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MEMORANDUM

SUBJECT: ETOFENPROX (ETHOFENPROX): Decision Regarding
Reclassification Consideration by the HED
Carcinogenicity Peer Review Committee

FROM: SanYvette Williams-Foy, D.V.M. *SanYvette Williams-Foy 8/27/96*
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THROUGH: Clark Swentzel, Section Head *Clark Swentzel 8/27/96*
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and

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The HED Carcinogenicity Peer Review Committee (CPRC) met on May 15, 1996 to evaluate additional information submitted by the registrant, Mitsui Toatsu, regarding the carcinogenic potential of etofenprox. Their objective was to demonstrate a threshold mechanism for the thyroid tumors in rats. Their request was for reconsideration of and reclassification from a Group C chemical with a Q* to a Group D or E chemical.

The CPRC determined that the reclassification was not totally supported because: 1) A thyroid-pituitary imbalance is not supported; 2) Induced cellular hypertrophy via thyroid follicular stimulation at the TSH receptor sites is marginally supported; 3) Microsomal enzyme induction in the liver is weakly supported; 4) Lesion progression is not supported; 5) There was a dose-response only for combined tumors; and 5) Structure activity relationship is not supported. Negative genotoxicity is supported, however. Based on this, the Group C Q classification remains.



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MEMORANDUM

SUBJECT: ETOFENPROX (ETHOFENPROX): Second Visit to the Health Effects Division Carcinogenicity Peer Review Committee to Assess Additional Information

FROM: SanYvette Williams-Foy, D.V.M.
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TO: Esther Rinde, PhD.
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THROUGH: Clark Swentzel, Section Head
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and

Stephanie Irene, Ph.D., Acting Branch Chief
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Health Effects Division

The HED Peer Review Committee is requested to evaluate additional information submitted by the registrant, Mitsui Toatsu, regarding the carcinogenic potential of etofenprox. Their objective is to demonstrate a threshold mechanism for the thyroid tumors in rats. They have supplied additional information to support their request for reclassification from Group C with a Q* to a Group D or E. A data package consisting of a summary of studies submitted to the Office of Pesticide Programs as well as the Data Evaluation Reports of critical studies are attached.

A. BACKGROUND INFORMATION

Ethofenprox (2-(4-Ethoxyphenyl)-2-methylpropyl-3-phenoxybenzylether) is a phenoxybenzylether insecticide considered a synthetic pyrethroid by the manufacturer proposed for indoor, household use. With aerosol or fogger use in kitchens, indirect contamination of foods may reasonably be expected.

1. Carcinogenicity

The following studies were used in determining the carcinogenic potential of etofenprox:

1. "Etofenprox (MTI-500) Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats". Huntingdon Research Center, England. Study No. MTC 59/85581. Final Report Date 12/15/87. EPA MRID No. 404497-07.

Etofenprox was administered for 2 years in the diets of Sprague-Dawley rats at levels of 0, 30, 100, 700, or 4900 ppm, which came to 1.1, 3.7, 25.5 or 186.7 mg/kg/day in males and 1.4, 4.8, 34.3, or 249.1 mg/kg/day in females, respectively. There were no survival problems for either sex. For females, there was a statistically significant increase in comparison to controls for thyroid follicular cell adenomas at 4900 ppm and a significant positive trend in this tumor type for both sexes. There were no significant trends or pairwise comparisons for either sex in thyroid follicular carcinomas or thyroid parafollicular carcinomas. The incidence of thyroid follicular cell adenomas and carcinomas combined in the 4900 ppm group was statistically significantly increased compared to controls in both sexes and there were significant positive trends for these combined tumors for both sexes as well.

Historical control data were provided for thyroid tumors from studies conducted between 3/82 and 8/85. Combined thyroid follicular cell carcinomas and adenomas ranged from 3.6 to 16.7% in males, and from 0 to 6% in females. In the present study, the high dose percentages of these tumors were 16% for females and 24% for males, both outside the historical control ranges.

