PERMITTED DAILY EXPOSURE FOR ALBENDAZOLE

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 Albendazole 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:

Albendazole, also known as Albendazolum, is a medication used for the treatment of a variety of parasitic worm infestations. Albendazole is currently used in a number of countries as a human and veterinary anthelmintic. It is useful for giardiasis, trichuriasis, filariasis, neurocycticercosis, hydatid, pinworm disease and ascariasis.

Common side effects include nausea, abdominal pains and headaches. Potentially serious side effects include bone marrow suppression. Liver inflammation has been reported and those with prior liver problems are at greater risk. Albendazole is a broad-spectrum anti-helminthic agent of the benzimidazole type.

3. IDENTITY OF THE ACTIVE SUBSTANCE:

Albendazole is a white to yellowish powder. It is freely soluble in anhydrous formic acid and very slightly soluble in ether and in methylene chloride. Albendazole is practically insoluble in alcohol and in water.

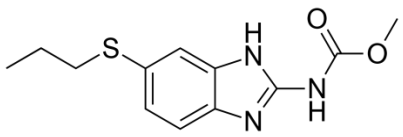
IUPAC NAME: Methyl [5-(propylthio)-1H-benzoimidazol-2-yl] carbamate

Chemical Abstract Services (CAS) Registry Number: 54965-21-8

Molecular Weight: 265.333 g/mol g·mol−1

Chemical Formula: $C_{12}H_{15}N_3O_2S$

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

Albendazole is a broad-spectrum anthelmintic. The principal mode of action for Albendazole is by its inhibitory effect on tubulin polymerization which results in the loss of cytoplasmic microtubules.

Mechanism of Action: Albendazole causes degenerative alterations in the tegument and intestinal cells of the worm by diminishing its energy production, ultimately leading to immobilization and death of the parasite. It works by binding to the colchicine-sensitive site of tubulin, thus inhibiting its polymerization or assembly into microtubules. As cytoplasmic microtubules are critical in promoting glucose uptake in larval and adult stages of the susceptible parasites, the glycogen stores of the parasites are depleted. Degenerative changes in the endoplasmic reticulum, the mitochondria of the germinal layer, and the subsequent release of lysosomes result in decreased production of adenosine triphosphate (ATP), which is the energy required for the survival of the helminth.

Pharmacokinetic data

Absorption: Poorly absorbed from the gastrointestinal tract due to its low aqueous solubility. Oral bioavailability appears to be enhanced when co-administered with a fatty meal (estimated fat content 40 g).

Metabolism: Hepatic. Rapidly converted in the liver to the primary metabolite, Albendazole Sulfoxide, which is further metabolized to Albendazole sulfone and other primary oxidative metabolites that have been identified in human urine.

Route of Elimination: Albendazole is rapidly converted in the liver to the primary metabolite, Albendazole Sulfoxide, which is further metabolized to Albendazole sulfone and other primary oxidative metabolites that have been identified in human urine. Urinary excretion of Albendazole Sulfoxide is a minor elimination pathway with less than 1% of the dose recovered in the urine. Biliary elimination presumably accounts for a portion of the elimination as evidenced by biliary concentrations of Albendazole Sulfoxide similar to those achieved in plasma.

Acute Toxicity

Organism	Test type	Route	Dose (mg/kg	Effect	Reference
Women	TDLo	Oral	256	Blood: aplastic anemia	American Journal of Hematology., 53(53), 1996
Rat	LD50	Oral	2400	Null	Annales Pharmaceutiques Francaises., 40(55), 1982 [PMID:7103363]
Rat	LD50	Intravenous	265	Null	Drugs in Japan, -(99), 1995
Mouse	LD50	Oral	1500	Null	Acta Leidensia., 57(201), 1989
Hamster	LD50	Oral	10000	Null	Drugs in Japan, -(99), 1995

Findings in dead rats included urinary staining of abdomen, bloody discharge around nose, chromodacryorrhea and intestinal hemorrhage. Necropsy of dead rabbits showed intestines containing fluid and dilated with gas. Toxic signs in other species were not reported.

