PERMITTED DAILY EXPOSURE FOR QUETIAPINE FUMARATE

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 Quetiapine Fumarate 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:

Quetiapine is an atypical antipsychotic medication used for the treatment of schizophrenia, bipolar disorder and major depressive disorder. Despite being widely used as a sleep aid due its sedating effect, the benefits of such use do not appear to generally outweigh the side effects. It is taken by mouth.

Common side effects include sleepiness, constipation, weight gain, and dry mouth. Other side effects include low blood pressure with standing, seizures, a prolonged erection, high blood sugar, tardive dyskinesia, and neuroleptic malignant syndrome. In older people with dementia, its use increases the risk of death. Use in the third trimester of pregnancy may result in a movement disorder in the baby for some time after birth. Quetiapine is believed to work by blocking a number of receptors including serotonin and dopamine.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Quetiapine fumarate is a white to off-white powder. It is only very slightly soluble in ether, slightly soluble in water, and soluble in 0.1 N HCl

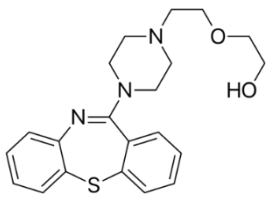
IUPAC name: 2-(2-(4-Dibenzo[b,f][1,4]thiazepine-11-yl-1-piperazinyl)ethoxy)ethanol

Chemical Abstract Services (CAS) Registry Number: 111974-69-7

Molecular Weight: 383.5099 g/mol g·mol−1

Chemical Formula: $C_{21}H_{25}N_3O_2S$

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	SEROQUEL XR (quetiapine fumarate extended-release), a dibenzothiazepine derivative, is a psychotropic agent. Quetiapine and the active plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. It is the direct and indirect effects of quetiapine and norquetiapine that contribute to the pharmacological activity of SEROQUEL XR. Quetiapine: Quetiapine exhibits affinity for brain serotonin 5HT2 and 5HT1A receptors (in vitro, Ki = 288 and 557 nM, respectively), and dopamine D1 and D2 receptors (in vitro, Ki = 558 and 531 nM, respectively). It is this combination of receptor antagonism with a higher selectivity for 5HT2 relative to D2 receptors, which is believed to contribute to the clinical psychotropic properties and low extrapyramidal symptoms (EPS) liability of Quetiapine compared to typical antipsychotics. Quetiapine also has high affinity for histamine H1 receptors (in vitro, Ki = 10 nM) and adrenergic α1 receptors (in vitro, Ki = 13 nM), with a lower affinity for adrenergic α2 receptors (in vitro, Ki = 782 nM), but no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors and at the norepinephrine reuptake transporter (NET).
Pharmacokinetics data	The pharmacokinetics of quetiapine and norquetiapine are linear within the clinical dose range. The kinetics of quetiapine are similar in men and women, and smokers and nonsmokers. Absorption: Quetiapine is well absorbed following oral administration. quetiapine achieves peak plasma concentrations at approximately 6 hours after administration (Tmax). quetiapine R displays dose-proportional pharmacokinetics for doses of up to 800 mg administered once daily. The maximum plasma concentration (Cmax) and the area under the plasma concentration-time curve (AUC) for quetiapine administered once daily are comparable to those achieved for the same total daily dose of Quetiapine, immediate-release formulation administered twice daily. The mean plasma concentrations for each dose of Quetiapine versus 300 mg of Quetiapine L over a 24-hour dosing interval under fasting conditions are shown in Figure 1. Steady-state peak molar concentrations of the active metabolite nor quetiapine are 35% of that observed for Quetiapine. In a study (n=10) examining the effects of food on the bioavailability of Quetiapine, a high-fat meal was found to produce statistically significant increases in the Quetiapine Cmax and AUC of 44% to 52% and 20% to 22%, respectively, for the 50-mg and 300-mg tablets. In comparison, a light meal had no significant effect on the Cmax or AUC of quetiapine. This increase in exposure is not clinically significant, and therefore Quetiapine can be taken with or without food. Distribution: Quetiapine has a mean apparent volume of distribution of 10±4 L/kg, and is approximately 83% bound to plasma proteins. Elimination and Metabolism: The elimination half-life of quetiapine is approximately 6-7 hours upon multiple dosing within the proposed clinical dosage range. Quetiapine is extensively metabolized by the liver, with the parent compound accounting for less than 5% of the dose in the urine and faeces, one week following the administration of radiolabelled quetiapine. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed in these patients. The elimination half-life of norquetiapine is approximately 12 hours. The average molar dose fraction of free

