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

OCT 28 1998

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: 5-Chloro-2-(2,4-dichlorophenoxy)phenol (Triclosan): Review of data on the safety of the active ingredient.

EPA Identification Numbers:

P.C. Code: 054901
DP Barcode:D250105

MRID's: N/A (summary report on toxicology)
Submission: S549776

TO: Robert Brennis
Regulatory Management Branch II / PM Team 32
Antimicrobials Division (7510W)

FROM: Timothy F. McMahon, Ph.D. 10/16/98
Senior Toxicologist
Risk Assessment and Science Support Branch (RASSB)
Antimicrobials Division (7510W)

THRU: Laura Morris Laura Morris 10/23/98
Team Leader, Team Two
RASSB
Antimicrobials Division (7510W)

and

Norm Cook, Chief
RASSB
Antimicrobials Division (7510W)
Norman J. Cook 10/28/98

Action Requested: Review of a report entitled "Implications for Human Health of the Triclosan Animal Safety Bioassay Data" and submitted to the Agency to determine if this information has any significant impact upon the Agency's safety assessment of Triclosan.

Background

Triclosan is an antimicrobial chemical used extensively in over the counter products such as soaps and toothpaste (uses regulated by the Food and Drug Administration) as well as other consumer products such as plastic cutting boards. For those uses regulated by the EPA under FIFRA, Toxicology data are required, and data requirements may vary depending upon the use pattern and potential exposure scenarios. For Triclosan, use sites under regulation by EPA include those with chronic exposure potential, such as textiles, plastic products, and household or domestic dwellings. For use sites such as these, chronic toxicity and carcinogenicity data are required. Previously, chronic toxicity and carcinogenicity data conducted with Triclosan in the rat were submitted by Ciba Specialty Chemicals and reviewed by the EPA's Health Effects Division. However, carcinogenicity data are required in two species under EPA testing guidelines for pesticide chemicals with chronic exposure potential. To this end, a 78 week carcinogenicity study was previously conducted by Colgate-Palmolive for fulfilling FDA Toxicology data requirements, but the data were never submitted to EPA for review. In the present submission, a summary of the hepatic effects (neoplastic and non-neoplastic) of Triclosan observed in the mouse study was presented. In addition, the report contained several other sections, including background material on theories of carcinogenesis by non-genotoxic agents, and summaries of other toxicity data on Triclosan, much of which has been reviewed by the EPA. What is relevant to this submission for purposes of risk assessment are the results of the 78 week mouse study. Although EPA has not yet obtained a copy of the full study, it is worth presenting the summary data on the mouse carcinogenicity study as this study showed a positive tumorigenic response to oral administration of Triclosan.

Summary of Mouse Carcinogenicity Data

In this study, male and female CD-1 mice were administered Triclosan in the diet at dose levels of 0, 10, 30, 100, or 200 mg/kg/day for 18 months. Hematological effects were observed in both male and female mice and included decreased hemoglobin levels, decreased red cell count, increased platelets, increased mean corpuscular volume, and decreased mean corpuscular hemoglobin concentration. Clinical chemistry examination showed dose-related increases in alanine aminotransferase and aspartate aminotransferase and decreased serum cholesterol. No specific data were presented in this submission to show the time of onset or the magnitude of the above changes vs. control.

A dose-related increase in absolute liver weights were observed for both male and female mice.

These data are shown below:

Effect of Triclosan on Liver weight and Liver Pathology in Male and Female CD-1 Mice						
Dose Group (mg/kg/day)	Absolute Liver Weight (g)		Relative Liver Weight (%)		Incidence of Liver Nodules/Masses	
	Male	Female	Male	Female	Male	Female
0.00	1.973±0.529	1.526±0.274	5.26	5.07	3/70	2/71
10	2.221±0.846	1.618±0.296	5.92	5.12	10/70	1/71
30	2.388±0.688	1.859±0.729	6.27	5.96	16/70	1/70
100	3.731±0.959	2.727±0.977	9.62	8.77	28/70	3/70
200	5.210±1.286	3.765±1.063	13.89	11.95	41/70	18/70

According to the report, the following non-neoplastic effects were observed in the liver: Hepatocellular necrosis; hepatocellular hypertrophy; microgranulomas; and brown pigment in hepatocytes, Kupffer cells, and or biliary canaliculi. The non-neoplastic lesions were stated to increase in incidence and severity with dose of Triclosan. The brown pigment was primarily ceroid or lipofuscin positive, a characteristic of peroxisome proliferators. At the two highest doses, enlarged hepatocytes with eosinophilic granular cytoplasm, oval cell hyperplasia, single cell necrosis, and diffuse hepatocytomegaly were observed. At lower doses, the hypertrophy was more centrilobular.

With regard to tumors, significant increases in the incidence of liver tumors were observed at doses of 30 mg/kg/day and greater in both sexes of mice, as summarized below:

Effect of Triclosan on Liver Tumor Incidence in Male and Female CD-1 Mice						
Dose Group (mg/kg/day)	Adenoma		Carcinoma		Adenoma or Carcinoma	
	Male	Female	Male	Female	Male	Female
0.00	5/70	0/70	2/70	0/70	6/70	0/70
10	7/70	1/70	3/70	0/70	10/70	1/70
30	13/70*	3/70*	6/70*	1/70	17/70**	3/70*
100	22/70**	6/70**	11/70**	1/70	32/70**	6/70
200	26/69**	11/70**	24/69**	14/70**	42/69**	20/70**

*$p < 0.05$, **$p < 0.01$ vs control.

No further data were provided in this report characterizing the histopathology of the liver tumors. However, the report contained a section discussing the nature of tumor formation in the mouse liver beginning on page 61. In this section, the report noted that in tests for genotoxicity, Triclosan produced negative results, implying that the mechanism for tumor formation may be non-genotoxic. Possible mechanisms of tumor formation for Triclosan include: tumors associated with peroxisome proliferation; tumors associated with induction of hepatic xenobiotic metabolism; and tumors associated with regenerative hyperplasia resulting from sustained hepatoxicity. In the case of Triclosan, the available data appear to point in the direction of a mechanism involving cell proliferation, but as noted, none of the above mentioned mechanisms can be excluded at this point, as Triclosan has been shown to have effects on peroxisome proliferation, induction of hepatic metabolism, and effects on cell proliferation. It is noted that there are species differences in the toxic response to administration of Triclosan. Rats develop many of the hepatotoxic responses as mice, but do not show a positive tumorigenic response in the liver. Hamsters do not show hepatotoxcity, but have been observed with testicular and renal toxicity after chronic administration of Triclosan. There may be a basis for the species differences in toxicity as related to metabolism of Triclosan. This question has not been investigated, although there is a wealth of data on both the metabolism and toxicity of Triclosan in various species.

RASSB's Conclusions

RASSB has examined the submitted report on the toxicity and carcinogenesis of Triclosan, with particular emphasis on the data available for the mouse carcinogenicity bioassay submitted

previously to and reviewed by the Food and Drug Administration, but not previously submitted to EPA for review. The data for the mouse study made available in the present submission provide evidence of a positive tumorigenic response in the mouse as a result of chronic exposure to Triclosan in the diet. EPA considers this information vital to the risk assessment for Triclosan, and requests that the full study be made available to EPA for review, as the present submission does not contain sufficient detail to make an informed decision on the carcinogenic potential of Triclosan using EPA's criteria.