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

MEMORANDUM NOV 6 1981

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

DATE: Oct. 29, 1981

SUBJECT: Proposed tolerance for the pesticide chemical Carbaryl in or on proso millet and flax. Petitions # 1E2497 and 1E2498, respectively. Caswell # 160

FROM: John Brantner, Ph.D. JAB 10/29/81
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TO: Clinton Fletcher
Minor Uses S/R

Action Request: The petitioner, IR-4, National Director Dr. R. H. Kupelian, on behalf of the IR-4 Technical Committee and the Agricultural Experiment Station of North Dakota requests the establishment of a tolerance for the residues of the insecticide carbaryl (1-napthyl N-methylcarbamate) in or on the raw agricultural commodity millet straw and seed at 1 ppm and flax straw and seed at 5 ppm resulting from the applicaton of carbaryl to the growing agricultural commodity, as proposed in Section B of this review.

Comments: RCB advises (memo from M. Nelson, Chemist, dated June 3, 1981) that the following carbaryl tolerances be established. Tox recommendations are based on these levels):

PP# 1E 2497 3 ppm in or on proso millet grain
100 ppm in or on proso millet straw.

PP# 1E 2498 5 ppm in or on flax seed
100 ppm in or on flax straw.

RCB also concludes (M. Nelson memo, June 3, 1981) that the existing tolerances for meat, milk, poultry and eggs will adequately cover any residues associated with the present petitions.

Section B - The amount, time, and frequency of application.

millet and flax: for control of grasshoppers and armyworms, apply 1 to 2 lb. active ingredient per acre. Treat when insect infestation approaches economic levels and signs of crop injury are visible. Do not apply within 42 days of harvest.

Recommendations: See comments at end of review

Note: There are no existing regulatory actions against carbaryl.

Review:

No toxicology data is contained in the petition, Union Carbide data is referenced (letter signed by J. S. Lovell authorizing use of Union Carbide data accompanied petition). The following summary of Tox considerations was extracted from Dr. Reto Engler's July 5, 1978 review of Petition # 8E2035.

Data base for tolerances:

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)
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)

*See below discussion on teratogenicity regarding the Carbaryl Decision Document.

Decision Document on Carbaryl:

A 1980 pre-RPAR review document (Notice of determination not to initiate an RPAR; FR 45:81869, 1980) considered the evidence regarding the teratogenic, fetotoxic, oncogenic, mutagenic, neurototoxic and viral enchancement effects of carbaryl. A copy of the FR notice and the associated Decision Document on carbaryl are attached to this (the present) review. The only studies reviewed in the Decision Document that showed effects at doses lower than 10 mg/kg/day (the NOEL based on the rat chronic feeding study considered above in the data base for tolerances) were two dog teratology studies, and these two studies were of questionable scientific validity, as discussed below.

Consideration of the Decision Document is relevant to the present registration action on carbaryl since the studies considered in the pre-RPAR review document comprise an additional data base for assessing the toxicity of carbaryl and for evaluating the NOEL for carbaryl.

Teratogenicity/Fetotoxicity: The Agency recognizes that carbaryl has been tested for teratogenic and fetotoxic effects in an extremely wide variety of mammalian species (mouse, rat, gerbil, hamster, guinea pig, rabbit, swine, sheep, monkey and dog). Of those studies from which definite conclusions may be drawn, carbaryl has been shown to produce terata in the guinea pig, rabbit and dog, of which defects were found in only one species (the dog) at doses below those causing maternal toxicity. In the dog studies the treated pregnant females had difficulty giving birth, a possible sign of carbaryl-induced maternal toxicity. In the Agency's judgement, the quality of the dog studies performed by Smalley et al. (1968) and Imming et al (1969), which were conducted more than a decade ago, does not meet current scientific standards. Insufficient numbers of animals were included in the dose groups, and inadequate attention was paid to the condition of the bitches throughout the period of dosing and to maternal and fetal blood levels of the compound.

In view of the fact that there are adequate prenatal studies in eight species, it would appear that carbaryl is not a potent teratogen. The same close dose relationship exists between maternal toxicity and forms of adverse fetal effects other than teratogenicity, i.e. fetotoxic effects. An epidemiological study of New Jersey residents showed there to be no difference between the birth defect rate for municipalities in three counties sprayed with carbaryl (for gypsy moth control) as compared to non-sprayed municipalities.

Mutagenicity: Carbaryl has been extensively tested for mutagenic effects. Carbaryl has been reported to produce gene (point) mutations in bacteria, mammalian cells in culture, and Drosophila. Carbaryl has been found to produce chromosomal aberrations in mammalian cells in culture, in plants and in whole animals; and carbaryl has been shown to cause primary DNA damage in cultured human cells. However, there are several inadequacies in the above mutagenicity studies.

