-	Journal of Laboratory and Clinical Medicine., 33(325), 1948
Rabbit	LD50	Oral	250	-	Journal of Laboratory and Clinical Medicine., 33(325), 1948
Rabbit	LD50	intravenous	49	-	Journal of Laboratory and Clinical Medicine., 33(325), 1948

Repeated Dose Toxicity (Chronic Toxicity)

Doxylamine succinate, a commonly used antihistamine, was administered as an admixture in the feed to groups of male and female Fischer 344 rats at dose levels of 0,500,1000, and 2000 parts per million (ppm) (based on free amine) for 65 weeks (9 per group) or two years (48 per group). There were no significant treatment-related differences in survival in either sex. Compared to controls, final body weights of rats in the 2000 ppm group were reduced 8.4% and 22.8% in males and females, respectively. Treatment-related, non-neoplastic lesions were found primarily in the liver and parotid salivary gland. Liver lesions consisted of fatty change and degeneration in both sexes; hyperplasia (resulting from degeneration due to leukemia) and atypical cells in males; and hypertrophy, chronic inflammation, and mixed cell foci in females. Both sexes exhibited a

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SUMMARY OF HAZARD IDENTIFICATION:	
	treatment-related increase in cytoplasmic alteration in the salivary glands. **Liver neoplasms were found only in the highest dose group of male rats.** The trend test was significant (p 4 0.05) for increased incidence of hepatocellular adenoma and carcinoma with increasing doses of Doxylamine, but the increased incidence of either lesion in the high dose group was not significant compared to that in controls. However, when animals with carcinoma or adenoma were combined, the trend test remained significant *6) S* 0.01), and the incidence of the highest dose group was significantly increased *6) 6* 0.05) over that in controls. No treatment-related increase in neoplasms was found in females, but Doxylamine produced a marked dose-related decrease in mammary fibroadenomas. Although not statistically significant, a very rare pineal gland tumor was found in 1 male and 1 female rat in the 2000 ppm group.
Carcinogenicity	Studies of Doxylamine's carcinogenicity in mice and rats have produced positive results for both liver and thyroid cancer, especially in the mouse. The carcinogenicity of the drug in humans is not well studied, and the IARC lists the drug as "not classifiable as to its carcinogenicity to humans". **1. Studies of Cancer in Humans** **1.1 Case report** In a series of 200 children included in a case–control study of primary intracranial neoplasm, the authors mention 'the surprising coincidence' of two girls with a posterior fossa pilocytic astrocytoma whose mothers had taken Bendectin® [which contains doxylamine, dicyclomine and pyridoxine] (Giuffrè *et al*., 1990). **1.2 Case–control studies** In a study of childhood cancer in England, 615 cases and 1230 controls were considered to be eligible for the study (Birch *et al*., 1985). The parents of 555 children (response rate, 90%) in whom an incident cancer (171 leukaemias, 74 lymphomas, 78 central nervous system tumours and 232 other cancers) had been diagnosed in the regional paediatric oncology clinics of three Health Service regions of England were interviewed (McKinney *et al*., 1985). For each case, two controls matched on age and sex were selected, one on the list of the same general practitioner as the case child and the other from paediatric hospital admissions, with response rates of 72% and 64%, respectively. Controls who refused to participate were replaced, to obtain a total of 1110 controls. Information on the drug use of the mother during pregnancy was obtained by interview and also, whenever possible, from the combined information from obstetric records (88%) and general practitioners' notes (91%). The odds ratio for all cancers associated with use of Debendox® during pregnancy as reported by the mother was 0.69 and that obtained from medical records was 0.99. Although the odds ratio was significantly increased in relation to medically recorded use for 1–2 months (odds ratio, 10; 95% confidence interval [CI], 1.8–57), there was no dose–response relationship, the odds of Debendox® reported by the mother were below 1 for any duration of use. For the group of leukaemias and lymphomas combined, the odds ratio was 1.0 with both exposure ascertainment methods, and those for other cancers were 0.47 with the mothers' recall and 0.95 with medical records. A case–control study was conducted on patients under 18 years in the member and affiliate institutions of the Children Cancers Study Group in Canada and the USA

