PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

PERMITTED DAILY EXPOSURE FOR RISPERIDONE

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 Risperidone 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:

Risperidone is an atypical antipsychotic. It is used to treat schizophrenia, bipolar disorder, and irritability associated with autism. It is taken either by mouth or by injection into a muscle. The injectable version is long-acting and lasts for about two weeks.

Common side effects include movement problems, sleepiness, dizziness, trouble seeing, constipation, and increased weight. Serious side effects may include the potentially permanent movement disorder tardive dyskinesia, as well as neuroleptic malignant syndrome, an increased risk of suicide, and high blood sugar levels. In older people with psychosis as a result of dementia, it may increase the risk of dying. It is unknown if it is safe for use in pregnancy. Its mechanism of action is not entirely clear, but is believed to be related to its action as a dopamine antagonist and serotonin antagonist.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Risperidone is a white or almost white powder. It is practically insoluble in water (pH=8.7), freely soluble in dichloromethane, and soluble in methanol and 0.1N HCl.

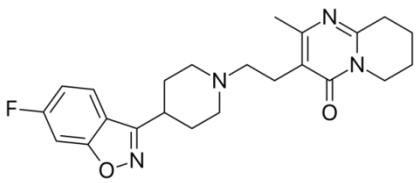
IUPAC name: 3-[2-[4-(6-fluoro-1,2-benzoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-6,7,8,9-tetrahydropyrido[1,2-a]pyrimidin-4-one

Chemical Abstract Services (CAS) Registry Number: 106266-06-2

Molecular Weight: 410.485 g/mol g·mol−1

Chemical Formula: $C_{23}H^{27}FN_4O_2$

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	Risperidone, a benzisoxazole derivative, is a novel antipsychotic drug which binds with high affinity to serotonin type 2 (5-HT2), dopamine type 2 (D2), and α1-adrenergic receptors. Risperidone binds with a lower affinity to the α2-adrenergic and histamine H1 receptors. Risperidone does not bind to dopamine D1 receptors and has no affinity (when tested at concentrations > 10-5 M) for muscarinic cholinergic receptors. Due to the lack of muscarinic receptor binding, Risperidone is not expected to produce anticholinergic adverse effects. Receptor occupancy was also demonstrated in vivo in humans. Using positron emission tomography, Risperidone was shown to block both 5-HT2A and dopamine D2 receptors in three healthy volunteers. Although Risperidone is a potent D2 antagonist, which is considered to improve the positive symptoms of schizophrenia, it causes less depression of motor activity and induction of catalepsy in animal models than classical antipsychotics. Risperidone has also been found to be one of the most potent known antagonists of 5-HT2A (cloned human receptor); 5- HT2A antagonism has been shown to reverse deficits in several in vivo animal models predictive of novel antipsychotic activity (PCP-induced social deficit, microdialysis assessment of dopamine output in prefrontal cortex, glutamate antagonist-induced hyperlocomotion). Balanced central serotonin and dopamine antagonism may reduce extrapyramidal side effect liability.
Pharmacokinetics data	**Absorption:** Risperidone was well absorbed after oral administration, had high bioavailability, and showed dose-proportionality in the therapeutic dose range, although inter-individual plasma concentrations varied considerably. Mean peak plasma concentrations of Risperidone and 9- hydroxyrisperidone were reached at about 1 hour and 3 hours, respectively, after drug administration. Food did not affect the extent of absorption; thus, Risperidone can be given with or without meals. **Distribution:** Risperidone is rapidly distributed. The volume of distribution is 1-2 L/kg. Steadystate concentrations of Risperidone and 9-hydroxyrisperidone were reached within 1-2 days and 5- 6 days, respectively. In plasma, Risperidone is bound to albumin and alpha1-acid glycoprotein (AGP). The plasma protein binding of Risperidone is approximately 88%, that of the metabolite 77%. **Metabolism:** Risperidone is extensively metabolized in the liver by CYP 2D6 to a major active metabolite, 9-hydroxyrisperidone, which appears approximately equi-effective with Risperidone with respect to receptor-binding activity. (A second minor pathway is N-dealkylation). Consequently, the clinical effect of the drug likely results from the combined concentrations of Risperidone plus 9-hydroxyrisperidone. The hydroxylation of Risperidone is dependent upon debrisoquine 4-hydroxylase, i.e. the metabolism of Risperidone is sensitive to the debrisoquine hydroxylation type genetic polymorphism. Consequently, the concentrations of parent drug and active metabolite differ substantially in extensive and poor metabolizers. However, the concentration of Risperidone and 9-hydroxyrisperidone combined, did not differ substantially between extensive and poor metabolizers, and elimination half-lives were similar in all subjects (approximately 20 to 24 hours). **Excretion:** One week after administration, 70% of the dose is excreted in the urine and 14% in the faeces. In urine, Risperidone plus 9-hydroxyrisperidone represents 35-45% of the dose. The remainder is inactive metabolites.

