Kepone: Position Document 1
[OP-66019]

Kepone Working Group
Environmental Protection Agency

Section IA. Summary Checklist

Reviewer _____

CRPAR Checklist - Active Ingredient

decachloro - octahydro - 1,3,4 methano - 2H - cyclobuta (c,d) pentalen -2-one

ACTIVE INGREDIENT: _____ COMMON NAME: Chlordecone APPROX. 1974 PROD. VOL.: 840,000 lb.

TRADE NAME: Kepone

USES:

Insecticide X Fungicide ___ Plant Growth Reg ___

Herbicide ___ Disinfectant ___ Other _____

Criteria	Study Triggers 162.11 Criteria Yes	No	Ref.	No Study Found	2nd Verification Needed?
Acute Toxicity - Humans, Domestic Animals					
1. Dermal $LD_{50} \leq 40$ mg/kg (formulated) (Dust 1 label 5% active) EC (conc. _____) WP (conc. _____) G (conc. _____) Dermal LD_{50} of 20% = 410 mg/kg 5% = 1620 mg/kg (rabbits)		X	Pest Pet 0E0919 Doc # 108276		
2. Dermal $LD_{50} \leq 6$ g/kg (diluted for spray) Chlordecone products are not available in these formulations. EC (conc. _____) WP (conc. _____) G (conc. _____)		X			
3. Inhalation $LC_{50} \leq 0.04$ mg/liter (formulated) Test at 10% concentration, only chlordecone dust label EC (conc. _____) WP (conc. _____) G (conc. _____) at 5% active. No significant difference in weight gain or liver or lung pathology among chlordecone dust & plain dust exposed mice & controls Mice exposed 19 hrs. over 10 day period.		X	Pest Pet 0E0 919 Doc, # 091574		
Applicable PERS data					
46 cases human poisoning (primarily children) In only one case was the causitive agent confirmed. No deaths were attributed to acute poisoning.					

Criteria	Study Triggers 162.11 Criteria Yes	No	Ref.	No Study Found	2nd Verification Needed?
Chronic Toxicity					
1. Oncogenic effects - man or mammals (species: rats & mice ; exposure: oral)	X		IB (1) and (2)		
2. Mutagenic effects (tests: _____, _____, _____)					
3. Other chronic effects - man or mammals					
a. teratogenic					
effect: _____					
dosage: _____					
b. neurotoxic					
effect: tremors		X*			
dosage: _____					
c. reproduction					
effect: testicular atrophy 50 & 80 PPM reduced reproduction in rates & mice		X*	IB(3), (4) and (5)		
dosage: 5 to 37.5 PPM					
d. other: _____, _____					

* No trigger at this time. Issue unresolved.

Criteria	Study Triggers 162.11 Criteria Yes	No	Ref.	No Study Found	2nd Verification Needed?
Chronic Toxicity (continued)					
4. Reductions in non-target organism population evidenced by: PERS data		X		X	
monitoring data Massive amounts destroyed beneficial bacteria (sewage treatment) in Hopewell, Va		X			
petition studies (residue, leeching, and toxicity)					
5. Fatality to endangered species		X		X	
Lack of Emergency Treatment					
1. No antidote or first aid treatment		X			
Acute Toxicity - Wildlife (calculation on attached sheet) Not applicable See Discussion.					
1. Mammal: feed residue ≥ acute oral LD_{50}		X			
2. Avian: feed residue ≥ subacute dietary LC_{50}		X			
3. Aquatics: 6" concentration ≥ 1/2 acute LC_{50}		X			
Applicable PERS data:					
Applicable monitoring data: None except these resulting in use of peanut butter baits for fire ants. There are currently no registrations permitting this use.					
Others: (specify)					

		Yes	No
Monitoring Data	Data available in Hopewell area (atypical)		
Soil	Kepone generally not looked for is monitoring programs		
Water			
Air			
FDA Market Basket	Not examined for Kepone residues		
USDA Aphis			
Incident Reports			
Tolerances	.005 PPM bananas .01 PPM banana peels(Pet. 0E0919) Agency currently revising		
#Formulations/Products			

References:

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Section I.B Data Supporting Kepone RPAR Triggers