Other findings included:

- 1) Statistically significant decreases in body weight gain in both sexes (13.2% in males, 7.2% in females) at the high dose;
- 2) Significantly ($p < 0.05$) increased thyroid weights in high dose males at week 26 and mid and high dose males at week 107; some cystic follicles in females (4/50 controls vs. 13/50 at 4900 ppm); increased follicle cell height in 5/10 females at 4900 ppm at 26 weeks; and decreased T3 levels in high dose females at week 25;
- 3) Significantly increased liver weights in both sexes at 4900 ppm at 26, 52, and 107 weeks; enlarged livers in both sexes at the high dose at 26 and 52 weeks and high dose males in the main study (at 2 years); centrilobular hepatocyte enlargement in high dose males and females at terminal sacrifice (0 in controls vs. 5/27 males, 8/26 females), with similar increases at 26, but not 52 weeks (9 males and 3 females); focal areas of eosinophilic hepatocytes in mid and high dose males and

high dose females; high dose females also showed vacuolated eosinophilic hepatocytes; and hepatocyte necrosis/inflammation in high dose females (5/27 vs. 0 in controls).

The high dose tested (4900 ppm) was considered adequate for carcinogenicity testing based on the results in males (e.g. body weight) and on the effects seen in both sexes in the 13 week study at 10,800 ppm. In the female, the level appeared to approach one that would have caused significant toxicity. Further, the Committee indicated that the selection of 4900 ppm as a high dose based on the effects seen in 90 days at 10,800 ppm, which included liver histopathology and significant body weight changes, was reasonable.

2. "Ethofenprox (MTI-500) Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Mice". Huntingdon Research Center, England. Study No. MTC 58/85582. Final Report Date 1/6/86. EPA MRID No. 404497-09.

Ethofenprox was administered for 108 weeks in the diets of CD-1 mice at levels of 0, 30, 100, 700, or 4900 ppm, which came to 3.1, 10.4, 75.2 or 546.9 mg/kg/day in males and 3.6, 11.7, 80.9, or 615.5 mg/kg/day in females, respectively. For females, there were no survival differences and no significant increase in any tumors. For males there were statistically significant increases in deaths at the 100 and 4900 ppm doses by pairwise comparison, and a significant increasing trend in mortality. Male mice had a significant dose related trend in renal cortical adenomas alone and combined carcinomas and adenomas. There were no significant pairwise comparisons, however. The incidence of the carcinomas (1/58) in high-dose males was higher than in the control groups of 7 out of 9 studies cited for their historical control incidence.

Other effects included:

- 1) Significantly decreased body weights in males at 700 and 4900 ppm;
- 2) Liver weights increased in high-dose (4900 ppm) males at weeks 26 ($p < 0.05$), 52 ($p < 0.05$), and 104 (not sig.); in high-dose (4900 ppm) females only at week 104 ($p < 0.05$);
- 3) Gross pathology revealed only effects on the kidneys, namely cortical scarring in 4900 ppm males at weeks 26 and 52 and "pale kidneys" in 3/12 4900 ppm males at week 52;
- 4) Non-neoplastic lesions included dose-dependent dilated/basophilic renal tubules in treated males and females, with increased severity at the high dose; and centrilobular liver cell enlargement in 4900 ppm males at 52 weeks.

The high dose tested caused pronounced toxicity in males and some clear toxic effects in females, i.e. kidney lesions. Thus, the dose levels used in the study were judged to be adequate for assessing carcinogenicity.

2. Mutagenicity

There were a variety of acceptable mutagenicity studies, including 2 negative Salmonella assays, a negative micronucleus assay, 2 negative human lymphocyte clastogenicity studies; and negative studies for DNA damage/repair and unscheduled DNA synthesis.

3. Structure Activity Relationships

While the registrant considered Ethofenprox a pyrethroid, it differs in structure in that it lacks a carbonyl group.