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SUMMARY OF HAZARD IDENTIFICATION:

Acute Toxicity

Organism	Test type	Route	Dose (mg/kg)	Effect	Reference
Child	TDLo	Oral	0.268	Sense organs and special senses: other: eye; behavioral: tremor; behavioral: changes in motor activity (specific assay)	Annals of Pharmacotherpy., 30(360), 1996 [PMID:8729889]
Women	TDLo	Oral	2.20	Cardiac: arrhythmias (including changes in conduction); vascular: bp elevation not characterized in autonomic section	Therapie., 52(155), 1997 [PMID:9231512]
Women	TDLo	Oral	2	Cardiac: arrhythmias (including changes in conduction); cardiac: pulse rate increase without fall in bp; vascular: bp elevation not characterized in autonomic section	Journal of Clinical Pyschopharmacology., 17(325), 1997
Women	TDLo	Oral	0.4	Behavioral: muscle contraction or spasticity); cardiac: pulse rate increase without fall in bp	American Journal of Emergency Medicine., 16(498), 1998 [PMID:9725965]
Women	TDLo	Oral	0.88	Behavioral: somnolence (general depressed activity); cardiac: arrhythmias (including changes in conduction)	American Journal of Emergency Medicine., 16(498), 1998 [PMID:9725965]
Women	TDLo	Oral	1.84	Behavioral: hallucinations, distorted perceptions; behavioral: headache; vascular: bp lowering not characterized in autonomic section	Journal of Clinical Psychiatry., 56(514), 1995 [PMID:7592504]
Man	TDLo	Oral	0.428	Brain and coverings: changes in surface eeg; behavioral: anorexia (human; behavioral: alteration of operant conditioning	Journal of Clinical Psychiatry., 58(323), 1997
Man	TDLo	Oral	0.114	Behavioral: wakefulness; behavioral: euphoria; behavioral: excitement	American Journal of Psychiatry., 153(1234), 1996
Women	TDLo	Oral	648	Behavioral: changes in motor activity (specific assay); behavioral: ataxia; behavioral: muscle contraction or spasticity)	Journal of Clinical Psychiatry., 59(478), 1998
Rat	LD50	Oral	56.6	Null	Journal of Pharmacology and Experimental Therapeutics., 244(685), 1988 [PMID:2450200]
Rat	LD50	Subcut aneous	98	Sense organs and special senses: ptosis: eye; behavioral: somnolence (general depressed activity); lungs, thorax, or respiration: dyspnea	Kiso to Rinsho. Clinical Report., 27(2991), 1993
Rat	LD50	Intrave nous	34.29	Behavioral: tremor; behavioral: convulsions or effect on seizure threshold	Kiso to Rinsho. Clinical Report., 27(2991), 1993
Mouse	LD50	Oral	63.1	NULL	Journal of Pharmacology and Experimental Therapeutics., 244(685), 1988 [PMID:2450200]
Mouse	LD50	Intrave nous	26.9	NULL	Journal of Pharmacology and Experimental Therapeutics., 244(685), 1988 [PMID:2450200]
Dog	LD50	Oral	18.3	Behavioral: Muscle Weakness; Lungs, Thorax, Or Respiration: Respiratory Stimulation; Gastrointestinal: Hypermotility, Diarrhea	Kiso to Rinsho. Clinical Report., 27(2991), 1993
Dog	LD50	Intrave nous	14.1	NULL	Journal of Pharmacology and Experimental Therapeutics., 244(685), 1988 [PMID:2450200]
Man	TDLo	Oral	3.42	Behavioral: hallucinations, distorted perceptions; cardiac: ekg changes not diagnostic of above	Annals of Emergency Medicine., 22(1908), 1993 [PMID:7694530]

