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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

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OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review of Cyromazine (2nd)

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and

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Science Analysis Branch
Health Effects Division (7509C)

TO: George T. LaRocca/Linda DeLuise
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Registration Division (7505C)

THROUGH: Stephanie R. Irene Ph.D. Stephanie R. Irene
Acting Director, Health Effects Division (7509C)

The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on Sept. 14, 1994 to discuss and re-evaluate the weight-of-the-evidence on cyromazine, with particular reference to its carcinogenic potential. The CPRC concluded that cyromazine should be re-classified as Group E, based on a submission of data from a re-examination of the tissues from the mouse and rat studies.

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Carcinogenicity Peer Review of Cyromazine (2nd)
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SUMMARY

Cyromazine was previously classified as a Group C - possible human carcinogen, and the Reference Dose (RfD) methodology was recommended to be used for estimation of human risk (Peer Review of Cyromazine, dated April 20, 1993).

The Group C classification was based on a statistically significant increase in mammary tumors in the female mouse, at a dose that may have been insufficient for an adequate assessment of carcinogenic potential, and to a lesser degree, the same tumor type in the rat. Rat bladder tumors produced by the cyromazine metabolite, melamine, were not considered applicable to the cancer potential of cyromazine. (Melamine is discussed more fully in a separate document: Peer Review of Melamine, dated July 21, 1993.)

The registrant subsequently conducted a re-examination[1], by a reviewing pathologist and a pathology working group (PWG), of the tissues from the cyromazine chronic feeding and carcinogenicity in the rat and mouse. [Details are provided in Sections D and F of this document.]

The consensus of the CPRC was that the re-examination of the tissues in question was performed in an acceptable manner. Based on these revised data, there were no statistically significant increases in tumors in the treated groups, and there were no statistically significant trends. Therefore, the classification of cyromazine has been revised to Group E.

[1]The re-examination was neither requested, nor required by the Agency.

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A. Individuals in Attendance at the meetings:

1. Peer Review Committee: (Signatures indicate concurrence with the peer review unless otherwise stated.)

Stephanie R. Irene

William Burnam

Karl Baetcke

Esther Rinde

Elizabeth Doyle

Yin Tak Woo

2. Reviewers: (Non-committee members responsible for data presentation; signatures indicate technical accuracy of panel report.)

Stephen Dapson[2]

Mike Ioannou

Lori Brunsman

Bernice Fisher

Lucas Brennecke[3]
(PAI/ORNL)

3. Other Attendees:

Edwin Budd, David Anderson, B.H. Chin (HED)

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[2]Also a member of the PRC for this chemical; signature indicates concurrence with the peer review unless otherwise stated.

[3]Signature indicates concurrence with pathology report.

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B. Material Reviewed

The material available for review consisted of the most recent Carcinogenicity Peer Review Document (April 20, 1993), additional information provided by the registrant on the carcinogenicity study in the mouse and the carcinogenicity study in the rat (mouse oncogenicity study with cyromazine: pathology quality assessment and pathology working group peer review of female mammary glands; rat oncogenicity study with cyromazine: pathology quality assessment and pathology working group peer review of female mammary glands; reevaluation of the significance of neoplasms of the mammary gland in female rats and mice) and other data summaries prepared and/or supplied by Dr. Stephen C. Dapson (secondary review by Dr. Yiannakis M. Ioannou and Dr. Marcia van Gemert). Tables and statistical analysis by Lori Brunsman and Barnice Fisher. The material reviewed is attached to the file copy of this report.

C. Background Information

Cyromazine (N-cyclopropyl-1,3,5-triazine-2-4-6,-triamine), is an insect growth regulator used to control bugs on celery, head lettuce and as a "feed through" insecticide in chicken feed to control fly larva (Larvadex). This chemical was previously classified by the CPRC as a Group C carcinogen with a Reference Dose (RfD) methodology recommended (Peer Review of Cyromazine, dated April 20, 1993). This second peer review was convened to evaluate the registrant's submission of data from a re-examination of the tissues from the mouse and rat studies, and to re-evaluate the weight-of-the-evidence for cyromazine.

Melamine, a chemical intermediate in the manufacture of amino resins and plastics as well as a contaminant and/or a metabolite of several pesticides, is a metabolite of cyromazine. Dietary administration of melanine was associated with tumors of the urinary bladder in male rats only and only at high doses. The CPRC concluded that it is unlikely that melamine exposure would pose a carcinogenic hazard to humans from the pesticidal usage of cyromazine, based on a mechanistic evaluation of the bladder tumors in the male rat (the only tumors observed) and considerations of dietary and occupational exposure (Peer Review of Melamine, dated July 21, 1993).

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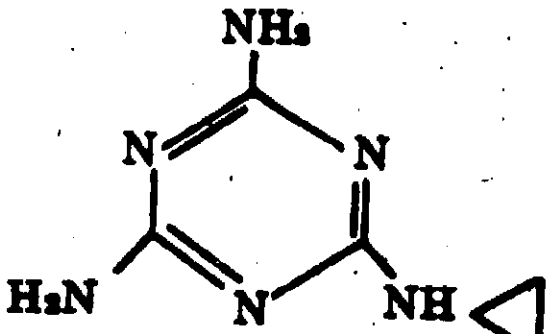
The following is the structure of cyromazine:



Cyromazine

D. Evaluation of Carcinogenicity

The HED Carcinogenicity Peer Review Committee met previously and evaluated the weight-of-evidence for cyromazine with particular reference to its carcinogenic potential. The HED CPRC agreed that cyromazine should be classified as a Group C - possible human carcinogen, and recommended that for the purpose of risk characterization, the Reference Dose (RfD) methodology should be used at this time for estimation of human risk (Peer Review of Cyromazine, dated April 20, 1993).

