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Tolerances for Triforine (see below)
Pesticide Petition 7F1921

Dr. E. Wilson, PM

Toxicology Branch

Petitioner: EM Laboratories, Elmsford, N.Y.

Tolerances requested

5.0 ppm in or on peaches
0.1 ppm in or on blueberries
0.1 ppm in or on cranberries

Recommendation

Do not establish tolerance. We request a submission of the confidential formulation(s) in order to determine the exempt status of the inert ingredients; we also request an identification of the 6.5 E and 20 EC formulation and confirmation that these were used in the toxicity studies submitted with the Section 18 exemption on blue berries; otherwise the formulation(s) cannot be registered.

Further comment: The petitioner has submitted a label (Canadian) of a 1.9 E formulation; this label is entirely inadequate, with regard to signal word and precautionary statement, for registration in the U.S.

The toxicity data submitted on the a.i. are adequate and complete to support the required tolerances, the ADI for man would not be exceeded (see review for details).

Substance identification

1. N-N (1,4-piperajiucdiyl-bis-(2,2,2-trichloroethylene))-bis-formamide

2. W-524

3. Funginex (formulation)

No prior petitions. Section 18 granted in 1977 for use on blueberries.

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REVIEW

A. Acute and subacute toxicity tests were reviewed in connection with a Section 18 exemption request on blueberries by the State of Washington. Acute tests on a 6.5E and a 20EC formulation were also reviewed but since they are not pertinent for this application they are not listed in the following. The studies reviewed are as follows:

1.	Acute tests (technical)	
	Oral LD_{50} (mice)	6 g/kg
	Oral LD_{50} (rats)	16 g/kg
	Dermal LD_{50} (rats)	>10 g/kg
	Skin and eye irritation	not irritating
2.	90-day Feeding (rat)	NEL 500 ppm
3.	90-day Feeding (dog)	NEL 100 ppm
4.	Teratology (rat)	negative (1.6 g/kg)
5.	Mutagenicity	negative (male dominant lethal test, mouse)

B. Studies Reviewed with this Petition

1. 2 year dog feeding study
Boehringer Sohn, March 20, 1974

Four animals per sex per level were exposed to 0, 10, 40, 100, and 1000 ppm in the diet.

Results: The weight development, hematology, clinical chemistry, urinalysis, grospathology, and organ weights showed no compound related effect. Histologically it was demonstrated that at the highest dose (1000 ppm) the Kupffer cells had an increased iron content, 2/8 high dose animals also showed an increase in iron content of bone marrow cells, and 5/8 animals in this group showed a shift to erythropoietic cells in the bone marrow. These findings are supported by the 90-day feeding studies, where at higher doses it was demonstrated that a loss of peripheral erythrocytes occured, which was compensated by increased erythropoiesis. The NEL for the 2 year dog study is 100 ppm or 2.5 mg/kg b.w./day.

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2. 2-year rat feeding study
Boehringer Sohn, June 1974.

Groups of male and female rats were fed the compound at 0, 25, 125, 625 and 3125 ppm. The control and high dose group consisted of 50 rats per sex, the three other groups of 35 rats per sex.

Results: All required parameters were investigated and no compound related effects were noted, with the exception of a slight anemia at the 6th week in the high dose animals. This condition was not persistent throughout the study.

Pathology and histopathology. All animals underwent gross pathology. A predetermined series of animals was to be sacrificed at end of study; this number of survivors was however reduced by the number of animals dieing. For example, in the control group 31 (13 M & 18 F) were sacrificed at the end or in the high dose group 29 animals (18 M & 11 F). All dieing animals and animals with tumors were histologically examined, as well as animals from the intermediate feeding levels. There was generally no differences among the groups with respect to pathological changes including neoplastic changes, however, the incidence of nodular hypaplasia of small bile ducts (mostly seen in males) appeared to be increased in treatment groups (4/40 control; 7/30, 25 ppm; 5/30, 125 ppm; 8/30, 625 ppm and 21/40, 3125 ppm). Statistically these incidences are however, not significant and furthermore there is no dose dependency.