Fenvalerate, a pyrethroid somewhat related to ethofenprox, has been tested in rats at doses up to 250 ppm and in mice at doses up to 1250 ppm and reported not to be carcinogenic. However, in a single dose 2 year rat study, 1000 ppm in the diet caused spindle cell sarcoma in males. Fenvalerate also has been reported to cause cytogenetic effects in mouse bone marrow, but cytogenetic studies available on ethofenprox are negative.

It should be noted that ethofenprox contains a dibenzyl ether moiety. Dibenzyl ether has been associated with carcinogenicity. However, available metabolism data on ethofenprox in rats and dogs indicate that the molecule remains intact and is not split at the ether linkages.

4. Carcinogenicity Peer Review Committee (CPRC) Findings

The Peer Review Committee met on 5/31,89 (Memo from W. Sette 4/12/90) and concluded that, based on the weight of evidence, etofenprox should be classified as a Group C, possible human carcinogen. A quantitative risk assessment (B. Fisher, 1/9/90) indicated that the unit risk, Q_1 of etofenprox is 5.1×10^{-3} (mg/kg/day). This estimate is based upon thyroid follicular cell tumors (adenomas and/or carcinomas).

The Group C classification was based on: toxicologically significant increases in combined thyroid adenomas/carcinomas in male and female rats; and the fact that their incidence was outside the historical control range. The Peer Review Committee also concluded that the kidney tumors in mice were not a significant carcinogenic effect because the effect was not statistically significant by pairwise comparison to

controls, because the incidence of carcinomas was within the historical control range, and because there was both significant kidney damage in mice with tumors and significant mortality in the high dose group.

B. Registrant's Rebuttal Concerning the Carcinogenicity of Etofenprox

Reference: Todhunter, J.A., Kumaroo, P.V., and Thilagar, A.K. (1995). Data, Information and Documentation in Support of a Reclassification Request for Etofenprox; SRS International Corp, Washington, DC/SITEK Research Laboratories, Rockville, MD; Study No. MIT095.R01; Study Completion Date: June 30, 1995. (Unpublished) MRID NUMBER: 43705301

Mitsui Toatsu has presented the following rationale for reclassification of etofenprox. They sponsored a series of in vitro investigations to examine the effects of etofenprox on rat thyroid cells in culture and re-examined the existing rat toxicity data. Based on the currently available data (the complete presentation by the registrant is included as an attachment) the registrant feels that:

a) Etofenprox can modulate thyroid tumor rates in rats by non-genotoxic mechanisms involving both increased turnover of thyroxine associated with induction of liver metabolic enzymes and by direct growth promoting effects on thyroid follicular cells. Since these effects will not be seen at doses which do not produce an imbalance of thyroid metabolism, assessment of allowable exposure should be by the standard uncertainty factor approach.

b) The effects of etofenprox seen in the rat are not expected to translate to the human due to the known and large differences in thyroxine metabolism between rats and humans, which results in rats being quite sensitive to the effects of thyroid imbalance on tumor rates while humans are not.

c) Etofenprox should be classified a Group E agent since it is not expected to produce thyroid tumor effects in humans at allowable daily intakes.

C. Additional Toxicity Data

1. Reference: Kumaroo, P.V. and Thilagar, A. K. (1995). Cytotoxicity of Etofenprox on Cultured FRTL-5 Cells: Relative Cell Growth, Relative Mitotic Index and Average Generation Time; SITEK Research Laboratories, Rockville, MD; Study No.

MTI-500-STK1; SITEK No. 0295-9101; Final Report Date: March 24, 1995. (Unpublished) MRID NUMBER: 43705301-A

EXECUTIVE SUMMARY: In an in vitro cytotoxicity assay (MRID No. 43705301-A), cultured rat thyroid follicular (FRTL-5) cells, were exposed to etofenprox (97.7%) at doses of 63-500 $\mu\text{g}/\text{mL}$ (Trials 1 and 2) or 8-63 $\mu\text{g}/\text{mL}$ (Trial 3) continuously for 96 hours. Cells were harvested at 24, 48, 72, and 96 hours, counted (all trials) and examined for the presence of mitotic cells (Trial 1 only). The test material was delivered to the test system in acetone. Results presented in MRID No. 43705301-B established optimal conditions for use in the study with etofenprox.