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SUMMARY OF HAZARD IDENTIFICATION:

	Man	TDLo	Oral	0.428	Sense organs and special senses: miosis (pupillary constriction): eye; cardiac: ekg changes not diagnostic of above; cardiac: pulse rate increase without fall in bp	American Journal of Emergency Medicine., 16(498), 1998 [PMID:9725965]
	Man	TDLo	Oral	3.85	Behavioral: convulsions or effect on seizure threshold; cardiac: ekg changes not diagnostic of above; cardiac: pulse rate	Journal of Toxicology, Clinical Toxicology., 37(893), 1999 [PMID:10630278]

Repeated Dose Toxicity (Chronic Toxicity)

Oral Toxicity Study in Wistar Rats (3 months): Groups of 20 male and 20 female Wista rats were administered Risperidone in the diet at doses of approximately 0, 0.63, 2.5 or 10 mg/100 g food/day. There was no drug-related mortality or effects on behaviour and physical appearance. There was an increase in body weight gain in females (low- and mid-dosed groups), a temporary and transient decrease in body weight gain in males (mid-dose group), and a persistent decreased body weight gain in both high-dosed groups. The following changes were observed in serum biochemistry: decreased aspartate aminotransferase in high-dosed males and mid- and high-dosed females; increased cholinesterase in high-dosed males. In females the weight of the adrenals was decreased. In high-dosed males, the weight of the adrenals was increased and the weight of the kidneys was decreased. The major histological findings at autopsy included stimulation of the mammary gland (mid- and high-dosed male and all treated female rats), decreased glandular development of the uterus with decreased vaginal cornification and epithelial thickness, and inflammatory cell infiltration in the prostate (mid- and high-doses).

Oral Toxicity in Wistar Rats (3 months + 1 month recovery): Groups of 10 male and 10 female Wistar rats (complemented with 5 male and 5 female rats in the control group and highdosed group for a 1-month recovery period) were administered risperidone by gavage at 0 (vehicle), 0.16, 0.63, 2.5 and 10 mg/kg body weight/day. There was no drug-related mortality. The findings were qualitatively similar to those observed in the 3-month study using the dietary route of administration. Laboratory examination revealed the following changes: a slight increase in hematocrit, hemoglobin and red blood cells (within the normal range); a slight increase, at the borderline of normal limits, in blood urea nitrogen in both males and females at 2.5 and 10 mg/kg body weight; a slight decrease in glucose (females at 10 mg/kg body weight), total protein (males and females at 10 mg/kg body weight), calcium, albumin and triglycerides (mostly within the normal range) at 10 mg/kg body weight in males. Urinalysis showed a slight decrease in specific gravity and creatinine in male and female rats dosed at 2.5 and 10 mg/kg body weight; a slightly increased pH (males and females dosed at 10 mg/kg body weight) and volume (males and females dosed at 2.5 and 10 mg/kg body weight); and increased appearance of bacteria at 10 mg/kg body weight (males and females). Gross and histopathological examination displayed prolactin-dependent changes similar to those seen in the 3-month study, consisting of mammary gland stimulation, changes in the prostate, and uterine and vaginal changes. After 1 month of recovery, most of the changes showed reversibility. Mammary gland stimulation was still present in the high-dosed animals.