Repeated Dose Toxicity (Chronic Toxicity)

Short-term studies:

Mice

In 2 separate experiments, groups of 10 male and 10 female Charles River CD1 mice were fed diets containing Albendazole for 90 days. Drug levels in food were

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SUMMARY OF HAZARD IDENTIFICATION:

adjusted so that animals received doses of 0, 5, 10, 20, 40 or 80 mg/kg bw/d in study 1 and 0, 200, 400, 800 or 1600 mg/kg bw/d in study 2.
All females and 5/10 males of the 1600 mg/kg group died spontaneously or were killed in a moribund condition. From week 9, ear lesions involving thickening and/or encrustation of the tips were observed in 2/10 males and 2/9 females at 800 mg/kg and 5/5 males in the 1600 mg/kg group. Food consumption was generally decreased in males given 400 mg/kg or more but weight gain was depressed only at 1600 mg/kg.

Rats

Groups of 15 to 20 male and female Charles River Sprague Dawley rats were given gavage doses of 0, 4, 25, 48 or 168 mg/kg bw/d of Albendazole in 0.5% Tween 80 for 4 weeks.
Toxic signs were produced in the 2 highest dose groups which included diarrhea, piloerection, nasal swelling with blood stained nasal discharge and death (7/30 rats at 48 mg/kg and 39/40 rats at 168 mg/kg died). Body weight gain was depressed at 48 mg/kg with weight loss at 168 mg/kg while food consumption was markedly reduced at 168 mg/kg and slightly reduced at 48 mg/kg.
Hematology, blood chemistry and urinalysis were measured after 1 and 4 weeks of treatment, except in the high dose rats which exhibited marked overt toxicity. Hemoglobin, hematocrit, erythrocyte and leucocyte counts were reduced at 48 mg/kg.
At autopsy, adrenal size was increased at 48 and 168 mg/kg, particularly in females. Testes were soft with reduced size and weight in 48 mg/kg males which survived 4 weeks. Testes size was not affected at the highest dose presumably due to early death of these males. Histopathology examination revealed hypoplasia in testes, bone marrow, spleen and lymph nodes in 48 and 168 mg/kg groups.
An additional group of 5 males and 5 females was given 48 mg/kg bw/d of Albendazole for 4 weeks, followed by withdrawal of treatment for 4 weeks. All drug-related changes were reduced in severity during the latter period indicating that the effects were reversible (Simon, 1979a).
Groups of 20 male and 20 female Long Evans rats were fed diets containing Albendazole for 91 days. Drug levels in food were adjusted so that animals received doses of 0, 2, 10 or 30 mg/kg bw/d. The control and high dose groups included an additional 10 males and 10 females for laboratory studies. There were no signs of toxicity and no effects on body weight, food consumption and ophthalmology parameters. Hematology, blood chemistry and urinalysis were studied after 1 and 3 months of treatment. Gross pathology and organ weights were examined in all rats while histopathology was carried out on 15 males and 15 females from control and high dose groups. Meaningful changes related to treatment were not observed (Killeen & Rapp, 1975a).
Groups of 100 male and female Charles River CD rats were fed diets containing Albendazole. The initial groups (F0) received doses of 0, 1, 2.5 or 5 mg/kg bw/d for 60 days and then throughout mating, gestation and post-natal periods. Similar size groups of F1 animals received 0, 5, 30 or 45 mg/kg bw/day. The treatment was intended to be for 2 years but excessive mortality necessitated termination of the

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SUMMARY OF HAZARD IDENTIFICATION:

study after 26 weeks.
There were no untoward effects in F0 rats. In the F1 animals, 92/100 males and 99/100 females of the 45 mg/kg bw/day group died by week 25. Prior to death these rats developed swollen cervical glands, followed by swelling of paws and the genital area, scabbing in the cervical area and emaciation (reduced weight gain and food intake).
Hematology was measured after 3 and 6 months of treatment. Hemoglobin, hematocrit, erythrocyte and leucocyte counts were decreased and reticulocytes increased in 45 mg/kg rats at 3 months. At 6 months, similar but slight hematological changes were seen in 30 mg/kg bw/day rats. Segmented neutrophils were particularly affected and this was confirmed by differential bone marrow counts in control and 30 mg/kg rats. Blood chemistry and urinalysis were studied after 3 months of treatment. In the 45 mg/kg bw/day group, plasma cholesterol was increased in males and females, potassium was increased in males, and albumin, plasma and erythrocyte cholinesterase were decreased in females. Urinary protein was increased in 30 and 45 mg/kg bw/day males.
Post mortems were carried out on all unscheduled deaths and approximately 60% of animals surviving to 26 weeks. Numerous gross alterations were noted in the high dose group including discoloration and/or nodules in the lungs, heart, lymph nodes, spleen, pancreas, liver, adrenal and kidney. Some of these organs were also enlarged or showed adhesions. Additionally, thymic tissue was often absent and testes were small and flaccid.
Group sizes were 20 to 25 males and females and dosing was continued for 4 months. Hematology was studied monthly. The 5 mg/kg rats were still unaffected. The red and white cell effects induced at 30 mg/kg were essentially normalized within a month of reducing the dose to 0 or 20 mg/kg. However, differential bone marrow counts at day 81 revealed a persistent depression of the myeloid line in the 20 mg/kg group. Gross post mortem examination of all animals showed no remarkable effects (Daly & Hogan, 1981).

Dogs

Groups of 4 to 5 male and female beagle dogs were given gavage doses of 0, 4, 16, 48 or 168 mg/kg bw/d of Albendazole in 2% Tween 80 for 4 weeks. Toxic signs, in a few dogs at the 2 highest dose levels, included diarrhea and vomiting with cardio-pulmonary disturbances in 1 dog. Death ensued in 1/10 dogs at 48 mg/kg and 6/10 dogs at 168 mg/kg, mainly in females. Heart rates showed marked increases in some 168 mg/kg females prior to death. Food intake was reduced at 48 mg/kg
and above and weight gain was depressed at 16 mg/kg and above.

Groups of 4 male and female beagle dogs were given 0, 2, 10 or 39 mg/kg bw/d Albendazole in capsules for 91 days. Ophthalmology, hematology, blood chemistry and unrinalysis were studied after 1 and 3 months; organ weights, gross and histopathology were examined in all dogs. There were no toxic signs or effects on body weight and food intake. No treatment-related effects were found (Killeen & Rapp, 1975b).

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SUMMARY OF HAZARD IDENTIFICATION:	
	Groups of 6 male and 6 female beagle dogs were given 0, 5, 30 or 60 mg/kg bw/d Albendazole in capsules for 6 months. Food intake was decreased in 30 and 60 mg/kg females, while weight gain was lower in 60 mg/kg males and females. Laboratory studies included hematology and blood chemistry monthly, urinalysis bimonthly and ophthalmology at termination. Hemoglobin, hematocrit and erythrocyte counts were slightly reduced at 60 mg/kg and leucocyte counts, particularly neutrophils, were reduced at 30 and 60 mg/kg. Autopsy on all dogs revealed decreased absolute and relative testes and uterine weights and slight increases in relative liver and kidney weights at 60 mg/kg. The incidences of small nodules in the stomach were increased in all treated groups but microscopically they were shown to be normal, sub-mucosal lymphoid follicles. Sternal bone marrow showed hypocellularity in 4/6 females in the 60 mg/kg group. **The NOEL was 5 mg/kg bw/day.** (Daly & Hogan, 1980).
Carcinogenicity	**Long-term/carcinogenicity studies:** **Mice** **Groups of 100 male and 100 female Charles River CD-1 mice were fed diets containing Albendazole for 25 months.** Drug levels were adjusted to provide doses of 0, 25, 100 or 400 mg/kg bw/d. Additional groups of 25 males and 25 females were given control and high dose treatments and used for hematology measurements. There were no toxic signs or effects on food intake and body weight. Hematology was studied after 3, 6, 12, 18 and 24 months in the main groups and monthly in the ancillary groups. Erythrocyte and leucocyte counts were decreased and platelets were increased at 400 mg/kg, particularly in females. A complete gross post-mortem examination was carried out on all mice. Full histopathology was undertaken on control and high dose mice. In intermediate groups, 6 major organs and grossly abnormal tissues were examined routinely. Flaccid or small testes, testicular tubular degeneration, oligospermia, and aspermia in epididymides were increased in 400 mg/kg males. Centrilobular hepatocytic vacuolation was increased in groups given 100 and 400 mg/kg. Eye opacities were noted in all groups; however, microscopically, cataracts were slightly increased only in 400 mg/kg males. The relationship of these ocular findings to treatment is questionable as the bulk of the cataracts were unilateral and such abnormalities are commonly obtained following repeated blood collection from the orbital sinus. The incidence of endometrial stromal polyps appeared to be increased over concurrent controls (Table 1) but a statistical evaluation of the results did not reveal significant differences between groups, and all incidences were within the historical control range for this laboratory based on 2 studies with 2 control groups in each. The NOEL was 25 mg/kg bw/d. (Daly & Knezevich, 1987a; Sauer,1985, 1987b; Selwyn 1987). **Rats** **Groups of 100 male and 100 female Sprague Dawley CD rats were fed diets containing Albendazole.** The initial groups (F0) received doses of 0, 1, 2.5 or 5