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SUMMARY OF HAZARD IDENTIFICATION:	
	in whom acute non-lymphoblastic leukaemia had been diagnosed between 1980 and 1984 (Robison *et al*., 1989). For each case, one control was selected by random-digit dialing and matched on age, race and telephone area code. Of the 262 eligible patients, 204 (78%) were interviewed, as were 78% of the 260 eligible controls. The two parents were interviewed separately by telephone on a wide range of topics. The matched-pair odds ratio for maternal use of Bendectin® or other tablets for morning sickness during pregnancy was 1.8 (95% CI, 0.98–3.2), although the mothers of patients did not report morning sickness more frequently than mothers of controls (odds ratio, 0.80). The risk increased with increasing duration of use (p = 0.05; test for trend), and the odds ratio for use for more than 10 weeks compared with less than 1 week was 2.8 ($p < 0.05$). **2. Studies of Cancer in Experimental Animals** **2.1 Oral administration** ***Mouse*:** Groups of 48 male and 48 female B6C3F1 mice, 31–40 days of age, were fed diets containing doxylamine succinate (purity, 100%) at a concentration of 0, 190, 375 or 750 mg/kg (dose based on the free amine) for 104 weeks. Additionally, groups of 12 males and 12 females were fed the same concentrations for 65 weeks, at which time all surviving animals were killed. The survival rates in each group at the end of 104 weeks varied from 88 to 96% for males and from 85 to 98% for females. Increased incidences of hepatocellular adenoma were seen in both males (6/60 control, 12/60 low dose, 17/59 mid dose ($p < 0.01$; Fisher's exact test) and 31/60 high dose ($p < 0.001$)) and females (0/58, 3/60, 0/60 and 9/60 ($p < 0.01$), respectively). Thyroid follicular-cell adenomas were observed in both males (1/58, 0/57, 11/57 ($p < 0.01$) and 5/58) and females (0/56, 0/60, 2/57 and 8/59 ($p < 0.01$)). Dose-related increases in the incidence of follicular-cell hyperplasia were also observed in both male and female mice (Jackson & Sheldon, 1993). *Rat*: Groups of 48 male and 48 female Fischer 344 rats, 31–40 days of age, were fed diets containing doxylamine succinate (purity, 100%) at a concentration of 0, 500, 1000 or 2000 mg/kg (dose based on the free amine) for 104 weeks. Additional groups of nine males and nine females received the same concentrations for 65 weeks, at which time animals were killed. The survival rates in each group at 104 weeks varied from 40 to 58% in males and from 56 to 69% in females. When compared with controls, the final body weight of high-dose males was reduced by 8.4% and that of females by 22.8%, suggesting that the maximal tolerated dose had been exceeded for the females. The incidence of hepatocellular adenoma and carcinoma combined in males was: control, 0/57; low dose, 0/57, mid dose, 0/57 and high dose, 5/57 (p δ 0.05; Fisher's exact test). The five liver tumours in males at the high dose comprised two adenomas and three carcinomas. There was no increase in the incidence of neoplasms in female rats (Jackson & Blackwell, 1993). **3. Other Data Relevant to an Evaluation of Carcinogenicity and Its Mechanisms** **3.1 Absorption, distribution, metabolism and excretion** **3.1.1 *Humans***