Oral Toxicity in Beagle Dogs (3 months): Groups of 4 male and 4 female Beagle dogs were administered risperidone orally in gelatin capsules at 0 (untreated), 0.31, 1.25 and 5 mg/kg body weight/day. All animals survived the 3-month study. Adverse clinical signs included dose-related sedation, miosis, soft faeces and congested conjunctiva. There was a

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SUMMARY OF HAZARD IDENTIFICATION:	
	transient decrease of body weight gain in high-dosed dogs during the first half of the study. Hematological and serum analysis revealed: dose-dependent decrease of hematocrit, hemoglobin and red blood cells (within normal range) in medium- and high-dosed dogs; a dose-related moderate increase in haptoglobin (within the normal range) at all doses; and a increase of cholesterol and phospholipids at the medium and high doses. Testicular and prostate weights decreased in a dose-related manner. Gross and histopathological examination revealed: increased presence of red blood cells in the spleen red pulp of the highdosed group; decreased glandular development of the uterus and reduced epithelial thickness of the vagina in all dosed females; an immature aspect of the prostate and incomplete spermatogenesis in mid- and high-dosed male dogs. **Oral Toxicity in Beagle Dogs (3 months + 2 months recovery):** Groups of 6 male Beagle dogs were administered risperidone orally in capsules at 0 (untreated), 0.31, 1.25 and 5 mg/kg body weight/day. Four dogs/group were sacrificed after 3 months and the remaining 2 after 5 months. There was no drug-related mortality and findings were similar to those of the first 3-month study. A dose-related sedation and an initial body weight decrease at all doses were present. Male dogs were studied in order to establish the effects of risperidone upon male genitalia and assess their reversibility. Erythrocytic parameters decreased in a dose-related manner; the changes were reversible. Haptoglobin, cholesterol and phospholipid levels increased dose-dependently; the changes were reversible. At the end of the treatment period only 2 low-dosed dogs ejaculated; at the end of the recovery period 2 low-dosed dogs were normal, 1 out of 2 medium-dosed dogs ejaculated normal sperm and out of 2 high-dosed dogs ejaculated poor quality sperm (reduced sperm motility and concentration). At the end of the treatment period, testosterone levels were dose-dependently reduced. At the end of the recovery period, the levels were still reduced in the 2 high-dosed dogs. Prostate and testicle weights were dose-dependently decreased and associated with immaturity. At the end of the recovery period, prostate weights remained slightly lower than in control animals. Dose-related increases in liver and spleen weights were reversible. **Oral Toxicity Study in Wistar Rats (12 months):** Groups of 20 male and 20 female Wistar rats were administered Risperidone in the diet at doses of approximately 0, 0.63, 2.5 and 10 mg/100 g food/day. Doses expressed as mg/kg were lower. There was no drug-related mortality. High-dose males and females exhibited decreased weight gain. At 2.5 mg/kg, serum analysis revealed slightly decreased potassium and blood urea nitrogen levels and a slight increase in cholinesterase (within normal limits) in males; and decreased alanine aminotransferase level in females. In addition to the changed serum variables seen at 2.5 mg/kg, dosing at 10 mg/kg resulted in a markedly decreased body weight gain; and a marginally reduced number of white blood cells and thrombocytes, decreased glucose, decreased urine creatinine and increased urine volume (within normal limits) in males, and decreased glucose, total protein and albumin in females. Most changes were slight. Histopathology indicated changes in the prostate and mammary glands of medium- and highdosed males and in the uterus, ovaries and mammary glands of all treated females. Medium- and high-dosed males showed diffuse hyperplasia of the pituitary, and in high-dosed males, the zona fasciculata of the adrenals was increased. **Oral Toxicity Study in Beagle Dogs (12 months):** Groups of 4 male and 4 female Beagle dogs were administered risperidone orally via gelatin capsules at doses of 0 (untreated),