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SUMMARY OF HAZARD IDENTIFICATION:

mg/kg bw/d for 60 days and then through mating, gestation and post-natal periods. Similar size groups of F1 animals received 0, 3.5, 7 or 20 mg/kg bw/d for 28 months. Additional groups of 25 males and 25 females were given control and high dose treatments and used for hematology measurements. An interim sacrifice of 10 males and females per group was made after 12 months.

Treatment-related effects were not observed in F0 animals. In the F1 animals, mortality was slightly increased after 24 months in 20 mg/kg males. There were no other toxic signs or effects on body weight and food consumption. Ophthalmology, hematology, blood chemistry and urinalysis parameters were studied after 3, 6, 12, 18 and 24 months of treatment. In the 20 mg/kg group, total leucocyte and neutrophil counts were decreased at 24 months, serum cholesterol was increased in females throughout the study and in males at some sampling times.

A complete gross post-mortem examination was carried out on all rats. Full histopathology was undertaken on control and high dose rats. In intermediate groups, 8 major organs and grossly abnormal tissue were examined routinely. The 20 mg/kg animals showed increased incidences of flaccid testes, degeneration/ atrophy of germinal and relative liver weights in males and hepatic fatty metamorphosis in males and females.

The NOEL was 7 mg/kg/d. (Daly & Knezevich, 1987b; Sauer, 1985, 1987a; Selwyn, 1987).

In vivo/In vitro Genotoxicity Studies

Special studies on Genotoxicity:

Results of Genotoxicity assays on Albendazole

Test system	Test Object	Concentration	Result
Ames Test	*S. typhimurium*	1-10,000 µg	Negative
Ames Test	*S. typhimurium*	0.5-1000 µg	Negative
CHO Chromosome	Chinese hamster	0.047-1.5µg/ml	Negative
Aberration assay	Ovary Cells	-	Negative
Transformation	BALB/3T3 mouse cells	10-100 µg/ml	Negative

Albendazole did not produce Bacterial mutations, Chromosomal aberrations or Morphological transformations in cultured mammalian cells. The 2-aminosulphone metabolite did not produce bacterial mutations.

Reproductive/Developmental Toxicity

Reproduction studies:

Rats

Groups of Long Evans rats were fed diets containing 0, 30, 75 and 150 ppm Albendazole for 3 successive generations, commencing 64 d before the initial mating. Each parental group consisted of 12 males and 24 females, which were bred to produce 2 litters each. Offspring from the second litters were selected to serve as parents of the subsequent generations. Drug intake was calculated to be, on average, 2.3, 5.8 and 11.6 mg/kg bw/d.

There were no toxic signs or effects on body weight, food consumption, mating, fertility, pregnancy rates, gestation length, litter size and weight. During lactation, pup survival and/or weight gain was depressed, but only in F1a and F2a litters given 11.6 mg/kg. The NOEL was 5.8 mg/kg bw/d. (Schroeder & Rinehart, 1980).

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SUMMARY OF HAZARD IDENTIFICATION:

Groups of 20 male Sprague Dawley CD rats were given gavage doses of 0, 1, 10 or 30 mg/kg bw/d Albendazole in 0.5% gum tragacanth, from 60 days prior to mating to the end of the breeding period. Males were mated 1 to 1 with untreated females. Half the dams were killed on gestation day 13, the remainder were allowed to deliver naturally and rear pups to weaning.

