



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

MAY 13 1982

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Jay Ellenberger (12)
Registration Division

THRU: Orville E. Paynter, Chief
Toxicology Branch
Hazard Evaluation Division (TS-769)

SUBJECT: Exemption from tolerance for the pesticide chemical
carbaryl (1-naphthyl-N-methylcarbamate) and its
hydrolytic product (1-naphthol) in Oysters, amended
(March 26, 1982) to propose a tolerance of 0.25 ppm.
Petition#1E2554 CASWELL#160

Action Requested:

The Oregon Department of Agriculture, through Mr. W.H. Koesan, Administrator, Plant Division, requests an exemption from tolerance for carbaryl and its hydrolytic product (1-naphthol) in oysters to permit the use of carbaryl for control of ghost and mud shrimp in oyster beds in Oregon State prior to seeding oysters. In a letter (March 26, 1982) subsequent to the petition, the original requested action was amended to propose that a tolerance level of 0.25 ppm for residues of carbaryl and its hydrolytic product in oysters be granted.

Recommendation:

- 1) Reviewed toxicity data in our files adequately support approval of a tolerance level of 0.25 ppm for residues of carbaryl and its hydrolytic product (1-naphthol) in oysters.
- 2) The registrant should be informed of suggestions made by the Scientific Advisory Panel (Item 2 in this Review).

Formulation to be Used:

Sevin Carbaryl Insecticide, active ingredient 80% by wt., EPA Reg.#264-316.

Review:

1. Previously submitted toxicity data

No formal toxicological data were submitted in the petition, but a letter dated September 22, 1981, from J.S. Lovell, Union Carbide Agricultural Products Co., Inc. authorized use of company data on Sevin Carbaryl insecticide in support of Oregon State's petition. The following summary of toxicity data was taken from Dr. John Brantner's review of Petitions 1E2497 and 1E2498, dated October 29, 1981. (Also, a complete listing of Toxicology Branch "one-liners" is attached hereto).

Oral LD ₅₀ - Rat	510 mg/kg
Rat Teratology	No teratologic effects at highest level tested (375 mg/kg)
Monkey Teratology	No effects at highest level tested (20 mg/kg)
Dog Teratology	No effects at 3 mg/kg, terata at higher levels tested (6.5 mg/kg) See discussion page 4
Dominant Lethal Assay (Rat)	NOEL = 200 mg/kg/day (highest level tested)
*Three-Generation Reproduction Study	NOEL = 200 mg/kg/day (highest level tested)
One-Year Dog Feeding Study	NOEL = 400 ppm
2-Year Rat Feeding Study	NOEL = 200 ppm, slight systemic effects at 400 ppm
18-Month Mouse Oncogenicity Study	Negative at 400 ppm (highest level tested)
18-Month Mouse Oncogenicity Study	Negative at 14 ppm (Bionetic Study)

*One-liner revised during present review

NOEL = 100 mg/kg/day in diet
= 25 mg/kg/day via intubation

2. Scientific Advisory Panel

A Special Subcommittee of the FIFRA Scientific Advisory Panel convened to review scientific findings by EPA on carbaryl; the committee's report, dated September 19, 1980, is attached hereto. They determined that carbaryl:

- 1) is not carcinogenic,
- 2) is a weak mutagen,
- 3) is teratogenic in the dog and another study should be performed in this species;
- 4) has no reproductive toxicity in experimental animals,
- 5) should be studied further concerning its effects on human sperm morphology in workers manufacturing carbaryl and on testicular and sperm morphology and development in a rodent species,
- 6) has an interesting viral enhancement effect that should be further studied, but no regulatory action on this basis is necessary, and
- 7) dermal absorption through human skin should be studied.

They also concluded that additional epidemiology studies in man are not necessary but carbaryl's effect on wild rodent populations should be pursued and EPA should consider a label change to warn women of childbearing age about possible teratogenic effects.

3. Decision Document

The Agency data base of toxicological information on carbaryl also includes a 1980 pre-RPAR review document (Decision Document) and discussion of the document in the Federal Register (Determination Not To Initiate A Rebuttable Presumption Against Registration [RPAR] of Pesticide Products Containing Carbaryl; Availability of Decision Document, FR Vol. 45, No. 241, December 21, 1980 Notices). Evidence was considered regarding the teratogenic, fetotoxic, oncogenic, mutagenic, neurotoxic and viral enhancement effects of carbaryl. A decision was reached to return the pesticide to the registration process and to require additional data to support existing registrations and to negotiate appropriate label changes to ensure that exposure is held to reasonable levels.

Although all of the above-listed possible "triggers" to the RPAR process were addressed in the Document and discussion, the issues of major concern were the possible teratogenic/fetotoxic, mutagenic, oncogenic and viral enhancement effects.

Carbaryl has been studied in a wide variety of species for teratogenicity (mouse, rat, gerbil, hamster, guinea pig, rabbit, swine, sheep, monkey and dog); however some of these studies have been flawed for one reason or another. The pesticide was fetotoxic in the mouse, rat, and gerbil and teratogenic in guinea pigs, rabbits and dogs; but only in the dog were effects (terata) seen at levels not also causing maternal toxicity. However, quality of the dog studies has been questioned and the Agency is considering whether they should be repeated using a protocol meeting current standards.

Gene mutations were induced by carbaryl in bacteria, fruit flies, and cultural mammalian cells and chromosomal effects have been noted in mammals, plants and in cultural mammalian cells. Adverse gonadal effects have been observed in rodents and abnormal sperm head morphology has been seen in workers exposed to carbaryl. Yet the evidence that carbaryl (and/or its active metabolites) reached germinal tissue is only suggestive. Although the weight of evidence indicates that carbaryl may have the potential to act as a mutagen, it is not intrinsically a potent one in the reported studies.

It was concluded that adequate studies have been performed which show that carbaryl is non-oncogenic. Some Russian studies were suggestive of a positive effect but attempts to obtain sufficient data for an evaluation have been unsuccessful.

The finding of viral enhancement by carbaryl in one study is considered preliminary in nature and does not constitute a basis on which to conclude that the pesticide poses a human hazard in terms of this activity.

4. ADI and TMRC Considerations

The proposed tolerance will not essentially alter the percentage of the ADI utilized. This value, expressed only to two significant places, will remain at 78.03% since the contribution from this tolerance in oysters to the TMRC is only 0.00011 mg/day/1.5 kg, thus increasing this latter value from 4.6817 to 4.6818 mg/day/1.5 kg. A copy of the computer printout is attached.

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VDC
5/6/82
H. J. O. P.