Compound insolubility at doses ≥ 63 $\mu\text{g}/\text{mL}$ interfered with assay results (Trial 1); undissolved test material was removed from the treated cultures prior to cell counts in Trial 2. The data indicated that 125, 250 and 500 $\mu\text{g}/\text{mL}$ etofenprox had a slight but dose-related stimulatory effect on cell growth at 24 hours. Cytotoxicity ($\approx 50\%$ decrease in cell growth) was seen at 32-63 $\mu\text{g}/\text{mL}$. We do not concur with SRS International Corp.'s claim that etofenprox induced an increase in mitotic figures.

Guidelines do not exist for this test system nor is it required to satisfy a specific guideline data requirement. The results do, however, provide insight into the possible mechanisms of etofenprox-induced thyroid tumors; the study is, therefore, classified as Supplementary.

2. Kumaroo, P.V. (1995). Cytotoxicity of Etofenprox on the Cultured FRTL-5 Cells; SITEK Research Laboratories, Rockville, MD; Study No. MTI-500-STK1; SITEK No. 0295-9103; Final Report Date: April 3, 1995. (Unpublished) MRID NUMBER: 43705301-C

EXECUTIVE SUMMARY: In an in vitro cytotoxicity assay (MRID No. 43705301-C), cultured rat thyroid follicular (FRTL-5) cells, were exposed to etofenprox (97.7%) at doses of 10-400 $\mu\text{g}/\text{mL}$ (Trial 1) or 10-200 $\mu\text{g}/\text{mL}$ (Trial 2) continuously for 24, 48 or 72 hours. Cells were washed, reexposed to the above doses for an additional 5 hours, harvested and lysed; the incorporation of ^{14}C -methionine into protein was measured. The test material was delivered to the test system in acetone but it was not clear whether acetone-treated cultures were included in the study.

No conclusions can be reached. The lack of a dose response in conjunction with the high variability of the data renders the findings inconclusive.

Guidelines do not exist for this test system nor is it required to satisfy a specific guideline data requirement. Since no conclusions can be reached, this study is classified as Unacceptable.

3. Kumaroo, P.V. (1995). Effect of Etofenprox on TSH Stimulation of ³H-TdR Uptake in FRTL-5 Cells; SITEK Research Laboratories, Rockville, MD; Study No. MTI-500-STK1; SITEK No. 0295-9105; Final Report Date: March 24, 1995. (Unpublished)
MRID NUMBER: 43705301-D

Optimization/Validation Study: Kumaroo, P.V. (1995). Effect of TSH on the ³H-TdR Uptake in FRTL-5 Cells; SITEK Research Laboratories, Rockville, MD; Study No. MTI-500-STK1; SITEK No. 0295-9104; Final Report Date: March 24, 1995. (Unpublished)
MRID NUMBER: 43705301-E

EXECUTIVE SUMMARY: In an in vitro cytotoxicity assay (MRID No. 43705301-D), cultured rat thyroid follicular (FRTL-5) cells were exposed to etofenprox (97.7%) doses of 5-200 µg/mL in the presence of 130 µIU/mL thyroid stimulating hormone (TSH) and tritiated thymidine (³H-TdR) for 24, 48 or 72 hours. Cell extracts were assayed for ³H-TdR incorporation into DNA. The test material was delivered to the test system in acetone but it was not clear whether acetone-treated cultures were included in the study. Results presented in MRID 43705301-E established the 50% stimulatory dose of TSH for use in the study with etofenprox.