Collectively, all these factors strongly suggest that carbaryl may act as a potential human mutagen. To cause heritable effects in man, however, a chemical with intrinsic mutagenicity must reach the germinal tissue. Evidence that carbaryl and/or its active metabolites reaches the gonads is only suggestive. Gonadal effects in males - e.g. abnormal sperm morphology, reduction in the number of spermatogonia and spermatozoa in the seminiferous tubules, and reduced sperm motility-have been observed in rodents exposed to carbaryl, however, most of these reports are flawed in terms of the rigor of the experiments performed or by inadequate presentation of data. In contrast, there are two studies that report no significant gonadal effects due to carbaryl. Two epidemiological studies of gonadal effects in carbaryl-exposed male carbaryl production workers were reviewed by the Agency in the October 1980 document. One study showed that the carbaryl-exposed workers had a higher precentage of depressed sperm counts than controls, but the difference was not statistically significant. The second study showed a statistical correlation between working in a carbaryl-exposed area and an alteration of human sperm (abnormal sperm head morphology). However, this study had serious weaknesses in its methodology, and also it did not demonstrate that carbaryl was the causative agent since the workers were exposed to pesticides other than carbaryl.

Other toxic effects: Several studies that have been performed to assess the oncogenic potential of carbaryl have shown it to be non-oncogenic. In contrast, Russian studies done in 1970 may have indicated some oncogenic effects for carbaryl but the studies could not be properly evaluated. Agency attempts to obtain further information necessary to evaluate the Russian studies have been unsuccessful.

Neurotoxic effects were observed in chickens and pigs, but at dose levels that were very much higher than the NOEL. Viral enchancement has been observed in one study on carbaryl, but the study was preliminary in nature and no definitive conslusions could be drawn regarding a human health hazard in terms of viral enhancement.

SAP Recommendations:

The FIFRA Scientific Advisory Panel (SAP) convened on 7/23/80 to review the Agency's scientific findings on carbaryl. A copy of the 9/19/80 memo from Dr. W. Fowler which expresses the SAP's findings is attached to the present memo, and the SAP's opinions and recommendations are summarized here: (1) Carbaryl is a widely applied insecticide and there is widespread human exposure. (2) Carbaryl was not teratogenic in several species tested, but appeared to be teratogenic in the dog, and an additional teratogenic study should be performed with this species. (3) Current data indicate that carbaryl is non-oncogenic and does not cause reproductive effects, and additional testing is not recommended in these areas. (4) Carbaryl is a weak mutagen; further testing is not recommended. (5) Follow-up studies of the reported changes in human sperm morphology in workers involved in carbaryl manufacture are recommended. In addition, the effect of several dose levels of carbaryl on testicular morphology and the development and morphology of sperm should be studied in an appropriate rodent species. (6) Additional epidemiology studies of the type previously conducted are not recommended.

Comments:

These requested tolerances will result in an increase in the % of ADI utilized from 77.97% to 78.03%; this increment does not represent a significant increase in exposure. The TMRC will be increased from 4.6781 to 4.6817, an increase of 0.0036 mg/day/1.5 kg (a 0.077% increase) as a result of the proposed tolerances.

File last updated 8/19/81

ACCEPTABLE DAILY INTAKE DATA

RAT, Older NOLL mg/kg	ppm	S.F.	ADI mg/kg/day	MPI mg/day/60kg
10.000	200.00	100	0.1000	6.0000

