PP-470
TXR-002481

002481

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Petitions Control Branch (PM-13)

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Petitions Review Branch (FOD-230)

File: OBF#FF0654

Evaluation of toxicology data presented in support of petition for residue tolerances of Bandane (mixture of 2-chloro-N,N-diallyl acetamide and trichlorobenzyl chloride).

Petition Petition No. FF0 654
11531/

Monsanto Chemical Company
St. Louis, Missouri
(IF 4-765)

Two product formulations shown below are involved.

Bandane Granular consisting of:

Active Ingredients

| | |
|---|---|
| 2-chloro-N,N-diallylacetamide (CDAA) | 11.7 |
| Trichlorobenzyl chloride (TCBC) | 23.3 |

Inert Ingredients [redacted]

Bandane Liquid consisting of:

Active Ingredients

| | |
|---|---|
| 2-chloro-N,N-diallylacetamide (CDAA) | 23.7 |
| trichlorobenzylchloride (TCBC) | 50.3 |

Inert Ingredients [redacted]

The petitioner requests negligible tolerances (0.5 ppm) with respect to each of the active ingredients when used, pre-emergence, on field corn, silage corn, sweet corn and popcorn at a single application at rates of 30 lbs per acre for Bandane granular and 4.5 quarts per acre for the Bandane liquid.

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both Captan and one of its active ingredients N-(trichloromethylthio)-4-cyclohexene-1,2-dicarboximide (Captan) have been previously registered with EPA on a no residue basis.

Toxicological Data Reviewed

1. Acute Oral Lethality in Rats Younger Lab Y59-40; 08/4/59

| | | |
|---|---|---|
| No. of animals used | - | 22 (12 males & 10 females) |
| Method of administration | - | Intubation |
| Dosage levels | - | 871, 1000, 1150, 1320 mg/kg |

Results

Mortality with increasing dosage was found to be 0/3, 3/7, 3/5, 4/5. The oral $LD_{50}$ was determined as 1065 mg/kg with limits of 937-1230 mg/kg. Survival time was overnight to forty-eight hours, most deaths occurring overnight. Symptoms included severe diarrhea, weakness and tremors. At autopsy on selected animals which died, gross observation showed inflammation of the gastric mucosa and liver and kidney congestion.

2. Minimum Lethal Dose by Skin Absorption in Rabbits

| | | |
|---|---|---|
| No. of animals used | - | 6 (3 male and 3 female) |
| Method of administration | - | By application to the clipped, intact skin then covered with plastic. |
| Dosage Levels | - | 750, 400, 600, 800, 1000, 1500 mg/kg. |

Results

Mortality with increasing dosage was found to be 0/1, 0/1, 0/1, 1/1, 1/1, 1/1. Animals died in 4 to 6 hours. The Minimum Lethal Dose by Skin Absorption was thus between 600 and 800 mg/kg. Symptoms included rapid onset of weakness followed by convulsions and coma. Gross findings at autopsy on animals which died was pulmonary hyperemia.

3. Skin Irritation in Rabbits

| | | |
|---|---|---|
| No. of animals used | - | 3 |
| Method of administration | - | By application to the clipped, intact skin, then covered with plastic for 24 hours. Washed with soap and water after 24 hours. |
| Dosage level | - | Not given. |



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Results:

Scoring of skin irritation was that of Draize et.al. Jour. of Pharm. and Exp. Therapeutics 82, pp. 1344.

Scores at 24 and 72 hours after removal of the patches were 6.0 and 4.6 respectively. Both erythema and eschar formation were noted. Randox-T is classed as a severe skin irritant.

4. Eye Irritation in rabbits

| | | |
|---|---|---|
| No. of animals used | = | 3 |
| Method of administration | = | Instillation into the conjunctival sac. |
| Dosage level | = | 0.1 ml |

Results:

Scoring of the eye irritation was that of Draize et.al. op.cit. Pp. 59.0 at 48hrs Moderately severe edema and erythema as well as copious lacrimation were observed. Moderate dulling of the cornea and iridial congestion were seen. Scores at 24 and 72 hours were 51.3 and 37.6 respectively. Slight conjunctival effects were still present at 7 days. Randox-T is classed as a moderately severe eye irritant.