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	quetiapine and the active human plasma metabolite norquetiapine is <5% excreted in the urine. Major routes of metabolism of quetiapine involve oxidation of the alkyl side chain, hydroxylation of the dibenzothiazepine ring, sulphoxidation, and phase 2 conjugation. The principal human plasma metabolites are the sulfoxide, and the parent acid metabolite, neither of which are pharmacologically active. In vitro investigations established that CYP 3A4 is the primary enzyme responsible for cytochrome P450-mediated metabolism of quetiapine. Norquetiapine is primarily formed and eliminated via CYP3A4. Quetiapine and several of its metabolites (including norquetiapine) were found to be weak inhibitors of human cytochrome P450 1A2, 2C9, 2C19, 2D6 and 3A4 activities in vitro. In vitro CYP inhibition is observed only at concentrations approximately 5 to 50-fold higher than those observed at a dose range of 300 to 800 mg/day in humans.
Acute Toxicity	Single dose studies were conducted in mice and rats by the oral and Intraperitoneal routes and in dogs by the oral route. The principal clinical signs in mice, rats and dogs of decreased motor activity, ptosis, loss of righting reflex, tremors, ataxia, prostration and convulsions were consistent with the pharmacological activity of the drug. The lowest oral doses causing lethality were 250 mg/kg in mouse and 500 mg/kg in rat; no deaths occurred at the highest oral dose tested (750 mg/kg) in dogs. The highest parenteral non-lethal doses were 100 mg/kg in both mouse and rat.
Repeated Dose Toxicity (Chronic Toxicity)	In multiple dose studies in rats, dogs and monkeys (refer to Table 10 for individual study details), anticipated central nervous system effects of an antipsychotic drug were observed with Quetiapine (e.g., sedation at lower doses and tremor, convulsions or prostration at higher exposures). Hyperprolactinaemia, induced through the dopamine D2 receptor antagonist activity of Quetiapine or its metabolites, varied between species, but was most marked in the rat. A range of effects consequent to this were seen in the 12-month study including mammary hyperplasia, increased pituitary weight, decreased uterine weight and enhanced growth of females. Reversible morphological and functional effects on the liver, consistent with hepatic enzyme induction, were seen in mouse, rat and monkey. Thyroid follicular cell hypertrophy and concomitant changes in plasma thyroid hormone levels occurred in rat and monkey. Pigmentation of a number of tissues, particularly the thyroid, was no associated with any morphological or functional effects. Transient increases in heart rate, unaccompanied by an effect on blood pressure, occurred in dogs. Posterior triangular cataracts seen after 6 months in dogs at 100 mg/kg/day were consistent with inhibition of cholesterol biosynthesis in the lens. No cataracts were observed in cynomolugus monkeys dosed up to 225 mg/kg/day, or in rodents. Monitoring in clinical studies did not reveal drug-related corneal opacities in man. No evidence of neutrophil reduction or agranulocytosis was seen in any of the toxicity studies.

Species/Strain	Route	Study Duration	Number/ Group/Sex	Dose (mg/kg/day)	Salient Observations
Rat Hla:(SD)/BR	Oral gavage	4 weeks dosing and 4 weeks withdrawal	14	0 25 50 150	Ptosis at all doses. Body weight gain decreased at 150 mg/kg/day. Liver weight was increased and uterus, spleen and pituitary weights were decreased in all dose groups. Epididymis and

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SUMMARY OF HAZARD IDENTIFICATION:

					heart weight was decreased at 150 mg/kg/day. Deciduoma-metrial gland changes at 50 mg/kg/day.
Rat Hla:(SD)BR	Oral gavage	6 months dosing and 4 weeks withdrawal	29	0 25 50 150	Ptosis at all doses. Reduced body weight gain at 50 mg/kg/day and 150 mg/kg/day. Plasma TSH increased and T3 reduced at 150 mg/kg/day. Pigment deposition and hypertrophy of thyroid follicular cells at 50 mg/kg/day and 150 mg/kg/day. In all dose groups, mammary gland hypertrophy/hyperplasia, atrophy and/or mucification of cervical/vaginal mucosa. Liver weight increased at all doses with hepatocellular vacuolation at 150 mg/kg/day. No adverse-effect dose level was 25 mg/kg.
Rat Crl:(WI)BR	Oral gavage	12 months of dosing then 5 weeks withdrawal	20	0 10 25 75 250	Hypoactivity and hyperprolactinaemia and sequelae (all doses). 27% decrement in body weight gain (250 mg/kg/day). Liver enlargement (75 and 250 mg/kg/day), hepatocyte fat vacuolation (dose related) and centrilobular hypertrophy with increased expression of CYP2B1/2 and CYP3A at 250 mg/kg/day. Increased TSH and T4 and thyroid follicular cell hypertrophy (250 mg/kg/day). Thyroid pigmentation (all doses). Adrenal cortical vacuolation (75 mg/kg/day and above). Increased pancreatic glucagon secreting cells (75 mg/kg/day and above). Increased alveolar macrophages (75 mg/kg/day and above).
Dog Beagle	Oral tablets	4 weeks	3	0 25 50 100	Decreased motor activity, ataxia, somnolence, miosis, increased heart rate and hypothermia were observed for animals in all compound-treated groups. In general the incidence was dose-related and decreased with time. All effects reversed on withdrawal.
Dog Beagle	Oral tablets	6 months dosing and 8 weeks withdrawal	3 or 4	0 25 50 100	Up to 8 weeks transient sedation and increased heart rate. Dose-related decreases in body weight gain. At 100 mg/kg/day 13-26% decrease in plasma cholesterol and prominent posterior Y sutures, swelling of lens fiber tips and 3/8 females with cataracts; 1 epileptiform seizure, 4/8 muscular twitching. 50 mg/kg/day was the no adverse-effect dose level.
Dog Beagle	Oral Tablets	12 months dosing and 8 weeks withdrawal	4z	0 10 25 50 100	Sedation, miosis, abnormal gait and muscular tremors occurred at doses of 25 mg/kg/day and above, mainly in the first 10 weeks. Cataracts in animals given 100 mg/kg/day. Histopathological lenticular changes in 5/8 dogs given 50 mg/kg/day. At 100 mg/kg/day 13/14 dogs showed histological

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					lenticular alterations, consistent with the ophthalmological observations. Fine brown granules in the epithelial cells of the lacrimal glands at all doses.
Cynomolgus monkey	oral gavage	13 months	4	0, rising dose for 4 weeks with one week at each dose level then 43.5 for 52 weeks	Signs of sedation from week 2, duration and severity increased with dose. 43.5 mg/kg/day was considered to be the maximum tolerated dose. Abnormal staring behaviour in 2 animals. Plasma prolactin reduced. No compoundrelated histopathological changes. No effect on plasma cholesterol. No ophthalmological changes were observed.
Cynomolgus monkey	oral gavage	14 weeks	3	6, 12, 24, 36, 48, 60, 84, 108, 132, 150, 180, 225, 285 and 350. Rising doses administered 3 doses/day. One week at each dose level	Sedation from 24 mg/kg/day, after which the duration and severity increased with dose, until at 225 mg/kg/day prostration occurred. Doses at 285 and 350 mg/kg/day caused reduction in body weight and food consumption, ataxia, increased incidence of prostration and one animal died at 350/mg/kg/day. Reductions in red blood cell parameters, plasma bilirubin, cholesterol (20-40% at 285 mg/kg) and ALP activity. No compound-related histopathological changes.
Cynomolgus monkey	oral gavage	56 weeks dosing 4 weeks withdrawal	4	0, rising dose for 4 weeks then 25, 100 and 225 mg/kg/day administered as 3 doses/day	Dose-related incidence and severity of behavioural changes. No abnormal signs on drug withdrawal. 40-60% reduction in plasma cholesterol at 225 mg/kg/day with delta-8-cholestanol present at 15% of cholesterol level at 100 and 225 mg/kg/day. No lens opacities. Minor lens changes at all doses with no lens pathology. Transient elevation of prolactin and mild mammary gland hyperplasia (in males) and T3 levels reduced and mild thyroid follicular cell hypertrophy at 100 and 225 mg/kg/day. Red cell indices reduced and liver enlargement with hepatocyte hypertrophy and fat deposition at 225 mg/kg/day

Carcinogenicity

Duration	Species	Route	Dose (mg/kg/day)	End Point	Effect
2 year	Rat	Oral	250	LOAEL	Thyroid, Tumors, Mammary gland
2 year	Mouse	Oral	250	LOAEL	Thyroid, Tumors

Results from the 2-year carcinogenicity studies performed in mice and rats (and mouse sighting studies) are summarized in Table 11. In the rat study (doses 0, 20, 75 and 250 mg/kg/day) the incidence of mammary adenocarcinomas was increased at all doses in female rats, consequential to prolonged hyperprolactinaemia. In male rat (250 mg/kg/day) and mouse (250 and 750 mg/kg/day), there was an increased

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SUMMARY OF HAZARD IDENTIFICATION:

incidence of thyroid follicular cell benign adenomas, consistent with known rodent-specific mechanisms resulting from enhanced hepatic thyroxine clearance.