Trigger	Data	Test				Results
		Species	Length of Test	Dosages Resulting in Observed Effects		
Oncogenicity	(1) Report on Technical Grade Chlordecone. Carcinogenesis Program, Division of Cancer Cause & Prevention, National Center Institute, January 1976	RATS (Osborne-Mendel)	112 weeks	Oral Males Females	24 ppm 26 ppm	Statistically significant increase over controls ($P < .05$) of incidence of hepatocellular carcinomas
		MICE (B6C3F1)	90 weeks	Males Females 	20 ppm 23 ppm 20 ppm 40 ppm	
	(2) Toxicological Studies on Decachloro-Octahydro - 1, 3, 4- metheno-2H-cyclobuta (cd) pentalen-2-one. Data submitted in conjunction with Pesticide Tolerance Petition OE0919. Allied Chemical Co. July 1, 1961	RATS (Albino)	Periods between one & two years			Differences of opinion by four examining clinical pathologists existed as to the nature of observed hepatocellular carcinomas, the most serious diagnosis by an examining pathologist, is listed below:
				Oral Males (one) Males (one) Females (three) Females (one)	 25 ppm 25 ppm 10 ppm 25 ppm	 Hepatocellular carcinoma Evolving carcinoma Hepatocellular carcinomas Evolving carcinoma

Trigger	Data	Test			
		Species	Length of Test	Dosages Resulting in Observed Effects	Results
Reproduction	(3) Good, Ernest E., George W. Ware and David F. Miller, Effects of Insecticides on Reproduction in the Laboratory Mouse: I. Kepone, Journal of Economic Entomology, Vol 58, p. 754 (1965)	MICE (mixed lot used in initial test subsequent 3 tests BALB/C)	120 days	Oral 5 ppm to 37.5 ppm	Reduced reproduction rate in chlordecone-fed mice and in their progeny
	(4) Toxicological Studies on Decachloro-Octahydro-1,3,4- metheno-2H -cyclobuta (cd) pentalen-2-one. Data submitted in conjunction with Pesticide Tolerance Petition OE0919. Allied Chemical Company.	RATS	3 months	Oral Males 50 ppm 80 ppm	Testicular atrophy
	(5) Huber, James J., Some Physiological Effects of the Insecticide Kepone in the Laboratory Mouse, Toxicology and Applied Pharacology, Vol. 7, p. 516 (1965)	MICE (BALB/C)	130 days 160 days	Oral 10 to 37.5 ppm 40 ppm	Reduced reproduction rate No reproduction

Acute Toxicity to Humans and Domestic Animals

Discussion: Available data indicate chlordecone does not meet the criteria for RPAR trigger.

Does Chlordecone Meet or Exceed the Criteria for Oncogenic Effects on Man or other Mammals

Discussions:

Part 162.11(a)(3)(ii)(A) specifies that if the compound induces oncogenic effects in experimental mammalian species or in man as a result of oral, inhalation or dermal exposure; or induces mutagenic effects, as determined by multitest evidence; a rebuttable presumption shall arise. Available data indicate that chlordecone induces oncogenic effects in both sexes of mice and rats as a result of oral exposure. "The Report on Carcinogensis Program, Division of Cancer Cause and Prevention, National Cancer Institute, released in January 1976, reports the results of a long-term study on the oncogenic effects chlordecone on both sexes of Osborne-Mendel rats and B6C3F1 mice. Chlordecone was administered orally for a period of 80 weeks. The mice were sacrificed after 90 weeks and the rats after 112 weeks; moribund animals were sacrificed and necropsied. None of the control rats developed hepatocellular carcinomas. For the mice 16% of the male controls and none of the female controls developed heptacellular carcinomas. Pathological diagnosis revealed a statistically significant increase ($P < .05$) in the incidence of hepatocellular carcinomas in rats fed an average 24 ppm (males) and 26 ppm (females) and in mice fed an average of 20 and 23 ppm (males) and 20 and 40 ppm (females). Extensive hyperplasia of the liver was also reported in both species. This report presents a clear indication of chlordecone's oncogenicity.

