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April 30, 2001

MEMORANDUM

SUBJECT: *CARBARYL* - 2nd Reassessment Report of the FQPA Safety Factor Committee.

NOTE: THIS REPORT REPLACES THE PREVIOUS REPORT OF THE FQPA SAFETY FACTOR COMMITTEE DATED DECEMBER 13, 2001 (HED Doc. No. 013891).

FROM: Brenda Tarplee, Executive Secretary
FQPA Safety Factor Committee
Health Effects Division (7509C)

THROUGH: Ed Zager, Chairman
FQPA Safety Factor Committee
Health Effects Division (7509C)

TO: Virginia Dobozy, Risk Assessor
Reregistration Action Branch 1
Health Effects Division (7509C)

PC Code: 056801

The Health Effects Division (HED) FQPA Safety Factor Committee (SFC) met on April 16, 2001 to re-evaluate the hazard and exposure data for carbaryl and maintained that the FQPA safety factor (as required by the Food Quality Protection Act of August 3, 1996) should be retained at 10x when assessing the risks posed by this pesticide. This report replaces the previous report of the FQPA Safety Factor Committee dated December 13, 1999 (HED Doc. No. 013891).

I. HAZARD ASSESSMENT

(*Correspondence:* V. Dobozy to B. Tarplee dated April 02, 2001)

Since the last FQPA SFC meeting (November 29, 1999), the toxicology data base for carbaryl was re-evaluated by the HED Hazard Identification Assessment Review Committee (HIARC) on March 1, 2001.

1. Adequacy of the Toxicology Database

The toxicology data base for carbaryl is incomplete. There is a data gap for the multi-generation reproduction study in rats. The registrant has stated that this study is in progress.

Acceptable guideline prenatal developmental studies in rats and rabbits have been submitted to the Agency. Additionally, there is a developmental neurotoxicity study for carbaryl, however, there is uncertainty about the developmental neurotoxicity NOAEL/LOAEL. Significant changes in some of the brain morphometric measurements were observed in offspring at the high dose; only control and high dose groups were examined. EPA requested that measurements of the low- and mid-dose groups be completed. The registrant responded that the requested examinations were not possible because the tissues of the low- and mid-dose animals have been stored in a fixative for two years, which caused shrinkage. Therefore, comparison to the control group, which was not similarly stored, would not be valid. A re-examination of the control and high-dose groups was conducted. The re-assessment uncovered errors in some measures and confirmed some of the original findings. The additional statistical analyses, which attempted to account for multiple comparisons, rendered far fewer statistically significant findings, but some results, including data on pup cerebellar length, remained statistically significant. The decrease in the length of the cerebellum in 10 mg/kg/day (high dose) female pups is still regarded as a treatment-related effect.

At the March 1, 2001 HIARC meeting, the Committee concluded that, while the alterations were limited to the cerebellum in females, they were most likely treatment-related. However, the toxicological significance of the finding is unknown as: there was no evidence of a functional effect resulting from the cerebellar alterations, such as gait dysmetria or ataxia; there was no compensatory increase in other portions of the brain, as could be anticipated in response to the decrease in the cerebellar measurements; there was no change in the weight of the cerebellum to accompany the decrease in the cerebellar measurements; and there were no alterations in the morphometric measurements in males.

2. Determination of Susceptibility

The HIARC concluded that there is no evidence of increased fetal susceptibility in the prenatal developmental studies in rats and rabbits. Since there is a data gap for the multi-generation reproduction study in rats, susceptibility following pre-/post-natal exposure to

carbaryl cannot be assessed. Likewise, an assessment of susceptibility in the developmental neurotoxicity study cannot be made since critical information is not available.

The FQPA SFC recommended that morphometric measurements such as those in question in the developmental neurotoxicity study be made in the multi-generation reproduction study in rats in an attempt to address the uncertainties associated with the effect of concern (i.e., morphometric changes observed in the high dose animals which cannot be assessed at the lower doses). The HIARC concurred with this recommendation.

3. Open Literature Findings

In the scientific literature, there are two relatively recent studies which demonstrated effects on sperm at high doses (50 and 100 mg/kg/day) of carbaryl. The results of these two studies indicated that carbaryl caused weight reductions in the testes, epididymides, seminal vesicles, prostate and coagulating glands of young rats; changes in testicular enzymes; decreased sperm counts and sperm motility; increased sperm morphological abnormalities; and moderate atrophy of seminiferous tubules of the testes.