Species/Strain	Route	Study Duration	Number/ Group/Sex	Dose (mg/kg/day)	Salient Observations
Mouse C57BL/ 10jfCD/1/Alpk	Oral in diet	90 days	25	0, 50, 100, 200, 300, 400	Reductions in body weight at 100 mg/kg or greater. Seminiferous tubular atrophy severity increased at 100 mg/kg and above. Centrilobular hepatocyte enlargement at 200 mg/kg and above. At 50 mg/kg the only effect was an increase in liver weight in females.
Mouse C57BL/ 10jfCD/1/Alpk	Oral in diet	90 days	15	0, 300-800, 400- 1,100 (Rising dose maximal at 6 weeks)	Reduced body weight, liver weight increase and hepatocyte hypertrophy in both dose groups. Ovary weight decreased in high dose females and testicular weight decreased in low and high dose males. Low and high dose females had dose related decreases in number of corpora lutea. The parotid salivary gland had dose-related increased basophilia. Males had dose-related seminiferous tubular atrophy. Urinary bladder hyaline droplets and pigmentation in the epithelium in both groups.
Mouse C57BL/ 10jfCD/1/Alpk	Oral in diet	2 Years	100, 50, 50, 50, 50	0, 20, 75, 250, 750 (Rising dose maximal at 6 weeks)	Thyroid follicular cell hypertrophy and pigmentation. Increased incidence of thyroid follicular cell benign adenomas (incidence of 0%, 0%, 0%, 8% and 58% in males only at 0, 20, 75, 250 and 750 mg/kg/day, respectively). No other increases in tumour incidence. Other non-neoplastic changes similar to sighting studies.
Rat/ Crl:(WI)BR	Oral by gavage	2 Years	100 50 50 50 50	0 20 75 250	Increased incidence of mammary adenocarcinomas in all groups of females (incidence of 10%, 26%, 22% and 32% in females given 0, 20, 75 and 250 mg/kg/day respectively). Increased incidence of follicular adenoma of the thyroid gland in males, but not females, given 250 mg/kg/day (incidence of 6%, 6%, 0% and 32% in males given 0, 20, 75 and 250 mg/kg/day respectively). Significant reductions in subcutaneous fibromas, thyroid parafollicular cell adenomas, uterine stromal polyps and carcinoma of the oral cavity.

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SUMMARY OF HAZARD IDENTIFICATION:

In vivo/In vitro Genotoxicity Studies

Study Type	Cell Type/Organism	Result
In Vitro Bacterial Mutagenicity (Ames)	*Salmonella*	Positive
In Vitro Chromosome Aberration	Human Lymphocytes	Negative
In Vivo Micronucleus	Rat	Negative

Genetic toxicity studies with Quetiapine show that it is not a mutagen or a clastogen. There was no evidence of mutagenic potential in reverse (Salmonella typhimurium and E. coli) or forward point mutation (CHO-HGPRT) assays or in two assays for chromosomal aberrations (human peripheral blood lymphocyte clastogenesis assay and the rat bone marrow erythrocyte micronucleus assay).

Reproductive/Developmental Toxicity

Duration	Species	Route	Dose (mg/kg/day)	End Point	Effect
Embryo/Fetal Development	Rat	Oral	25	NOAEL	Not teratogenic, Embryo toxicity, Fetotoxicity
Embryo/Fetal Development	Rabbit	Oral	25	NOAEL	Not Teratogenic, Embryo toxicity, Fetotoxicity
Peri/Postnatal Development	Rat	Oral	20	NOAEL	No effects at maximum dose
Reproductive & Fertility	Rat	Oral	25	NOAEL	Negative

Species/Strain	Route	Study Duration	Number/ Group/Sex	Dose (mg/kg/day)	Salient Observations
Rat Alpk:APfSD Segment I Male fertility	Oral	males dosed for a total of 14 weeks	Fo generation: 1st pairing: 100 M, 200 F, 25 M, 50 F/Gp 2nd pairing: 25 M, 50 F/Gp (Groups I & IV only)	0, 25, 50, 150 males only dosed, to the end of the first pairing period	First pairing: Reduced weight gain and marked clinical signs at all quetiapine dose levels. Reduced fertility in males dosed 150 mg/kg/day (longer precoital with second female). Second pairing: Effects on reduced fertility reversed, no difference between control and quetiapine dosed animals.
Rat Alpk:APfSD Segment I Female fertility	Oral	9 months Fogeneration: dosed to d14 prior to pairing up to d24 pp in animals assigned to litter	Fo generation: 264 M/132 F 66 F/Gp 33 M/Gp - not dosed F1 generation: 239 F/120 M 50 F/Gp (49 Gp I) 25 M/Gp	0, 1, 10, 50 50 mg/kg/day dose reduced to 1 mg/kg/day from d17 gestation to d6 pp to avoid litter loss F1 generation not dosed	Inhibition of oestrus cyclicity during dosing at 50 mg/kg/day, females became pseudopregnant or with protracted periods of dioestrus, increased precoital interval and reduced pregnancy rate. Slight reduction in body weight gain during pregnancy and lactation at 50 mg/kg/day. No effects on fertility or reproduction in the F1 generation.
Rat Alpk:APfSD Segment II Teratology	Oral	21 days females dosed d6 to d15 gestation	Fo generation: 22 F 22 F 22 F 22 F		Reduced weight gain and adverse clinical signs at 50 and 200 mg/kg/day. No effects on fetal survival. Fetal weight reduced at 200