5. Vapor Inhalation (rats)

| | | |
|---|---|---|
| No. of animals used | = | 5 (males) |
| Method of administration | = | Inhalation of vapor concentration produced by bubbling air at 14 l/minute through 20 ml of Randox-T contained in a 250 ml gas washing bottle then passing the air successively through a five gallon bottle and a 70 liter exposure chamber. |
| Nominal concentration | = | Not determined. |
| Length of exposure | = | 6 hours. |

Results:

No deaths occurred. Lacrimation was produced. Moderate ocular and nasal inflammation developed during the exposure period. No severe symptoms developed either during the exposure or the 14-day post-exposure observation period.

The Randox-T used in the foregoing studies is presumed to be the Randox-T liquid preparation.

6. ...-day subacute toxicity study in rats IBT C 4810 ; 03/29/67

| | | |
|---|---|---|
| Material used<br>Randox T | - | A mixture of 3.1 lbs of Randox technical (2-chloro-N,N-diallylacetamide) and 0.3 lbs of trichlorobenzyl chloride. |
| No. of animals | - | 40; 4 groups of 5 animals (3 males and 3 females per group) |
| Method of administration | - | Admixture to the diet. |
| Diet concentrations | - | 0, 20, 62 & 200 ppm. |

Parameters studied were:

Mortality

Behavorial reactions

Body weights - determined weekly

Food consumption - determined weekly

Hematology, clinical blood chemistry and urinalysis were performed for all groups prior to the test; at 45 days for the control and high level animals; for all groups just prior to termination.

Hematology included hemoglobin, hematocrit, erythrocyte count and total and differential leucocyte counts.

Clinical blood chemistry included urea nitrogen, glucose, serum alkaline phosphatase, SGOT, SGPT.

Urinalysis included glucose, albumin, pH and microscopic elements.

Organ weights and organ to body weight ratios were obtained in each group for liver, kidney, spleen, heart, brain, gonad, adrenal and thyroid.

Pathology including microscopic examination of adrenal, thoracic aorta, bone marrow, brain (cerebrum, cerebellum, pons), caecum, colon, esophagus, eyes, gall bladder, gonad, heart, kidney, liver, lung, lymph node (cervical & mesenteric), muscle, optic nerve, pancreas, parathyroid, sciatic nerve, pituitary, prostate, submaxillary gland, skin, duodenum, jejunum, ileum, spleen, stomach (cardia, fundus, pylorus), trachea, thymus, thyroid, uterus, urinary bladder.

Results:

No significant abnormalities were found, although there is a suggestion at the 200 ppm level of a decrease in the rate of weight gain which was more evident in males than in females. Sixty two ppm is considered to



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represent a "no effect" level. In terms of each of the ingredients this represents levels of approximately 20.7 ppm for the Kandox and 41.3 for the trichlorobenzyl chloride.

7. 90-Day Subacute Oral Toxicity Study in Rats IBT #4809 ; 04/20/67

Material used - A mixture of 3.1 lbs of Kandox, technical and 6.3 lbs of trichlorobenzyl chloride.

No. of animals - 80; 4 groups of 20 animals (10M and 10F per group).

Method of Administration - Admixture to the diet.

Diet concentration - 0, 20, 62 and 200 ppm.

Parameters studied were:

Mortality

Behavioral reactions

Body weights - determined weekly

Food consumption - determined weekly

Hematology, urinalysis and clinical blood chemistry were performed at 30 days and just prior to termination.

Hematology included hemoglobin, hematocrit, erythrocyte count and total and differential leucocyte counts.

Urinalysis included glucose, albumin, pH, specific gravity, microscopic elements.

Clinical blood chemistry included urea nitrogen, serum alkaline phosphatase and isocetric dehydrogenase.

Organ, and organ to body weight ratios for liver, kidney, spleen, gonad, heart and brain.

Pathology including microscopic examination in surviving animals of the control and high level group of heart, trachea, lung, liver, pancreas, esophagus, stomach (cardia, fundus, pylorus), duodenum, jejunum, ileum, caecum, colon, spleen, lymph node, thymus, kidney, urinary bladder, testes, ovary, seminal vesicle, prostate, uterus, pituitary, adrenal, submaxillary, thyroid, parathyroid, intercostal muscle, bone marrow, peripheral nerve, spinal cord, brain (cerebrum, cerebellum, pons).