The test material was insoluble at ≥50 µg/mL. A slight inhibition (≈ 30%) of ³H-TdR uptake was seen in cultures treated with 100 or 200 µg/mL etofenprox following 72-hours of exposure. However, higher levels, which appeared to cause marginal stimulation of TSH-deprived cell (see MRID No. 43705301-A), were not tested. The data suggest that etofenprox may compete for TSH receptor sites but the action is marginal and was not confirmed in a repeat trial.

Guidelines do not exist for this test system nor is it required to satisfy a specific guideline data requirement. As part of the overall body of in vitro cytotoxicity assay findings with etofenprox, it may provide some insight into possible mechanisms of etofenprox-induced thyroid tumors. This study is, therefore, classified as Supplementary.

D. Weight of Evidence Considerations

The weight-of-evidence for the determination of the carcinogenic potential of etofenprox is presented below:

1. Etofenprox, when administered in the diets of Sprague-Dawley rats at levels of 0, 30, 100, 700, or 4900 ppm in the diet for 2 years, was associated with: a statistically significant increase in comparison to controls for thyroid follicular cell adenomas in females at 4900 ppm and a significant positive trend in this tumor type for both sexes. There were no significant trends or pairwise comparisons for either sex in thyroid follicular carcinomas or thyroid parafollicular carcinomas. The incidence of thyroid follicular

cell adenomas and carcinomas combined in the 4900 ppm group was statistically significantly increased compared to controls in both sexes and there were significant positive trends for these combined tumors for both sexes as well. Historical control data were provided for thyroid tumors from studies conducted between 3/82 and 8/85. Combined thyroid follicular cell carcinomas and adenomas ranged from 3.6 to 16.7% in males, and from 0 to 6% in females. In the present study, the high dose percentages of these tumors were 16% for females and 24% for males, both outside the historical control ranges.

2. CD-1 mice were fed 0, 30, 100, 700 or 4900 ppm of etofenprox in their diet for 108 weeks. For females, there were no survival differences and no significant increase in any tumors. Male mice had a significant dose related trend in renal cortical adenomas alone and combined carcinomas and adenomas. There were no significant pairwise comparisons, however. The incidence of the carcinomas (1/58) in high-dose males was higher than in the control groups of 7 out of 9 studies cited for their historical control incidence.

3. A variety of mutagenicity studies on gene mutation, chromosomal aberrations, and DNA synthesis and repair were negative.

4. No good analogues were found on etofenprox and data on Fenvalerate were only weakly positive and not similar to etofenprox. Analogy to the carcinogenicity of the dibenzyl ether moiety was limited by the metabolism data that indicated that this moiety would not be cleaved from the parent etofenprox molecule.

5. Re-evaluation of the in vivo studies, by the registrant, lead to the conclusion that etofenprox produces centrilobular toxicity in the liver, evidenced by a dose dependent increase in vacuolated hepatocytes in the centrilobular region. This type of effect is commonly associated with induction of the microsomal oxidases in the liver, in which increases have been shown to increase turnover of T3 and T4 and, thus, a turning on of TSH production.

6. Etofenprox appears to directly stimulate thyroid follicular cell growth, but not cellular proliferation, in vitro, and, possibly, may compete for TSH receptor sites. However, the registrant has provided only marginal data to support their contention that etofenprox induces follicular cell tumors via direct stimulation of these cells at the TSH receptor sites, not through disruption of thyroid hormone homeostasis. The data from the chronic toxicity/carcinogenicity study in rats do not support the latter mechanism, therefore, the registrant has not provided

conclusive data to support a mechanism for the induction of these tumors.

The following summary describes what the submitted data for etofenprox demonstrate relative to pertinent criteria in the Assessment of Thyroid Follicular Cell Tumors by Hill, et al. (May 9, 1994).

1. A thyroid-pituitary imbalance is not supported.
2. Induced cellular hypertrophy via thyroid follicular stimulation at the TSH receptor sites is marginally supported.
3. Microsomal enzyme induction in the liver is weakly supported.
4. Negative genotoxicity is supported.
5. Structure activity relationship is not supported.
6. Lesion progression is not supported.
7. There was a dose-response only for combined tumors.