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SUMMARY OF HAZARD IDENTIFICATION:	
	0.31, 1.25 and 5 mg/kg body weight/day. All animals survived the 12-month study. At the low dose, the main effects were related to the expected pharmacological action of risperidone, i.e. sedation and an interaction with the endocrine system (male and female genital tract changes). Mid and high dosing produced a slight to moderate toxicity that is similar to that described in the 3-month studies. Laboratory examination revealed slight anemia during the first 3 months (decreased hematocrit, hemoglobin and red blood cells); dose-dependent moderate increase of haptoglobin, cholesterol and phospholipids; and a slight decrease of potassium (high-dosed group). Organ weight changes included increases in spleen and pituitary weight and decreases in the weight of testes and prostate. Histopathology examination showed changes in the male and female genital tract, namely prostatic changes (fibrosis and clear basal cells), degenerative changes in the testicles of some dogs, decreased glandular development of the uterus, and the absence of corpora lutea. In addition, an increased number of red blood cells were seen in the spleen.
Carcinogenicity	**Carcinogenicity Study in Albino Swiss Mice (18 months):** Four groups of 50 male and 50 female mice received Risperidone orally through the diet, at doses of approximately 0, 0.63, 2.5 or 10 mg/kg body weight/day. A slightly increased mortality was present in medium- and high dosed females. In female mice at all doses, body weight gain was increased. Hematological (decreased erythrocytic parameters and an increase in platelets) and serum biochemical changes (decrease in glucose and increase in cholinesterase; and in females only increase in cholesterol, phospholipids, haptoglobin, total protein, calcium and albumin) were similar to those observed in rat chronic toxicity studies. Organ weight changes included increases in liver, spleen and heart weight. The weight of gonads in both sexes and the weight of adrenals in females were decreased. Gross and histopathological examination demonstrated an increased incidence of non-neoplastic, prolactin-dependent changes in the accessory sex glands (coagulating gland, seminal vesicle), pancreas, and pituitary gland in the medium- and high-dosed males. In females, at all doses, the changes involved increased (mammary gland, pituitary gland), or decreased (female genital tract) prolactin-dependent modifications. Neoplastic Changes: there was a positive trend for mammary adenocarcinomas and pituitary gland adenomas in females. Regarding prolactin-independent neoplasia, there was a positive trend for lung tumours in female animals (the incidence was within the range of historical controls). **Carcinogenicity Study in Wistar Rats (25 months):** Four groups of 50 male and 50 female rats received Risperidone orally through the diet at doses of approximately 0, 0.63, 2.5 or 10 mg/100 g food/day. Mortality was increased in medium- and high-dosed males, and high-dosed females. In males at all doses and in mid- and high-dosed females, toxicity was expressed by decreased body weight gain, deterioration in general condition (males) and some changes in hematological and biochemical parameters. Organ weight changes included increased adrenal and decreased gonad weights. Macroscopically, changes were seen in the mammary and pituitary gland, testes and uterus. Histopathological examination revealed prolactin-mediated non-neoplastic changes in the mammary gland, the pituitary gland and in the male and female genital tract at all doses, as well as renal pathology. Neoplastic changes included a dose-related increase in mammary gland adenocarcinoma in both males and females and an increase in pancreatic endocrine adenoma in males. Neoplasms of the female genital tract (vagina, cervix,