Published Tolerances

CROP	Tolerance	Food Factor	mg/day/1.5kg
Blackberries(15)	12.000	0.03	0.00540
Boysenberries(17)	12.000	0.03	0.00540
Collards(37)	12.000	0.08	0.01472
Dewberries(52)	12.000	0.03	0.00540
Beet greens(13)	12.000	0.03	0.00540
Kale(75)	12.000	0.03	0.00540
Loganberries(86)	12.000	0.03	0.00540
Mustard Greens(99)	12.000	0.06	0.01104
Parsley(110)	12.000	0.03	0.00540
Raspberries(135)	12.000	0.03	0.00540
Spinach(150)	12.000	0.05	0.00920
Swiss Chard(158)	12.000	0.03	0.00540
Turnip Greens(166)	12.000	0.03	0.00540
Apples(2)	10.000	2.53	0.37950
Apricots(3)	10.000	0.11	0.01686
Asparagus(5)	10.000	0.14	0.02146
Bananas(7)	10.000	1.42	0.21308
Beans(9)	10.000	2.04	0.30600
Blueberries(18)	10.000	0.03	0.00450
Broccoli(19)	10.000	0.10	0.01533
Brussel Sprouts(20)	10.000	0.03	0.00450
Cabbage,sauerkraut(22)	10.000	0.74	0.11037
Carrots(24)	10.000	0.48	0.07205
Cauliflower(27)	10.000	0.07	0.01073
Cherries(30)	10.000	0.10	0.01533
Chinese Cabbage(177)	10.000	0.03	0.00450
Citrus Fruits(33)	10.000	3.81	0.57179
Cranberries(44)	10.000	0.03	0.00450
Cucumbers,inc pickl(46)	10.000	0.73	0.10884
Eggplant(53)	10.000	0.03	0.00450
Escarole/endive(56)	10.000	0.03	0.00450
Grapes, inc raisins(66)	10.000	0.49	0.07358
Konlrabi(76)	10.000	0.03	0.00450
Lettuce(84)	10.000	1.31	0.19622
Melons(92)	10.000	2.00	0.30046
Nectarines(100)	10.000	0.03	0.00450
Okra(103)	10.000	0.07	0.01073
Olives(104)	10.000	0.06	0.00920
Peaches(114)	10.000	0.90	0.13490
Pears(116)	10.000	0.26	0.03832
Peas(117)	10.000	0.69	0.10424
Peppers(120)	10.000	0.12	0.01840
Plums,inc prunes(125)	10.000	0.13	0.01993
Pumpkin,inc squash(131)	10.000	0.11	0.01686
Salisfy(142)	10.000	0.03	0.00450
Sorghum(147)	10.000	0.03	0.00450

Strawberries(152)	10.000	0.18	0.02759
Summer Squash( )	10.000	0.03	0.00450
Tomatoes(163)	10.000	2.87	0.43122
Corn,all types(38)	5.000	2.51	0.18825
Cottonseed(41)	5.000	0.15	0.01125
Beets(14)	5.000	0.17	0.01303
Horseradish(77)	5.000	0.03	0.00225
Poultry(128)	5.000	2.94	0.22075
Parsnips(111)	5.000	0.03	0.00225
Peanuts(115)	5.000	0.36	0.02683
Radishes(133)	5.000	0.03	0.00225
Rice(137)	5.000	0.55	0.04139
Rutabagas(139)	5.000	0.03	0.00225
Salisfy(142)	5.000	0.03	0.00225
Soybeans(148)	5.000	0.92	0.06886
Turnips(165)	5.000	0.05	0.00383
Almonds(1)	1.000	0.03	0.00045
Filberts(58)	1.000	0.03	0.00045
Pecans(118)	1.000	0.03	0.00045
Walnuts(167)	1.000	0.03	0.00045
Potatoes(127)	0.200	5.43	0.01628
Eggs(54)	0.500	2.77	0.02078
Sweet Potatoes(157)	0.200	0.40	0.00120
Chestnuts(153)	1.000	0.03	0.00045
Celery(26)	10.000	0.29	0.04292
Maple syrup(201)	0.500	0.03	0.00023
Lentils(83)	10.000	0.04	0.00613
Dandelion(194)	12.000	0.03	0.00540
Wintersquash(171)	10.000	0.03	0.00450
Pistachio nuts(210)	1.000	0.03	0.00045
Wheat(170)	3.000	10.36	0.46633
Cattle(26)	0.100	7.18	0.01078
Goats(62)	0.100	0.03	0.00005
Hogs(69)	0.100	3.43	0.00515
Sheep(145)	0.100	0.19	0.00029
Horses(208)	0.100	0.03	0.00005
Kidney(203)	1.000	0.03	0.00045
Liver(211)	1.000	0.03	0.00045
Milk&Dairy Products(93)	0.300	28.62	0.12877

MPI	TMRC	% ADI
6.0000 mg/day/60kg	4.6593 mg/day/1.5kg	77.66

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Unpublished,Tox Approved PP 6E1874,6E1848,3E1036

CROP	Tolerance	Food Factor	mg/day/1.5kg
Rye(140)	3.000	0.03	0.00135
Oats(102)	3.000	0.36	0.01610
Barley( )	3.000	0.03	0.00135

MPI	TMRC	% ADI
6.0000 mg/day/60kg	4.6701 mg/day/1.5kg	77.97

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Current Action PP# 1E2497,1E2498

CROP	Tolerance	Food Factor	mg/day/1.5kg
Millet(94)	3.000	0.03	0.00135
Flax Seed(182)	5.000	0.03	0.00225

MPI	TMRC	% ADI

6.0000 mg/day 0kg 4.6817 mg/day/1.5k 78.03

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