In males treated with 30 mg/kg, weight gain was lower and 4 animals died or were killed moribund. Toxic signs were piloerection and bloody nasal discharge at 30 mg/kg and dried blood around the nose at 10 mg/kg. The ability to impregnate females was unaffected, despite the finding in the 30 mg/kg group of reduced testicular size, together with focal testicular hypoplasia in 8/10 rats. In the 10 mg/kg group, there were a few hypoplastic seminiferous ducts reported in 4 of the 5 rats examined.

Uterine examinations on gestation day 13 showed fewer implantations (not significant) at 30 mg/kg with no effect on resorptions. In females allowed to deliver, weight gain was lower during gestation in 30 mg/kg dams, probably reflecting the reduced litter size and weight. Postnatal growth, physical and behavioral development were unremarkable. The NOEL was l mg/kg bw/day. (Boutemy, 1980).

Special studies on teratogenicity:

Mice

Groups of 21 to 26 pregnant Charles River CD-1 mice were given gavage doses of 0, 2, 5, 10 or 30 mg/kg bw/d Albendazole in 0.5% methylcellulose. Treatment was on gestation days 6 to 15 and females were killed on gestation day 18.
There was no overt maternal toxicity or effect on resorption incidence, fetal weight and external, visceral and skeletal development of fetuses (Killeen & Rapp, 1975c).

Rats

Groups of 25 pregnant Charles River CD rats were given gavage doses of 0, 5, 20 or 40 mg/kg bw/d Albendazole in 0.5% methylcellulose. In each group 19 rats were treated on gestation days 16 to 20 and 6 were treated from gestation day 16 to lactation day 20.
There was no maternal toxicity or effect on gestation or parturition. At 40 mg/kg, litter size and weight were reduced at birth and remained depressed during lactation. A total of 6, 17, 4 and 55 pups died in the 0, 5, 20 and 40 mg/kg groups, respectively. Small lungs and kidneys and anasarca in the 40 mg/kg pups were possibly related to treatment, but an unequivocal conclusion was not possible in view of the low number of control pups examined. The authors concluded that developmental and behavioral characteristics were unrelated to Albendazole treatment, but detailed supporting data were not provided. The NOEL was 20 mg/kg bw/day. (Johnson, 1981).

A series of studies was carried out at biodynamic in Long Evans rats. A similar

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SUMMARY OF HAZARD IDENTIFICATION:

protocol was used in each study, which included dosing on gestation days 6 to 15; sacrifice of dams on gestation day 20; maternal observations for overt toxicity, weight gain and uterine parameters; fetal examination for size, weight, and external, visceral and skeletal abnormalities.

Study A: Groups of 20 pregnant rats were given gavage doses of 0, 2, 5, 10 or 30 mg/kg bw/d Albendazole in 0.5% methylcellulose. Maternal weight gain and survival were lower at 30 mg/kg. At this dose, there was a high incidence of resorptions, surviving fetuses showed reduced size, weight and multiple gross, visceral and skeletal malformations. Limb abnormalities such as micromelia, ectromelia, curved femur and microfetalis were also seen in other treated groups. However, the incidences were low, they were not dose-related and they were observed only in 1 or 2 liters per group (Killeen & Rapp, 1975e; Christian, 1984, 1987a.).

Study B: Groups of 19-20 pregnant rats were given gavage doses of 0, 0.5, 2, 5 or 10 mg/kg bw/d Albendazole in 0.5% methylcellulose. Fetuses of the 10 mg/kg group revealed reduced size and weight, retarded skeletal ossification and increased incidences of micromelia and microfetalis (which included shortened long bones in fore and hind limbs) (Killeen & Rapp, 1976; Christian, 1984, 1987a).

Study C: Groups of 30 to 60 pregnant rats were fed diets containing 29% freeze dried liver, obtained from cattle 48 hours after a single oral dose of 0 or 27.5 mg/kg bw Albendazole. Drug intake was calculated to represent 0.42 mg/kg bw/d Albendazole equivalents. The only possible treatment-related observation was shortened limb bones in 2/248 treated fetuses from 2 different litters. These effects were not seen in 460 controls and the authors noted that they were an infrequent finding at bio-dynamics (Hogan & Rinehart, 1977).