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	The pharmacokinetics of doxylamine succinate was determined in 16 healthy male volunteers after administration of a single oral dose of 25 mg. The mean peak plasma concentration was 99 ng/mL, the peak time was 2.4 h after the dose, the elimination half-time was 10.1 h, and the apparent oral clearance was 217 mL/min (Friedman & Greenblatt, 1985). Clearance of a single oral dose of 25 mg of doxylamine succinate was slower (174 versus 240 mL/min) in older men (60–87 years) than in younger men (20–43 years), but no difference was seen in women (Friedman *et al.*, 1989). *N*-Desmethyldoxylamine, *N*,*N*-didesmethyldoxylamine and their respective *N*-acetyl conjugates were identified as urinary metabolites after oral administration of 50 mg of doxylamine succinate to a single volunteer (Ganes & Midha, 1987). Approximately 1% of an oral dose of 75–100 mg of doxylamine succinate was recovered in the urine of male volunteers as quaternary ammonium-linked glucuronides (Luo *et al.*,1991). **3.1.2 *Experimental systems*** Total urine and faecal recovery of radiolabel after oral administration of [14C]- doxylamine succinate at 13.3 or 133 mg/kg bw to male and female Fischer 344 rats was > 90%, regardless of sex and dose. The identified unconjugated urinary metabolites (representing 36–44% of the radiolabel) included doxylamine *N*-oxide, *N*-desmethyldoxylamine, *N*,*N*-didesmethyldoxylamine and ring-hydroxylated products of doxylamine and desmethyldoxylamine (Holder *et al.*, 1987). The identified conjugated metabolites (representing 44–55% of the radiolabel) included doxylamine *O*-glucuronide, *N*-desmethyldoxylamine *O*-glucuronide and *N*,*N*-didesmethyldoxylamine *O*-glucuronide (Holder *et al.*, 1990). *N*-Acetyl conjugates of *N*-desmethyl- and *N*,*N*-didesmethyldoxylamine were tentatively identified in rat urine (Ganes *et al.*, 1986). 14C-Doxylamine succinate given as a single oral dose of 13 mg/kg bw to four female rhesus monkeys (*Macaca mullata*) was metabolized by at least four pathways: a major pathway to mono- and didesmethyldoxylamine via successive *N*-demethylation; a major pathway to side-chain cleavage products via direct side-chain oxidation and/or deamination; a minor pathway to the *N*-oxide; and a minor pathway to unknown polar metabolites (Slikker *et al.*, 1986). In two male squirrel monkeys (*Saimiri sciureus*) given 20 mg of doxylamine succinate orally twice daily for 1 week, only the *N*-acetyl conjugate of *N*,*N*-didesmethyldoxylamine was detected in the urine (Ganes *et al.*, 1986). Repeated oral administration of 7 mg/kg bw per day of Bendectin® during days 22–50 of gestation to three cynomolgus monkeys (*Macaca fascicularis*), four rhesus monkeys (*Macaca mulatta*) and five baboons (*Papio cynocephalus*) did not alter the pharmacokinetics of doxylamine (Rowland *et al.*, 1989). Analysis of fetal plasma samples by high-performance liquid chromatography demonstrated the presence of doxylamine and metabolites after a single intravenous injection of 13.3 mg/kg bw doxylamine succinate to three rhesus monkeys in late-term pregnancy (Slikker *et al.*, 1987, 1989). **3.1.3 *Comparison of animals and humans*** Similar demethylated metabolites and their *N*-acetylated derivatives have been determined in the urine of humans, monkeys and rats after oral doses of Doxylamine succinate. In addition, rats metabolized the compound by *N*-oxidation, aromatic hydroxylation and ether cleavage.

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SUMMARY OF HAZARD IDENTIFICATION:

4. Summary of Data Reported and Evaluation

4.1 Exposure data

Doxylamine succinate is an ethanolamine-based antihistamine used in the management of insomnia and, in combination with antitussives and decongestants, in the relief of cough and cold symptoms. It was widely used until the early 1980s in combination with other drugs to control nausea associated with pregnancy and is still registered for this use in at least one country.

4.2 Human carcinogenicity data

Two studies addressed the association between use of an anti-emetic drug containing doxylamine succinate during pregnancy and cancer during childhood in the offspring. The study in England showed no association with childhood cancer in general or with lymphohaematopoietic neoplasms, and no evidence of a dose–response relationship. The study from Canada and the USA on children with acute non-lymphoblastic leukaemia found an increased risk of borderline significance for self-reported use of a drug containing doxylamine succinate or other tablets for morning sickness during pregnancy and a trend of borderline significance with duration of use.

4.3 Animal carcinogenicity data

Doxylamine succinate was tested by oral administration in one study each in mice and rats. In mice, it increased the incidences of hepatocellular and thyroid follicular cell adenomas in males and females, although the thyroid response was not dose related in males. In rats, doxylamine succinate marginally increased the incidence of hepatocellular adenomas and carcinomas combined only in males.