Data submitted by Allied Chemical Company in conjunction with Pesticide Tolerance Petition OE0919, entitled "Toxicological Studies on Decachloro-Otahydro- 1, 3, 4-metheno-2H-cyclobuta(cd) pentalen-2-one" (Document No. 108253, July 1, 1961) also indicates that chlordecone is oncogenic in rats. Six groups of male and female albino rats were fed 0, 5, 10, 25, 50, and 80 ppm chlordecone respectively for periods of up to two years. Only seven male rats were examined at the 25 ppm dose level. Four clinical pathological examined the slides made from the liver tissue of these treated rats. Liver lesions in one rat were diagnosed as hepatocellular carcinoma by 2 pathologists and "evolving carcinoma" by one pathologist who also found "evolving carcinoma" in a second male rat at this feeding level. Of the sixteen female rats surviving at the 10 ppm feeding level, liver lesions in three were diagnosed as hepatocellular carcinoma by one pathologist. Of the nine female rats surviving at the 25 ppm level, liver lesions in one was diagnosed as "evolving carcinoma" by one pathologist. None of the 23 control rats developed heptocellular carcinomas.

The primary supportive data for this trigger is from NCI. The Allied Chemical Company test, which also indicates oncogenic effects, may not of itself be definitive enough to trigger for oncogenicity. The method of conducting the latter test, however, may have minimized the possibility of discovering heptocellular lesions. In the Allied test mice were numbered and survivors of a given numerical sequence were sacrificed and examined on selected dates. Examinations

were made only of rats surviving to these selected dates. Rats which died in the interim were not examined. It is probable that rats not surviving to a given examining date may have exhibited a higher incidence of hepatocellular lesions.

It must be observed that liver biopsies of humans suffering from chlordecone poisoning have shown this organ to have the highest content of chlordecone of any tissue in the body. Some samples have shown a mild toxic hepatitis on light microscopy.

Other Chronic or Delayed Toxic Effects

Discussion:

40 C.F.R. 162.11(a)(3)(ii)(B) provides that "(a) rebuttable presumption shall arise if a pesticide's ingredients . . . produces any other dosage up to a level, as determined by the Administrator, which is substantially higher than that to which humans can reasonably be anticipated to be exposed taking into account ample margins of safety . . . . ."

There may be difficulty in relating many pesticide uses to human exposure. The use of chlordecone baits is a case in point. The major use of kepone in the continental United States is as a roach and ant bait in houses and on lawns and gardens. Several registrations for kepone bait formulation enclosed or not enclosed in traps provide for general applications along baseboards, shelves, sills, or wherever ants may appear. Label directions do not always limit the amount of kepone bait that can be applied to a single room. Although these labels also provide a warning not to apply in areas accessible to children or domestic animals, the direction to apply where ants appear could result in application in areas clearly accessible. This is contradictory to the warning and could be followed before a warning is read.

Another use in which a certain amount of human exposure is entailed is the use of 5% chlordecone dust on banana plants in Puerto Rico. As noted on the CRPAR checklist (Section IA), there is only one registered product having this use. Directions call for surface application of 8 lbs. of active ingredient per acre and allow for application at six month intervals.

The direct hazard to humans would be a chronic dermal or inhalation effect. The acute toxic effects of chlordecone for these routes of exposure are, as noted, insufficient to trigger a RPAR.

The registered product label specifying this use prescribes a respirator for workers. The hazard of this use depends upon the degree of compliance with label directions. Label revisions might reduce neurological and reproductive hazards of chlordecone use. The words "might reduce the hazards" are used in connection with label revision because we obviously cannot insure that directions will be followed by all users nor do we currently know if they are being followed. Should we assume that label directions, if clear and precise and accompanied by adequate restrictions and warnings which if followed would mitigate or eliminate the human or wildlife exposure, are adequate to achieve those ends regardless of the nature of the given pesticide?

It is difficult to obtain information on the degree of label compliance for the multitude of users. The degree of compliance will obviously depend upon education and a host of socio-economic factors. Label directions of pesticides are one method the Agency possesses for controlling end use of pesticides. Many hazards to man, wildlife, and non-target species are possible through noncompliance with label directions of most pesticides.

To set a precedent of triggering an RPAR on this basis may be to insert an unnecessary stumbling block to an effective and necessarily expeditious review of the many possibly hazardous pesticides on the market and scheduled for Agency review. On the other hand, a RPAR is a mechanism through which information may be elicited. Because a presumption may be rebutted through the submission of exposure data or data showing that the Agency

presumption was erroneous, it does not constitute the Agency's final determination.