Study D: Groups of 20 to 22 pregnant rats were fed diets containing 10, 20 or 30% freeze dried liver, obtained from cattle 12 days after a single oral dose of 0 or 16.5 mg/kg bw Albendazole. Drug intake was calculated to be approximately 0.02, 0.04 and 0.06 mg/kg bw/d Albendazole equivalents. In the group given 30% exposed liver, resorptions were increased, 9 of which were in 1 female. If data from this rat were eliminated there were no significant effects. The overall NOEL for studies A to D was 5 mg/kg bw/day. (Schroeder & Rinehart, 1978).

Groups of pregnant Sprague Dawley rats were given gavage doses of 0, 5.3, 6.0, 6.62, 8.83, 10.6 or 13.25 mg/kg bw/d Albendazole or 9 of its animal metabolites at equimolar or higher doses. Treatments were on gestation days 8 to 15 and dams were killed on gestation day 21. The results were presented in summary form only.

Skeletal abnormalities were increased at dose levels of 6.62 mg/kg and greater with increases in resorptions and external malformations and decreased fetal weight at 8.83 mg/kg Albendazole and above. The major malformations were craniofacial and bone defects.

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SUMMARY OF HAZARD IDENTIFICATION:

Qualitatively similar findings were obtained with equimolar amounts of Albendazole Sulfoxide while the other metabolites A, B, E, F, G, J, I and H (section 2.1) were all ineffective. The concomitant administration of SKF-525-A, a microsomal oxidation inhibitor, almost completely suppressed the embryotoxic and developmental effects of Albendazole. The NOEL was 6 mg/kg bw/day. (Martin, 1980).

Groups of pregnant Sprague Dawley rats were given diets containing Albendazole or 40% freeze dried liver, obtained from cattle 24, 48 or 96 hours after a single oral dose of 0 or 20 mg/kg bw Albendazole. Drug levels in food were adjusted to provide 0, 12, 24 or 36 mg/kg bw/d but doses given through incorporation of liver could not be estimated. Treatment of rats was on gestation days 8 to 15 and dams were killed on gestation day 21. Albendazole doses of 24 and 36 mg/kg produced virtually 100% embryolethality, the single live fetus was small and had skeletal abnormalities. There were no effects at other exposure levels. The NOEL was 12 mg/kg bw/day. (Grannec, 1980).

Rabbits:

Groups of 15 pregnant New Zealand White rabbits were given gavage doses of 0, 2, 5, 10 or 30 mg/kg bw/d Albendazole in methylcellulose. Treatment was on gestation days 7 to 19 and does were killed on gestation day 30.

Maternal mortality was increased at 30 mg/kg but body weight comparisons were not meaningful due to wide variation within groups. The 30mg/kg group showed a reduction in implants, due largely to 2 does with corpora lutea but no implants, and increases in resorptions and ectrodactyly. Fetal size and weight were depressed at 10 and 30 mg/kg. The NOEL was 5 mg/kg bw/day. (Killeen & Rapp, 1975d).

Sheep:

In two separate experiments, groups of 15 to 44 Dorset Horn Cross and Clun mated ewes were given a single dose of 0, 7.5, 10, 15 or 20 mg/kg bw Albendazole by oral drench. Overall, there were 71, 43, 44, 43 and 42 animals in the 0, 7.5, 10, 15 and 20 mg/kg groups, respectively. Treatment was on gestation day 17 and ewes were allowed to deliver naturally.

There was no overt maternal toxicity but premature delivery was noted in more ewes of the 20 mg/kg group than in the others. All premature lambs in this group were stillborn, consequently the number of live lambs was reduced at 20 mg/kg, as was survival of the lambs to postpartum day 55. Some lambs were sacrificed in extremis or because they were considered commercially unviable, thus the total post-partum loss was 22/123, 4/67, 11/73, 12/73 and 39/61 in the 0, 7.5, 10, 15 & 20 mg/kg groups, respectively. Post-mortem examination of these lambs revealed increased incidences of prognathia, scoliosis, spina bifida and reduced tail at 20 mg/kg and displaced, poorly developed or absent kidneys at 15 and 20 mg/kg. The NOEL was 10 mg/kg bw/d. (Tesh & Harper, 1977).