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SUMMARY OF HAZARD IDENTIFICATION:	
	uterus) were decreased.
In vivo/In vitro Genotoxicity Studies	Risperidone had no mutagenic effects when tested by the DNA-repair test in rat hepatocytes, the Ames reverse mutation test in Salmonella typhimurium and Escherichia coli, the mammalian cell gene mutation test in mouse lymphoma cells, the sex-linked recessive lethal test in Drosophila melanogaster, the chromosome aberration test in human lymphocytes and Chinese hamster lung cells, and the micronucleus test in the mouse bone marrow cells.
Reproductive/Developmental Toxicity	**Fertility and General Reproductive Performance in Wistar Rats:** One hundred and ninety two Wistar rats were divided into groups of 24 males and 24 females. Risperidone, at approximately 0, 0.31, 1.25 or 5 mg/kg body weight/day was administered orally through the diet to males for a minimum of 60 days prior to and during mating. Females were dosed for a minimum of 14 days prior to mating (with equivalently dosed males) and further during the first part of pregnancy up to day 8. No drug- or dose-related mortalities occurred. Paternal and maternal effects were responsible for dose-dependent decreased and delayed mating behaviour (all doses), manifested by lower copulation indices, which caused lower pregnancy rates in rats receiving Risperidone. However, where copulation occurred, the pregnancy rates were normal. **Fertility Study in Male Wistar Rats:** One hundred and ninety-two Wistar rats were divided into groups of 24 males and 24 females. Risperidone, 0 (vehicle), 0.16, 0.63 and 2.5 mg/kg body weight/day was administered by gavage to male rats 60 days prior to and during mating to untreated female rats. No drug-related mortality occurred. Fertility, gestation and copulation indices and the cohabitation-mating interval were comparable between groups. Litter data were comparable between groups and no teratogenic effects were present. These findings indicate no adverse effects on male fertility. **Fertility Study in Female Wistar Rats:** One hundred and forty-four Wistar rats were divided into groups of 12 males and 24 females. Risperidone, 0 (vehicle), 0.16, 0.63 or 2.5 mg/kg body weight/day was administered by gavage to female rats from 14 days prior to mating (with untreated male rats) up to day 8 of pregnancy. All animals survived the study. A dose-related sedation was present in the medium- and high-dosed groups. The cohabitation-mating interval was slightly increased in the low- and medium-dosed groups. The interval was clearly prolonged in the high-dosed group. However, the number of corpora lutea was not affected indicating a normal ovulation rate once ovulation occurred. Fertility, copulation and pregnancy indices were comparable between groups, and in pregnant females, no adverse effects were observed in the offspring. No teratogenic effects were found. **Embryo toxicity and Teratogenicity Study in Sprague-Dawley Rats:** Two Segment II studies were conducted in Sprague-Dawley rats. Groups of 24 female rats received risperidone 0 (vehicle), 0.63, 2.5 or 10 mg/kg body weight/day by gavage from day 6 through day 16 of pregnancy. There was no drug-related mortality. The weights of the pups of the high-dosed group slightly decreased in one of the studies. Risperidone was not teratogenic at the doses studied. **Embryo toxicity and Teratogenicity Study in Wistar Rats:** Groups of 36 female rats were administered risperidone 0 (vehicle), 0.63, 2.5 or 10 mg/kg body weight/day by gavage from day 8 through day 18 of pregnancy. Twelve females per group were allowed to deliver naturally, followed by an evaluation of the second generation, whereas the others were sacrificed at the end of the pregnancy period following a Caesarean section.