Results:

No significant abnormalities were found in any of the parameters except the liver to body weight ratio. In this respect treated males showed statistically larger livers at all levels and treated females showed

similar changes at the two higher dose levels. Microscopic findings, however, were negative. The absence of any increase in isocitric dehydrogenase and serum alkaline phosphatase also suggests absence of liver effects. However, in a 3 week target organ study in rats there was considerable liver pathology at 1500 ppm. It would be desirable to obtain individual data for liver, body weight and food consumption if available.

Toxicological Data Dichlorobenzal Chloride

1. Acute Oral Toxicity in Rats

| | | |
|---|---|---|
| No. of animals used | - | 22 (13 males & 10 females) |
| Method of administration | - | Intubation |
| Dosage levels | - | 2510, 2830, 3310, 3800 mg/kg |

Results

Mortality with increasing dosage was found to be 1/5, 3/7, 3/3, 5/5. The oral $LD_{50}$ was determined as 3075 mg/kg with limits of 2800-3400 mg/kg. Survival time was overnight to five days, most deaths occurring overnight. Symptoms included salivation, diarrhea, lethargy and weakness. The animals were very irritable. Gross autopsy of those animals which died showed kidney discoloration and inflammation of the gastric mucosa.

2. Minimum Lethal Dose by Skin Absorption in Rabbits

| | | |
|---|---|---|
| No. of animals used | - | 7 (5 male & 2 female) |
| Method of administration | - | By application to the clipped intact skin and covered with plastic. |
| Dosage levels | - | 2000, 2500, 3000, 4000, 5000 & 7500 mg/kg. |

Results

Mortality with increasing dosage was found to be 0/1, 0/1, 0/1, 0/1, 0/1, 2/2. The Minimum Lethal Dose by Skin Absorption was thus between 5000 and 7500 mg/kg. Survival time was 2 and 3 days. Symptoms included loss of appetite, lethargy and weakness. Paralysis, if present, could not be distinguished from weakness. Gross findings at autopsy on the animals which died were pulmonary hyperemia and some evidence of liver dysfunction.

3. Skin Irritation in Rabbits

No. of animals used - 3

Method of administration - By application to the clipped, intact skin, then covered with plastic for 24 hours. After 24 hours washed with soap and water.

Dosage level - Not given.

Results:

Scoring of the skin irritation was that of Draize, et.al., op.cit. Scores at 4 and 48 hours after removal of the patches were 2.6 and 2.0 respectively. Both well defined erythema and slight edema developed. TCBC is classed as a moderate skin irritant.

4. Eye Irritation in Rabbits

No. of animals used - 3
Method of administration - Instillation into the conjunctival sac.
Dosage level - 0.1 ml.

Results:

Scoring of the eye irritation was that of Draize et.al., op.cit. In four hours edema sufficient to half close the eyelids as well as moderately severe erythema, copious lacrimation and moderate iritis was noted. These persisted through 24 hours. Some conjunctivitis remained in two animals at the seventh day. TCBC is classed as a moderately severe eye irritant.

5. Vapor Inhalation (rats)

No. of animals used - 6 (males)
Method of administration - Inhalation of vapor concentration produced by bubbling air at 14 l/minute through 100 ml of TCBC contained in a 250 ml gas washing bottle and then passing the air successively through a five gallon bottle and a 70 liter exposure chamber.
Nominal Concentration - Not determined.
Lengths of exposure - 6 hours.

Results:

No deaths occurred. Moderate nasal and ocular inflammation developed and cleared after several days. The animals did not exhibit normal activity or appetite until 3 - 4 days after exposure. No serious pulmonary complications were observed grossly. TCBC was considered to be moderately harmful to rats under these conditions.



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b. Abbreviated chronic oral toxicity study in rats

Material used - Trichlorobenzyl chloride.
No. of animals - 60; 3 groups of 20 animals (10 males and 10 females).
Method of administration - Admixture to the diet.
Diet concentrations - 0, 0.10, 0.30 per cent.

Parameters studied were:

Mortality

Behavioral reactions

Body weights - determined weekly

Food consumption - determined weekly

Hematology and urinalysis were performed initially and at termination.

Hematology included hemoglobin, hematocrit and total and differential leucocyte counts.

Urinalysis included reducing substances, albumin and microscopic elements.

