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

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Data waiver request for Trichloromelamine; Record No. 205204; Caswell # 877; Project # 8-0170

TO: C. Jeffery Kempter
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FROM: James N. Rowe. Ph.D. James N. Rowe 2/3/88
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THRU: Quang Q. Bui, Ph.D. Quang Q. Bui 2/11/88
Section Head, Section V
Toxicology Branch/HED (TS-769C)
and
Theodore Farber, Ph.D. W. Farber 2/10/88
Chief, Toxicology Branch
Hazard Evaluation Division (TS-769C)

ACTION: Review of Drackett Company submission re: Trichloromelamine Data Call-In dated March 4, 1987; Record No. 205204; Caswell # 877; Project # 8-0170

CONCLUSIONS/RECOMMENDATIONS:

Based on the assumption that Trichloromelamine (TCM) instantaneously breaks down into hypochlorous acid and melamine in the presence of organic material and therefore the TCM molecule is not present for subchronic or chronic exposure, the relative toxicity of the breakdown products have been evaluated. There is no evidence to presently indicate that hypochlorous acid presents a significant human hazard. Melamine, the second breakdown product of TCM, is not acutely toxic nor mutagenic. Cyromazine, a pesticide whose main metabolite is melamine, is a developmental toxicant in rabbits. However, margins of-safety for daily dermal or oral exposures to melamine, based on developmental toxicity (680, 407, respectively), do not indicate that exposure to melamine during the disinfection of food utensils presents an undue hazard to food workers involved in the washing of these utensils. Oncogenic risks for either dermal or oral exposure scenarios are not unduly high either ($10^{-5}$).

If RCB determines 1) that TCM instantaneously breaks down into the aforementioned constituents and 2) the exposure scenarios submitted by the registrants are acceptable, then it is recommended that the toxicology data requirements for TCM be waived. If on the other hand this is not found to be true, then the necessity for Tier I tests will have to be considered--as stated in the Data Call-In Notice for Subchronic and Chronic Toxicological Data for Antimicrobial Pesticide Active Ingredients dated March 4, 1987.

DATA EVALUATION RECORD

TRICHLOROMELAMINE

Trichloromelamine (N, N', N''-trichloro-s-triaminotriazine: TCM) is purported by the registrant to break down "instantaneously" in the presence of organic material to yield hypochlorous acid and melamine (pg. 3, Section III, Chemistry of Trichloromelamine; registrant submission). The data submitted by the registrant seem to support this contention but Toxicology Branch defers to RCB for an assessment of this statement. Based on this assumption, the issue is not the necessity for toxicology data for TCM but a determination of the toxicity of the breakdown products, hypochlorous acid and melamine.

Toxicity of hypochlorous acid

As noted by the registrant, hypochlorous acid has been evaluated previously by EPA in regard to the reregistration of pesticide products containing sodium and calcium hypochlorite salts as the active ingredients (Case Number 0029, February 1986; EPA No. 540/RS-86 154). The EPA concluded that there was no need for chronic or subchronic data due to the relatively small hazards associated with their use, the lack of significant chronic dietary exposure at the levels (0.2 to 1.0 ppm) presently used in drinking water, the lack of deleterious effects reported after over a century of use in water systems for disinfection and the fact that hypochlorites are generally recognized as safe for use as post harvest fungicides and as sanitizers of food handling utensils.

Toxicity of melamine

Acute toxicity/Mutagenicity/teratogenicity:

Melamine is minimally acutely toxic with oral LD50 values in B6C3F1 mice of 3.3 and 7.0 gm/kg b.wt. (male, females, respectively) and 3.2 and 3.8 gm/kg b.wt. in Fisher 344/N rats (males, females, respectively) (IARC Monograph, Vol. 39, pg. 341, 1986).

Melamine has not been shown to be mutagenic in the Ames test with various tester strains, in the HGPRT CHO cell forward mutation assay, in the UDS rat hepatocyte assay, in a sex-linked dominant lethal assay with Drosophila melanogaster or in the mouse bone marrow micronucleus test (IARC Monograph, Vol. 39, pg. 341, 1986).

Evidence for teratogenic effects in melamine, per se, are limited. In an intraperitoneal study, no toxicity or gross malformations were found in pregnant rats injected with 70 mg/kg b.wt. on gestation days 5 and 6, 8 and 9 or 12 and 13 (IARC Monograph, Vol. 39, pg. 340). However, Cyromazine, whose principal metabolite is melamine, has been adequately tested in rabbits (Core Minimum data; memo of Q. Bui to A. Heyward, dated 2/4/85). The developmental toxicity NOEL was established at 5 mg/kg/day with findings of cyclopia and diaphragmatic hernia at 10 mg/kg/day (developmental toxicity LEL).