4.4 Other relevant data

Doxylamine is converted to demethylated metabolites and their *N*-acetylated derivatives in humans, monkeys and rats. In rats, doxylamine is also metabolized via *N*-oxidation, aromatic hydroxylation and ether cleavage pathways. Doxylamine is a potent, phenobarbital-type inducer of cytochrome P450 enzymes in mice. No evidence of enzyme induction has been found in humans. Doxylamine succinate causes liver damage in mice; this effect may be related to its hepatocarcinogenicity. Doxylamine induces thyroxine glucuronidation in mice, with concomitant decreases in serum thyroxine and increases in serum thyroid stimulating hormone concentrations. This is the probable mechanism of action for the induction of thyroid tumours in animals. It has not been shown to be teratogenic in humans or experimental animals. No data were available on the genetic and related effects of doxylamine succinate in humans. It did not induce micronucleus formation in mice when given transplacentally or in hamsters. It did, however, induce chromosomal aberrations in mice treated transplacentally. Doxylamine succinate induced DNA damage in primary rat hepatocytes and inhibited intercellular communication, but it did not induce sister chromatid exchange in mammalian cells in culture or induce mutations in bacteria. Doxylamine succinate is considered not to be genotoxic.

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SUMMARY OF HAZARD IDENTIFICATION:	
	4.5 Evaluation There is *inadequate evidence* in humans for the carcinogenicity of Doxylamine succinate. There is *limited evidence* in experimental animals for the carcinogenicity of Doxylamine Succinate
In vivo/In vitro Genotoxicity Studies	**1.0 Effects on enzyme induction or inhibition and gene expression** **1.1 *Humans*** A randomized, placebo-controlled study was conducted in 48 healthy male volunteers to compare the effects of doxylamine succinate on the pharmacokinetics of antipyrine metabolites and the urinary excretion of 6®-hydroxycortisol. Normal renal function, an age between 18 and 40 years and a normal diet were the criteria for inclusion. Groups of 16 men received 12.5 mg of doxylamine succinate, placebo or 30 mg of phenobarbital orally every 6 h for 17 days. No statistically significant differences indicative of enzyme induction were observed (Thompson *et al.*, 1996). **1.2 *Experimental systems*** Doxylamine succinate caused a dose-dependent increase (up to 2.6-fold) in liver microsomal cytochrome P450 (CYP) enzyme activity in male and female B6C3F1 mice (aged 45–52 days) after 7 or 15 days on a diet containing the compound at a concentration of 0, 40, 375, 750 or 1500 mg/kg (expressed as free amine). Doxylamine succinate caused marked induction of CYP2B enzymes, as demonstrated by a large increase in the *O*-dealkylation of 7-pentoxyresorufin (up to 38-fold) and in the 16®-hydroxylation of testosterone (up to 6.9-fold). In addition, treatment resulted in a modest induction of CYP3A and CYP2A and a 50% increase in thyroxine glucuronosyltransferase activity. No induction of CYP1A, CYP2E or CYP4A was found. These results suggest that doxylamine is a phenobarbital-type inducer of liver microsomal CYP enzymes in B6C3F1 mice (Bookstaff *et al.*, 1996). Doxylamine inhibited aminopyrine *N*-demethylation by rat liver microsomes, with a median inhibitory concentration of 73 ⌈mol/L (Brandes *et al.*, 1994). **1.3 Genetic and related effects** **1.3.1 *Humans*** No data were available to the Working Group. **1.3.2 *Experimental systems*** Doxylamine succinate did not induce mutations in *Salmonella typhimurium*. It weakly induced unscheduled DNA synthesis in primary rat hepatocytes *in vitro* in the absence of an exogenous metabolic system. It inhibited gap-junctional intercellular communication, measured as metabolic cooperation, in Chinese hamster V79 cells. It did not induce sister chromatid exchange in human lymphocytes *in vitro* or micronucleus formation in hamster bone-marrow cells. In a transplacental system, a small dose-dependent induction of chromosomal aberrations, but no sister chromatid exchange or micronucleus formation, was found in the embryos of mice treated on day 11 of gestation1. **1.4 Mechanistic considerations** Doxylamine succinate is considered not to be genotoxic. It is a potent phenobarbital-type inducer of hepatic CYP2B enzymes in B6C3F1