Pathology including microscopic examination of heart, lung, liver, spleen, pancreas, esophagus, stomach, small intestine, large intestine, lymph node, adrenal, kidney, urinary bladder, thyroid, ovary and uterus, testes, brain, bone and bone marrow.

Results

Of the parameters studied effects were noted upon weight gain, food consumption and pathology. Weight gains were depressed in the male rats in both test groups and in the female rats fed the higher concentration of TCBC. Food consumption in the male test groups was somewhat lower than for the controls and was suggestive of dose correlation. No such pattern was seen for the females. There is a suggestion in the data that the body weight differences might be due to systemic toxic effects. Gross examination of the high-dose level animals revealed pale livers with distinctly granular textures. In the low-dose group degenerative liver changes were seen in 9 of the 10 males and in 5 of the 10 females. In the low-dose animals the livers were pale but were not granular. Microscopically, of the 10 organs and tissues examined, significant changes were found only in the liver. These included: (a) general derangement of hepatic chord formation (b) irregularity of cell and nuclear size; (c) the occurrence of degenerative forms of hepatic cells characterized by acidophilic alterations of cytoplasm and pyknosis of nuclei; (d) regenerative forms of hepatic cells characterized by mitotic activity or by bi-nucleate forms; (e) hepatic cell necrosis. No associated inflammatory infiltrate was found. No evidence of significant fatty alteration was noted. Pigment deposition was not

present. These microscopic changes were found to be dose related being most severe in the 0.3% dosage group and less severe but consistently present in the 0.1% dosage group, especially in the male animals.

Toxicological data on α-chloro-N,N-diallylacetamide were previously submitted in connection with Pesticide Petition No. 7F0 617 and are summarized therein.

Discussion:

1. Subacute oral toxicity studies in dogs with CDAA alone and in combination with TCBC did not produce any significant deviations in the parameters studied. In rats subacute feeding of CDAA alone produced no significant effects. However CDAA in combination with TCBC fed over a ninety-day period produced increased liver to body weight ratios as compared to the controls. For the males this occurred at all three feeding levels, for the females at the two higher levels. Microscopic and clinical biochemical findings, however, disclosed no abnormalities attributable to the compound. Definitive evidence of liver damage was obtained in rats fed TCBC at levels of 1500 and 3000 ppm over a three week period. The petitioner should provide liver weights, body weights and food consumption data for individual animals.

2. Acute oral toxicities ($LD_{50}$) obtained in rats were as follows:

| | | |
|---|---|---|
| CDAA & TCBC (Ratio 3.1 to 6.3) | = | 1865 mg/kg |
| TCBC | = | 1073 mg/kg |
| CDAA (In corn oil) | = | 0.70 ml/kg |

3. Minimum Lethal Dose by Skin Absorption in Rabbits were estimated to fall within limits indicated as follows:

| | | |
|---|---|---|
| CDAA & TCBC (Ratio 3.1 to 6.3) | = | 600-800 mg/kg |
| TCBC | = | 5000-7500 mg/kg |
| CDAA (using a 48.8% active material) | = | 100-200 mg/kg |

For the mixture above survival times were 4 to 8 hours. For the CDAA it was 4 hours to overnight. In the case of TCBC survival time was 2 to 3 days.

4. Topical application of Randox-T liquid preparation to rabbit skin and eye shows it to be a severe skin irritant and a moderately severe eye irritant. CDAA tested as a 48.8% active material produced severe skin irritation permanent blindness. TCBC was found to be a moderate skin irritant and moderately severe eye irritant.

5. Exposure for 6 hours to vapor concentrations produced from Randox-T liquid and TCBC produced no lethality and only minor effects in rats. Inhalation exposure to CDAA for 6 hours was lethal to all animals

exposed within 24 hours. This latter result is not, however, comparable to the first two since the conditions of the exposures were quite different.

CONCLUSIONS:

The combination of α-chloro-2,6-diallylacetanilide and trichlorobenzyl chloride in the ratio of 1:7 is tolerated when fed subacutely at concentrations up to 62 ppm without significant signs of toxicity in dogs. For rats there is increased liver weight that requires further exploration. The petitioner is requested to provide body weight, liver weight, and food consumption data.

RECOMMENDATION:

Final evaluation of the safety of this material awaits evaluation of the requested data.

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S-970 (Dr. Jacobson)
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