The observed NEL for this study is 625 ppm or 31 mg/kg/day.

3. Mouse oncogenicity study
Celamerk, September 4, 1975

40 animals per sex per level were exposed to 0, 30, 150, and 750 ppm in their diet. The mouse strain used is NMRI-EMD-SPF. The following 10 tissues of all mice were examined histologically: heart, lung, liver, gall bladder, spleen, kidney, adrenals, gonads, urinary bladder, and brain. Gross pathology was performed on all organs and any tumor was analysed histologically.

Results: The mortality was about 33% over the 18 month period without indication of compound effect, life span as well was not affected by compound. Only 10 mice were not analyzed because of decomposition. Gross and histopathology did not reveal any compound related effect with respect to pathological changes or incidence of tumors.

This study is a well conducted mouse oncogenicity test and shows that under the conditions tested the substance has no oncogenic potential. The highest dose tested was over 100 mg/kg/day and although no toxic effects were noted this level can be considered high enough in light of the NEL observed in other species (see above).

4. 3-generation reporduction study (rat)
Boehringer Sohn, May 31, 1974

At each generation 20 females and 10 males were used. The animals were exposed to 0, 100, 500, and 2500 ppm throughout the study. At each generation two matings were performed the offsprings of the second mating were used to carry the study on. Histopathology of 10 animals per sex per dose was carried out on 10 week old animals of the $F3_B$ generation, furthermore 10 per sex per dose of the $F3_B$ generation were prepared for analysis of skelettal malformation.

Results: Liter size, gestation, sex composition, fetus weights and fetal mortality during lactation were not affected by the compound. For reproductive effects the NEL is greater than 2500 ppm which is a level about 5 times in excess of the toxic level for the rat.

5. Metabolism study in the rat with ^3H labeled compound
Boehringer Sohn, October 27, 1971

It was demonstrated that after 48 hours 94% of the radioactivity is excreted by rats. After 168 hours 96% were excreted, 18% by fecal excretion and 78% by renal excretion. The excreted material was different from the parent compound. After p. o. application essentially two metabolites (10:90 ratio) with slower Rf values than the parent compound were found in the urine.

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6. Pharmacokinetics of triforine in the rat
Boehringer Sohn, October 3, 1974

The labelled compound used in this study was ^{14}C labeled in the side chain, whereas the ^{3}H labeled compound was not specifically labeled, but mostly in the ring. Comparative studies showed that ^{14}C labeled compound is excreted similarly to ^{3}H compound but that blood levels of ^{14}C are about twice as high. The conclusion of the studies is that the "major" metabolite is triforine from which one side chain has been removed. The other metabolite is disignated as "side chain" metabolite and was not completely identified. It is likely that the side chain in fact is intact which would mean that the metabolite is Chloralformamide (a natural degradation product of triforine).

Summary of Data Reviewed

2-year dog feeding study	NEL 100 ppm or 2.5 mg/kg bw/day
2-year rat feeding study	NEL 625 ppm or 31 mg/kg bw/day negative for oncogenicity
18 month mouse feeding study	negative for oncogenicity at 750 ppm or 100 mg/kg bw/day (highest level fed).
3-generation reporduction study (rat)	NEL (reproduction) 2500 ppm, highest feeding level
Metabolism (rat) two studies	Satisfactory to determine major metabolites.

ADI, maximum permissible intake (MPI) and maximal theoretical exposure (MTE).

Based on the NEL observed in the dog studies using a 100-X safety factor the ADI is 0.025 mg/kg bw/day; for a 60 kg man the MPI thus is 1.5 mg/day. The MTE is calculated as follows:

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peaches (5.0 ppm); food factor 1%	=	0.075 mg/day
cranberries and blueberries (0.1 ppm)		
Total food factor 0.13%	=	0.0002 mg/day
TOTAL MTE		0.0752 mg/day

It is thus concluded that the MTE does not exceed the MPI for man.

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