Margins-of-safety for "melamine" are presented below using the Cyromazine rabbit developmental toxicity study:

DEVELOPMENTAL TOXICITY MOS USING CYROMAZINE AS SURROGATE FOR MELAMINE:

| Daily exposure[a] (mg/60 kg b.wt) | | MOS* |
|---|---|---|
| Dermal(rinsewater) | = 0.00836 mg/kg b.wt. | 407 |
| Oral (drinking glass) | = 0.005 mg/kg b.wt. | 680 |

[a] see oncogenic section below for origin of exposure estimates

* MOS = $\frac{\text{developmental NOEL; 0.68 x Cyromazine NOEL(5 mg/kg/b.wt.)}}{\text{exposure}}$

(0.68 is the fraction by weight of melamine to Cyromazine)

Chronic toxicity/oncogenicity:

Melamine has been previously evaluated in conjunction with a parent compound, cyromazine, primarily from a chronic toxicity/oncogenicity standpoint (FR 49(83) 18120-18124, April 27, 1984). This endpoint is of primary concern in considering the chronic exposure to TCM, either from dermal exposure in the washing of utensils or ingestion of residues found on utensils washed with TCM solutions. After examining the chronic data generated by NTP and Ciba-Geigy, and the FDA Cancer Assessment Committee, it was the conclusion of EPA that the available data does not indicate a risk, or at worse, the oncogenic risk from ingestion of melamine is remote. These carcinomas were associated with bladder stones (calculi) and it is likely that the bladder tumors are produced only in the presence of the calculi. Nevertheless the EPA recommended using a quantitative risk assessment from the positive data for bladder tumors observed in male rats at the high dose level of 4500 ppm since a threshold effect can not be proven conclusively at this time.

In order to estimate the potential risk from exposure to melamine derived from the breakdown of TCM in contact with organic material, the Q* derived from the NTP study, alluded to above, has been used in conjunction with reasonable exposure estimate to project the potential oncogenic risk from dermal or oral exposure to melamine. These exposure estimates are based on data presented by the registrant with some modification to make the projected risks somewhat more conservative and to take into account dermal absorption data indicating higher potential absorption rates (based on Cyromazine) than recommended by the registrant:

"ONCOGENIC" LIFETIME RISK FOR MELAMINE:

Oral exposure from using TCM contaminated food utensils(drinking glass)

| Concentration§ | (mg/60 kg b. wt.)$^{-1}$ | Q* | Projected "risk" |
|---|---|---|---|
| 0.15 mg/L x 2 L¶ | .3/60 = .005 mg/kg x | 2.4 x $10^{-3}$[a] | = 1.2 x $10^{-5}$ |

¶ assuming ingestion of 2 liters of liquids per day
§ concentration on glass taken from Section V of registrant's submission
[a] Q* from memo of Q. Bui to A. Castillo, dated Dec 18, 1986 re: proposed tolerances for the combined residues of Cyromazine (Larvadex) and its metabolite, melamine...; Petition No. 6F 3422)

Dermal exposure from using TCM solution to wash food utensil

| Concentration§ x | Dermal surface[b](arms,hands) x | dermal absorption† |
|---|---|---|
| 123.5 mg/L | 2,030 $cm^2$ x.01cm (.0203 L) | 0.2 |

| x (mg/60 kg b. wt.)$^{-1}$ | x Q*[a] | Projected "risk" |
|---|---|---|
| 0.00836 mg/kg | (2.4 x$10^{-3}$) | = 2.0 x $10^{-5}$ |

§ potential concentration of melamine in rinsewater, taken from Section V of registrant's submission
† 20% dermal absorption (average of three concentrations used) assumed based on cyromazine dermal study 10 hour data (memo of S. Dapson to R. King, dated Aug 14, 1987 re: dermal absorption study in rats with Cyromazine; EPA Accession No. 40168601)
[a] Q* from memo of Q. Bui to A. Castillo, dated Dec 18, 1986 re: proposed tolerances for the combined residues of Cyromazine (Larvadex) and its metabolite, melamine; Petition No. 6F 3422)
[b] surface area of hands and forearms taken from Durham and Wolfe (1962); 0.01 cm = wetting area taken from registrant submission, pg. 19

Conclusions

Based on the assumption that Trichloromelamine (TCM) instantaneously breaks down into hypochlorous acid and melamine in the presence of organic material and therefore the TCM molecule is not present for subchronic or chronic exposure, the relative toxicity of the breakdown products have been evaluated. There is no evidence to presently indicate that hypochlorous acid presents a significant human hazard. Melamine, the second breakdown product of TCM, is not acutely toxic, nor mutagenic. Cyromazine, a pesticide whose chief metabolite is melamine, has reported developmental toxicity in rabbits. However, margins of-safety for daily dermal or oral exposures to melamine based on developmental toxicity (680, 407, respectively) do not indicate that exposure to melamine during the disinfection of food utensils presents an

undue hazard. Oncogenic risks for either dermal or oral exposure scenarios are not unduly high either ($10^{-5}$).

Therefore, if RCB determines that the contention of the registrant is essentially correct, i.e., that TCM instantaneously breaks down into the aforementioned constituents, then it is recommended that that the toxicology data requirements for TCM be waived. If on the other hand this is not found to be true, then the necessity for Tier I tests will have to be considered--as stated in the Data Call-In Notice for Subchronic and Chronic Toxicological Data for Antimicrobial Pesticide Active Ingredients dated March 4, 1987.