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SUMMARY OF HAZARD IDENTIFICATION:	
	There was no drug-related mortality. Dose-related sedation was present at all dosage levels. In the low and medium dosage groups no adverse effects on the litter were present. In the high dosage group, there was maternal toxicity (decreased weight gain) associated with decreased pup weight and slightly delayed ossification (reduced number of visible metatarsal bones). During the lactation period, pup weights were slightly increased and survival rates were normal. Risperidone was not teratogenic at the doses studied. In the undosed second generation, physical and behavioural development was comparable between groups and no adverse effects on fertility or on other reproduction parameters were observed. Placental transfer of risperidone occurs in rat pups. There are no adequate and well-controlled studies in pregnant women. However, there was one report of a case of agenesis of the corpus callosum in an infant exposed to risperidone in utero. The causal relationship to risperidone therapy is unknown (see WARNINGS AND PRECAUTIONS, Special Populations). **Embryo toxicity and Teratogenicity Study in New Zealand White Rabbits:** Groups of 15 female rabbits were administered risperidone at 0 (vehicle), 0.31, 1.25 or 5 mg/kg/day by gavage from day 6 through day 18 of pregnancy. Maternal toxicity was evidenced in the high dosage group by the death of 3 dams and by reduced body weight gain. At the doses studied, no embryotoxicity or teratogenic effects were seen. **Perinatal and Postnatal Study in Wistar Rats:** Groups of 24 female Wistar rats were administered risperidone orally through the diet, at approximately 0, 0.31, 1.25 or 5 mg/100 g food/day from day 16 of pregnancy through a 3-week lactation period. There was no drug-related mortality. Both body weight and food consumption decreased at all dose levels during lactation in a dose-dependent way. Duration of gestation was normal in all groups. The survival rate of pups was decreased in the high-dosed group with only 32% surviving. On day 4 of lactation, the body weight of pups in the high-dosed group was significantly less than that of controls. **Perinatal and Postnatal Study in Wistar Rats (with Second Generation Evaluation):** Groups of 24 female Wistar rats were administered Risperidone 0 (vehicle), 0.16, 0.63 or 2.5 mg/kg body weight/day by gavage from day 18 of pregnancy through a 3-week lactation period. All females were allowed to deliver naturally. No drug-related mortality was noted. Maternal adverse effects were evidenced by a small but significant increase in duration of gestation and by decreased food consumption and weight gain during lactation in the high-dosed dams. An increased number of stillborn pups was observed in the high-dosed group and survival was reduced at all doses probably due to decreased nursing. In the non-dosed second generation (F1), 10 females/group were mated with males from the same group. Pups were delivered by Caesarean section. There were no adverse effects on fertility or on other reproductive parameters. Observation of pups of the F2 generation indicated no abnormalities. Two-Generation Reproduction Study: One hundred and ninety-two Wistar rats were divided into groups of 24 males and 24 females. Risperidone, at approximately 0, 0.16, 0.63 or 2.5 mg/100 g food/day was administered orally through the diet to males for 60 days prior to and during mating. Females were dosed for 14 days prior to mating (with equivalently dosed males), during pregnancy and lactation until weaning of the first generation. There was no dosing of the second generation. No drug-related mortalities

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SUMMARY OF HAZARD IDENTIFICATION:	
	occurred. The cohabitation-mating interval increased with increasing dose levels. However, the duration of gestation was comparable between groups. Pregnancy and copulation indices decreased significantly in the high-dosed rats but all mated females became pregnant. During pregnancy, body weight gain decreased in the medium- and high-dosed females. Dosing during lactation resulted in a reduced body weight of the high-dosed dams. Teratogenic effects were not evidenced at any dose. Litter data including litter size, weight at birth, weight gain, and survival rate were comparable between controls and low- and medium-dosed rats. In the high-dosed rats, birth weight and survival rate were slightly lowered. The latter was related to decreased nursing behaviour. After weaning, physical and behavioural development were unaffected. In the non-dosed second generation, no relevant adverse effects on fertility or on other reproduction parameters were noted.
Highly Sensitizing Potential	**Risperidone**-induced **skin rash**. Antipsychotic agents are known to cause adverse **cutaneous** reactions in approximately 5% of the individuals of which exanthematous eruptions, **skin** pigmentation changes, photosensitivity, urticarial, and pruritus are common.

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** Initial dose: 2 mg orally per day Maintenance dose: 2 to 8 mg orally per day Maximum dose: 16 mg orally per day **Usual Adult Dose for Bipolar Disorder** Initial dose: 2 to 3 mg orally per day Maximum dose: 6 mg orally per day **Adverse Effects:** headache, **dizziness**, drowsiness, feeling tired; tremors, twitching or uncontrollable muscle movements; agitation, anxiety, restless feeling; depressed mood; dry mouth, upset stomach, diarrhea, constipation; weight gain; or. cold symptoms such as stuffy nose, sneezing, sore throat.

NOAEL/LOAEL	0.04 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)	1	1 year duration study in rodent.
F4: Severe Toxicity (1-	1	No any toxicity (Genotoxicity/Reproductive toxicity/

10)		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	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{0.04 (NOAEL) x 50}}{\text{5 x 10 x 1 x 1 x 5}}$ = 0.008 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Risperidone
- https://www.accessdata.fda.gov/drugsatfda_docs/nda/2006/020272Orig1s036,s041,020588Orig1s024,s028,s029,21444Orig1s008,s015.pdf
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