The data shown in Table 4 indicates a relationship between teratogenesis and peak plasma concentration of Albendazole Sulfoxide. Data from Bogan & Marriner (1984).

Relationship between plasma Albendazole Sulfoxide and teratogenesis

Species	Albendazole Dose	Peak Plasma	Teratogenic

PHARMA DEVILS

QUALITY ASSURANCE DEPARTMENT

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SUMMARY OF HAZARD IDENTIFICATION:

	(mg/kg/bw)		
Sheep	10	2.50	Yes
Cattle	10	0.57	No
Rabbit	30	8.82	Yes
Rat	10	6.6	Yes
Mouse	30	NA	No
Man	400 mg/person	0.16	No

Embryotoxic but not teratogenic

Highly Sensitizing Potential

Uncommon (0.1% to 1%): Hypersensitivity reactions (including rash, pruritus, urticaria).

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 THERAPY: For oral dosage forms (tablets):

- **For Hydatid disease of the liver, lung, and peritoneum:**
  - Adults weighing 60 kilograms (kg) or more: Dose is based on body weight and must be determined by your doctor. The dose is usually 400 milligrams (mg) 2 times a day, taken with meals for 28 days (1 cycle). This is followed by not taking Albendazole for 14 days, for a total of 3 cycles.
  - Adults weighing less than 60 kg: Dose is based on body weight and must be determined by your doctor. The dose is usually 15 mg per kg of body weight per day, divided into 2 doses, taken with meals for 28 days. This is followed by not taking Albendazole for 14 days, for a total of 3 cycles. The dose is usually not more than 800 mg per day.
  - Children: Use and dose must be determined by your doctor.
- **For Neurocycticercosis:**
  - Adults and children weighing 60 kilograms (kg) or more: Dose is based on body weight and must be determined by your doctor. The dose is usually 400 milligrams (mg) 2 times a day, taken with meals, for 8 to 30 days.
  - Adults and children weighing less than 60 kg: Dose is based on body weight and must be determined by your doctor. The dose is usually 15 mg per kg of body weight per day, divided into 2 doses, taken with meals, for 8 to 30 days.

ADVERSE EFFECT: Common side effects of Albendazole include:
Nausea,
vomiting,
Stomach and abdominal pain,
Headache,
Dizziness, or Temporary hair loss.

Serious side effects of Albendazole including:
Vision changes,
Yellowing eyes or skin,
Severe stomach or abdominal pain,
dark urine,
Unusual tiredness,

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	Easy bruising or bleeding, Signs of infection (e.g., fever, persistent sore throat), Changes in the amount of urine, Severe or persistent headache, Seizures, Confusion or Very stiff neck.
NOAEL/LOAEL	NOAEL of 5 mg/kg bw/day obtained in a 6-month sub-acute toxicity study in dogs.

APPLICATION OF ADJUSTMENT FACTORS:		
F1: Extrapolation between species	2	For extrapolation from Dogs 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 (6 months) study in non-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	$\frac{\text{NOEL or NOAEL or LOAEL (mg/kg/day) x Body Weight (kg)}}{\text{F1 x F2 x F3 x F4 x F5}}$ $= \frac{\text{5 (NOAEL) x 50}}{\text{2 x 10 x 10 x 1 x 5}}$ = 0.25 mg/day

5. REFERENCES:

- https://en.wikipedia.org/wiki/Albendazole.
- https://www.jstage.jst.go.jp/article/foodsafetyfscj/3/4/3_2015025s/_pdf/-char/en.
- https://pubchem.ncbi.nlm.nih.gov/compound/Albendazole#section=Populations-at-Special-Risk.
- http://www.inchem.org/documents/jecfa/jecmono/v25je02.htm.
- https://www.rxlist.com/albenza-drug.htm#indications.
- https://www.mayoclinic.org/drugs-supplements/albendazole-oral-route/proper-use/drg-20061505.