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	mice. In contrast, male volunteers given doxylamine succinate repeatedly showed no evidence of CYP enzyme induction. Doxylamine succinate, like phenobarbital, also induced thyroxine glucuronosyltransferase activity in mice, accompanied by decreased serum concentrations of thyroxine and increased serum concentrations of thyroidstimulating hormone. The lack of increased activity of liver enzymes associated with thyroxine metabolism and the increased thyroid-stimulating hormone concentrations in humans exposed to doxylamine succinate for longer than therapeutically recommended indicate that the compound would not be expected to produce thyroid tumours in humans at therapeutic doses. Doxylamine succinate damaged the liver in mice, and this effect may be related to its hepatocarcinogenicity.
Reproductive/Developmental Toxicity	**1.0 Reproductive and developmental effects** **1.1 *Humans*** Doxylamine succinate has rarely been used on its own, but it has been used extensively in pregnancy in combination with pyridoxine as BendectinP for the treatment of nausea and vomiting. Reviews of the extensive literature on BendectinP use, covering many thousands of women exposed during pregnancy, have concluded that the drug is not a human teratogen (Shiono & Klebanoff, 1989; McKeigue *et al*., 1994; Brent, 1995). **1.2 *Experimental systems*** No satisfactory studies on Doxylamine alone were available to the Working Group. Studies of Bendectin P in rats and non-human primates were available. Groups of 37–41 pregnant CD Sprague–Dawley rats were given 0, 200, 500 or 800 mg/kg bw Bendectin P by gavage daily on days 6–15 of gestation (day 0 being considered that on which a positive vaginal smear was found) and were killed on day 20 for examination of their fetuses by standard teratological techniques. The highest dose was very toxic to the dams, killing 17%, and a marked reduction in body-weight gain was observed at the two higher doses. The lowest dose was minimally toxic. A small increase in the frequency of resorptions was seen at the highest dose and reduced fetal weight and reduced skeletal ossification at 500 and 800 mg/kg bw per day. There was no increase in the number of fetuses with malformations, but the number of litters with malformed fetuses was increased at the highest dose, due mainly to an increase in the number of fetuses with short 13th ribs. No increase in the incidence of external or visceral malformations was observed in any group (Tyl *et al*., 1988). Groups of 21–24 pregnant cynomolgus monkeys (*Macaca fascicularis*) were given Bendectin P at an approximate dose of 0, 1.3, 3.3 or 13.3 mg/kg bw (as 2/5, 1 and 4 tablets/day per animal, corresponding to two, five and 20 times the human dose) by nasogastric intubation daily on days 22–50 of gestation. The fetuses were removed surgically just prior to term for examination. **No maternal toxicity and no embryofoetal toxicity or teratogenicity was observed** (Hendrickx *et al*., 1985).
Highly Sensitizing Potential	A very serious allergic reaction to this drug is rare.

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IDENTIFICATION OF CRITICAL EFFECTS:	
Sensitive Indicator of an adverse effect seen in non-clinical toxicity data	Two-year carcinogenicity studies in rats and mice have been conducted with Doxylamine Succinate. Doxylamine succinate is not likely to have human carcinogenic potential
Clinical therapeutic and adverse effects	**Clinical therapeutic dose:** 25 mg orally once a day 30 minutes before bedtime. Duration of Therapy: No more than 2 weeks consecutively. **Adverse effects:** Drowsiness, dizziness, headache, constipation, stomach upset, blurred vision, decreased coordination, or dry mouth/nose/throat may occur. If any of these effects persist or worsen, contact your doctor or pharmacist promptly.

NOAEL/LOAEL	NOAEL value for Doxylamine Succinate is 325 mg/kg.

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	Long duration study in rodent (2 Years).
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	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{325 (NOAEL) x 50}}{\text{5 x 10 x 10 x 1 x 5}}$ = 6.5 mg/day

5. REFERENCES:

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