In a published developmental study in Fisher 344 rats conducted by EPA's Health Effects Research Laboratory, carbaryl was administered from gestation day 6 through 19 at doses of 78 or 104 mg/kg/day. Clinical signs related to cholinesterase inhibition (tremor, motor depression, jaw clonus and lacrimation) were observed in dams but it is unclear if they occurred at both dose levels. There was also increased prenatal mortality at the high dose (104 mg/kg/day) and decreased pup weights at the low (78 mg/kg/day) doses.

In an unpublished developmental neurotoxicity study in SD rats from the National Health and Ecological Effects Research Laboratories at EPA and the National Institute for Environmental Health Sciences/National Toxicology Program carbaryl was administered by gavage at doses of 0, 6, 12 or 25 mg/kg/day. The chemical or its metabolite 1-naphthol was not present in pups' plasma above the limit of detection at any exposure concentration (0, 6, 12 or 25 mg/kg/day). There was a dose-related decrease in ChE activity in the brain and blood of dams at GD 19, and fetuses taken at that time also showed a very similar level of inhibition in fetal brain cholinesterase. There was a decrease in the number of live pups/litter at the high dose. There were no changes in cognitive function. Equivocal changes in Functional Observational Battery parameters were observed in male and female offspring.
In a recent epidemiology study, the effects of exposure of male farmers in Ontario, Canada, to agricultural pesticides and pregnancy outcome was investigated.[1] Miscarriage

[1] Savitz DA, Arbuckle T, Kaczor D, Curtis KM (1997). Male Pesticide Exposure and Pregnancy Outcome. Am J Epidemiol 146(12):1025-36.

risk was not associated with participation in farm activities for all types of chemical applications, but was increased in combination with reported use of thiocarbamates, carbaryl and unclassified pesticides on the farm (Odds ratio = 1.9, 95% C.I. 1.1-3.1). There was no association between use of carbaryl and preterm delivery, small for gestational age or altered sex ratio measurements.

II. EXPOSURE ASSESSMENT

1. Dietary (Food) Exposure Considerations
(*Correspondence:* V. Dobozy to B. Tarplee dated April 02, 2001)

Carbaryl is a broad spectrum insecticide registered for use on almost all crop groups and numerous miscellaneous commodities including pome fruit, stone fruit, legumes, cereal grains and fruiting vegetables. Permanent tolerances are established for residues of carbaryl in/on many agricultural commodities ranging from 0.1 to 100 ppm (40CFR§80.169). Transfer of residues to meat, milk, poultry, and eggs is possible and tolerances for these commodities are established. Codex MRLs have been established for numerous commodities including fruits, grains, forage/fodder, and livestock commodities.

Carbaryl is used on many foods which are highly consumed by infants and children, including bananas, citrus fruits, peaches, beans, carrots, milk, meats, cereal grains and soybeans (1993 NAS report, Pesticides in the Diets of Infants and Children). Residues of carbaryl, however, are primarily surface residues and are, therefore, likely to be significantly removed from raw fruits and vegetables during normal preparation such as washing and peeling. The HED Metabolism Assessment Review Committee (MARC) has determined that only parent carbaryl should be regulated for plants, however, for livestock commodities, free and conjugated forms of carbaryl, 5,6-dihydro-5,6-dihydroxy carbaryl, and 5-methoxy-6-hydroxy carbaryl should be regulated.

Additional data are required for the dermal use of carbaryl on poultry and its use in poultry houses. In the previously conducted dietary assessment, the current tolerance for poultry was used, and as a result, poultry was determined to be a significant contributor to the risk estimate.

A variety of residue data sources are available for carbaryl, including field trial data, Pesticide Data Program (PDP) monitoring data, FDA surveillance data, and recently submitted Carbamate Market Basket Survey data. A Quantitative Usage Analysis (QUA) was also provided by Biological and Economic Analysis Division (BEAD) for this pesticide (Frank Hernandez; July 21, 1998).

The HED Dietary Exposure Evaluation Model (DEEM) will be used to assess the risk from acute and chronic dietary exposure to carbaryl residues in food. Theses analyses will be conducted at the highest level of refinement available using PDP, FDA, carbamate market basket survey data and percent crop treated information where possible.