In addition, the effects of chlordecone exposure on many plant workers as well as the oncogenic and reproductive effects in laboratory mammals indicate that this compound is capable of extreme harm to man. Another pesticide compound may not trigger an oncogenic or mutagenic effect, yet may have other chronic effects which also indicate its potential harm to man. The triggering of RPAR by these other chronic effects is dependent upon human exposure. Can we always assume that adequate label precautions attempting to minimize human or wildlife exposure will always eliminate the hazard?

Reproduction

Discussion:

Several available studies on the effects of chlordecone on mammalian species indicate that chlordecone produces chronic effects on reproduction at levels ranging from 5-80 ppm. A 1965 experiment performed at Ohio State University on the effects of chlordecone on mouse reproduction revealed significant reductions in reproduction in mice fed chlordecone at dosages ranging from 5 ppm to 37.5 ppm.[1/] The progeny of the chlordecone-fed mice also suffered reductions in reproduction at the 5 ppm feeding level.

Another study performed at Ohio State University in 1965 revealed reduced numbers of progeny in mice fed chlordecone at 10-37.5 ppm dosages.[2/] At 40 ppm reproduction was entirely eliminated.

In addition, a 3 month rat study reported in Allied Chemical Company's Pesticide Tolerance Petition revealed testicular atrophy in male rats at dosage levels of 25, 50 and 80 ppm. Document No. 108285 pp. 16-17 (April 11, 1960).

Sperm analysis of chlordecone production workers exposed to extremely high levels showed absent or decreased sperm count with markedly decreased motility.

1/ Good, Ernest E., George W. Ware, and David F. Miller, Effects of Insecticides on Reproduction in the Laboratory Mouse: I. Kepone, 8 Journal of Economic Entomology 754 (1965).

2/ Huber, James J., Some Physiological Effects of the Insecticide Kepone in the Laboratory Mouse, 7 Toxicology and Applied Pharmacology 516 (1965).

Neurological Effects

Discussion:

Available studies on the effects of chlordecone on mammalian species indicates that chlordecone produces neurological effects at levels of 9.6 mg/kg and at levels ranging from 25-80 ppm. In a 20 day subacute oral toxicity study submitted in Allied Chemical Company's Pesticide Tolerance Petition 20 male rats fed 9.6 miligrams chlordecone per kilogram of body weight developed severe tremors after the fifth dose. In another chronic oral toxicity study submitted in Allied Chemcial Company's Pesticide Tolerance Petition, rats fed 80 ppm chlordecone developed tremors after the end of two weeks, rats fed 50 ppm developed tremors after three weeks, and female rats fed 25 ppm developed tremors upon stimulation after three months.

Tremors were also observed in test rodents at dosages ranging from 26 oppm to 40 ppm in the two year NCI study cited. It must be observed that in some of these tests effects were seen to be reversible upon cessation of feeding.

Tremors symptoms were almost invariably present in chlordecone plant workers subjected to extremely high exposure to kepone.

All of this is not surprising as the killing mode of action of this insecticide is its effect upon the insect's nervous system.

Fatality to Endangered Species

Discussion:

There appears to be no labeled use which would permit large scale use against fire ants. Except for the use against banana root borers, all other uses appear to be for homeowner use inside or outside the home. There is little or no possibility of hazard to endangered species from chlordecone in this regard.

The hazard to an endangered species or any species from the banana use, which is a surface application to the base of the banana stem, would appear to be primarily from runoff. We have no data on the extent of this runoff nor on residue levels in streams or in aquatic organisms. The extent of feeding by any wildlife at the base of banana plants is an unknown. There is no information presently available to the Agency that suggests that a species' survival is endangered by this use.

Acute Toxicity to Wildlife

Discussion:

There are currently no registered label directions permitting large scale use of chlordecone against fire ants. This would be the only possible use which might result in application to areas frequented by wildlife. As noted, the banana use is an unknown in this regard. This criteria for RPAR is specifically triggered only by application of pesticides to the feed crop of birds and mammals or by an aquatic use.

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This Position Document addresses the risks and benefits of pesticide products containing the subject active ingredient. The Agency has determined that the use of products containing the subject active ingredient may meet or exceed a risk criterion described in 40 CFR Part 154. Potential hazards will be examined further to determine the nature and extent of the risk, and considering the benefits of the subject active ingredient, whether such risks cause unreasonable adverse effects on the environment.

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