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					mg/kg/day. No major fetal abnormalities. Specific skeletal anomalies present associated with reduced fetal weight at 200 mg/kg/day.
Rat Crj: Wistar Segment II Teratology	Oral	21 days females dosed from d6 to d15 gestation	Fo generation: 13 F/group	0, 25, 50, 200	Adverse clinical signs at all dose levels. No effect on reproductive function of the dams or development of fetuses, behaviour or reproductive function of the offspring at any dose level.
Rabbit Dutch Belted Segment II Teratology	Oral	28 days females dosed d6 to d18 gestation	Fo generation: 20 F 20 F 20 F 20 F	0 25 50 100	Reduced weight gain and adverse clinical signs at all doses. No effects on fetal survival. Fetal weight reduced at 100 mg/kg/day. No major fetal abnormalities. Specific skeletal anomalies present associated with reduced fetal weight at 100 mg/kg/day.
Rat/ Alpk:APfSD Segment III Peri- & Postnatal	Oral	44 days dosed d16 to d21 pp	Fo generation: 20 F 20 F 20 F 20 F	0 1 10 20	Reduced weight gain during first 2 weeks of lactation 20 mg/kg/day. No effects on survival or development of offspring.

Results from the individual reproduction and teratology studies, performed with Quetiapine in rats and rabbits, are summarized in Table. Effects related to elevated prolactin levels (marginal reduction in male fertility and pseudopregnancy, protracted periods of diestrus, increased precoital interval and reduced pregnancy rate) were seen in rats, although these are not directly relevant to humans because of species differences in hormonal control of reproduction. Quetiapine had no teratogenic effects.

Highly Sensitizing Potential	A very serious allergic reaction to this drug is rare. However, get medical help right away if you notice any symptoms of a serious allergic reaction, including: rash, itching/swelling (especially of the face/tongue/throat), severe dizziness, trouble breathing.

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:** **Usual Adult Dose for Schizophrenia** **Immediate-Release (IR) Tablets**: Initial dose: 25 mg orally 2 times a day Maintenance dose: 150 to 750 mg orally per day in divided doses Maximum dose: 750 mg/day

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	Extended-Release (XR) Tablets: Initial Dose: 300 mg orally once a day Maintenance dose: 400 to 800 mg orally once a day Maximum dose: 800 mg/day **Maintenance Mono therapy**: Maintenance dose: 400 to 800 mg/kg orally once a day Maximum dose: 800 mg/day **Usual Adult Dose for Bipolar Disorder** **IR Tablets**: Initial Dose: 50 mg orally 2 times a day Maintenance dose: 400 to 800 mg per day in divided doses Maximum dose: 800 mg/day **Usual Adult Dose for Depression** **XR Tablets**: Initial Dose: 50 mg orally once a day Maintenance dose: 150 mg to 300 mg orally once a day Maximum dose: 300 mg/day **Adverse Effects:** Adverse effects associated with therapeutic use include dizziness, sleepiness (somnolence) dry mouth, constipation, difficult digestion (dyspepsia), low blood pressure on standing (orthostatic hypotension), increased heart rate (tachycardia). May cause harm to breastfed babies.

NOAEL/LOAEL	NOAEL of 30 mg/kg/day for rat and body surface equivalent criteria.

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	1 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)	5	NOAEL value is selected.
PK Correction	For PDE calculation no pharmacokinetic correction was carried out	

CALCULATION	
PDE Calculation	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{30 (NOAEL) x 50}}{\text{5 x 10 x 1 x 1 x 5}}$ = 6 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Quetiapine
- https://www.pfizer.com/system/files/products/material_safety_data/PZ01682.pdf
- https://patents.google.com/patent/WO2006049734A2/en
- https://www.drugs.com/dosage/quetiapine.html