2. Dietary (Drinking Water) Exposure Considerations
(*Correspondence:* V. Dobozy to B. Tarplee dated April 02, 2001)

The environmental fate data base for carbaryl is adequate for the characterization of drinking water exposure. Fate data indicate that parent carbaryl and its degradate 1-naphthol are fairly mobile and slightly persistent. In general they are not likely to persist or accumulate in the environment, however, under acidic conditions with limited microbial activity they may persist.

Because of the relatively limited persistence of the compound in the environment it is unlikely that non-targeted monitoring studies will detect the maximum concentrations that occur. Some non-targeted monitoring data are available but are of limited utility in developing EECs for ecological and human health risk assessment. Therefore modeling was used to estimate surface water and groundwater concentrations that could be expected from normal agricultural use. The results of the modeling are supported by the available monitoring data.

For developing surface water, EECs computer modeling with the EPA PRZM3.12 and EXAMS 2.97.7 programs were used to estimate the concentration of carbaryl in surface water. Index reservoir scenarios corrected for Percent Cropped Area (PCA) for representative crops were used. SCI-GROW was used to calculate a groundwater screening exposure value to be used in determining the potential risk to human health.

3. Residential Exposure Considerations
(*Correspondence:* V. Dobozy to B. Tarplee dated April 02, 2001)

Carbaryl is currently registered for many residential uses. Homeowner handler exposure scenarios exist for a variety of use patterns including applications of dusts to vegetables, ornamentals, and pets (dogs & cats); applications of ready-to-use products for nuisance insect control; applications of liquid sprays with a variety of hand equipment to gardens, trees, vegetables, and turf; and applications of granular formulations to turf. Carbaryl can be used in outdoor residential areas and to treat pets. Therefore, a number of residential post-application exposure scenarios exist for toddlers and children.

Several chemical- and scenario-specific studies designed to quantify exposures to homeowner applicators are available. There are a number of dislodgeable foliar residue studies for carbaryl that have been used for home gardening activities. Also, there are

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TTR data from 3 sites (CA, PA, GA) that have been used for the dermal risk assessments (i.e., transferability is >1%). Mouthing behaviors have been addressed using the new 5% factor for wet hands and not the TTRs as stipulated in the latest updates to the Residential SOPs. These data will be used, where appropriate, to calculate residue concentrations and exposures over time instead of using the Agency default assumptions. In addition, the latest Outdoor Residential Exposure Task Force (ORETF) data for homeowner applications to turf have been used which are also the same values that have been incorporated in the Residential SOPs. For any other remaining scenarios not addressed by the Aventis or ORETF data, PHED or the Residential SOPs were used.

III. SAFETY FACTOR RECOMMENDATION AND RATIONALE

1. FQPA Safety Factor Recommendation

The FQPA SFC recommended that the safety factor for protection of infants and children (as required by FQPA) should be **Retained at 10x.**

2. Rationale for Retaining the FQPA Safety Factor

The FQPA SFC concluded that the safety factor should be retained because:

- The toxicology data base for carbaryl is incomplete; there is a data gap for the multi-generation reproduction study in rats;
- an assessment of susceptibility following pre-/post-natal exposure to carbaryl could not be made due to the data gap for the multi-generation reproduction study in rats; and
- there is concern for the results of the developmental neurotoxicity study: a definitive NOAEL/LOAEL can not be established (the requested brain morphometric measurements in the low- and mid-dose groups can not be made) and fetal susceptibility cannot be determined.

3. Application of the Safety Factor - Population Subgroups / Risk Assessment Scenarios

When assessing **Acute and Chronic Dietary Exposures and Residential (Non-occupational) Exposures of All Durations,** the safety factor should be **Retained at 10x** for **All Population Subgroups** since there is concern for the results of the developmental neurotoxicity study; and since there is a data gap for the multi-generation reproduction study in rats which could provide information relevant to all population subgroups (regardless of age or gender).

FQPA SAFETY FACTOR COMMITTEE MEETING

APRIL 16, 2001
CARBARYL (Revisit)

Name	Division/Branch
Jose Rosario	HED/SIMB
Susan Makris	HED/TOX
Jon Flenchaus	OGC
Ray Kent	HED/RRB4
Jason Polmen	EFED
Felecia Fort	HED/RRB1
Jeff Dawson	HED/RRB1
Mike Metzger	HED/RAB1
Betty Shackleford	SRRD/RB3
Whang Phang	HED/RRB1
Susan Hanley	FEAD(HED)/GISB
Laurence Libelo	EFED/ERB IV
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