This classification was based on a statistically significant increase in mammary tumors in the female mouse, at a dose that may have been insufficient for an adequate assessment of the carcinogenic potential, and to a lesser degree, an increase of the same tumor type in the rat. Rat bladder tumors produced by the metabolite, melamine, were not considered applicable to the cancer potential of cyromazine.

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Additional Data

The registrant (Ciba-Geigy Corporation) met with the Agency on November 17, 1993 to discuss the findings on the re-examination of tissues from the cyromazine chronic feeding and carcinogenicity study done by a reviewing pathologist and a pathology working group (PWG).

1. Carcinogenicity - Mouse

a. Discussion of Tumor Data

For the re-examination of tissues from the mouse carcinogenicity study, the registrant stated that: "The results of the PWG [Pathology Working Group] re-examination indicate that the incidence of malignant neoplasms in the mammary gland of female mice exposed to 50, 1000, and 3000 ppm cyromazine in the diet for up to 24 months is similar to that present in the untreated control female mice. There is an absence of a clear dose response in the incidence in tumor multiplicity with exposure to cyromazine. The slightly increased incidence in Group IV [high dose] as compared to controls is not statistically significant and not considered to be associated with exposure to cyromazine."

The HED CPRC decided, based on the newly provided data from the registrant (tumor reread), that there was no statistically significant increase in tumors in the treated groups; there were no statistical trends and no dose response.

The following table (Table 1) compares the previous compilation of the tumor data with the tumor re-read provided by the registrant.

b. Adequacy of Dosing for Assessment of Carcinogenic Potential

Body weight gains in female mice were comparable to controls and there were no indications of toxicity reported. The study report stated that "there is a suggestion of a possibly slightly increased mortality" in high dose females; based on this the dosing in the female mouse was considered by the HED CPRC to be "marginally adequate".

The dosing in male mice was considered adequate, based on body weight gain reductions (12% at the mid-dose, 23% high-dose) relative to controls.

The HED CPRC agreed that no repeat of this study is necessary.

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TABLE 1
Cyromazine - Charles River CD-1 Mouse Study
Female Mammary Gland Tumor Rates[+] and
Exact Trend Test and
Fisher's Exact Test Results [p values]

Tumors:	Dose (ppm) 0		50		1000		3000	
	Original	Re-Read	Original	Re-Read	Original	Re-Read	Original	Re-Read
Adenocarcinomas	2/56	2/56	4/57	4/57	3/57	3/57	8/57	6/57
(%)	(4)	(4)	(7)	(7)	(5)	(5)	(14)	(11)
p =	0.023*	0.094	0.348	0.348	0.508	0.508	0.049B*	0.141
Adenoacanthomas	3/56	3/56	1/57	1/57	0/57	0/57	1/57	2/57
(%)	(5)	(5)	(2)	(2)	(0)	(0)	(2)	(4)
p =	0.235	0.467	0.302	0.302	0.118	0.118	0.302	0.492
Adenocarcinomas and/or Adenoacanthomas	5/56	4/56	5/57	5/57	3/57	3/57	9/57	7/57
(%)	(9)	(7)	(9)	(9)	(5)	(5)	(16)	(12)
p =	0.077	0.167	0.618	0.511	0.348	0.490	0.206	0.274

[+] = Number of tumor bearing animals/Number of animals examined

NOTE: Significance of trend denoted at control.
Significance of pair-wise comparison with control denoted at dose level.
If *, then $p < 0.05$. If **, then $p < 0.01$

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2. **Carcinogenicity - Rat**

a. **Discussion of Tumor Data**

For the re-examination of tissues from the rat carcinogenicity study, the registrant stated that: "The results of the re-examination by the PWG verify that there was no increase in the incidence of benign tumors of the mammary gland treatment, and further confirm that although the number of animals with malignant tumors in the mammary gland was slightly greater in Group IV [high dose] females as compared to the control females, this difference was not statistically significant and there was an absence of a dose response. There was no evidence of an increase in tumor multiplicity, either benign or malignant, in exposed female rats as compared to control female rats; and the incidence of mammary gland tumors in treated female rats in Study No. 382-081 did not exceed the historical control ranges reported at the testing laboratory."

The HED CPRC decided, based on the newly provided data from the registrant (tumor reread), that there were no statistically significant differences between the controls and treated groups in benign tumors (adenomas and fibroadenomas), malignant tumors (adenocarcinomas) or combined benign and malignant tumors (adenomas and/or fibroadenomas and/or adenocarcinomas); there were no statistical trends and no dose response.

The following table (Table 2) compares the previous compilation of the tumor data with the tumor re-read provided by the registrant.

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TABLE 2
Cyromazine - Charles River Sprague-Dawley Rat Study -Female Mammary Gland Tumor Rates[+] and Cochran-Armitage Trend Test and Fisher's Exact Test Results [p values]

Tumors:	Dose (ppm) 0		30		300		3000	
	Original	Re-Read	Original	Re-Read	Original	Re-Read	Original	Re-Read
Adenomas	3/53	3/53	8/58	4/58	6/58	1/58	8/59	5/59
(%)	(6)	(6)	(14)	(7)	(10)	(2)	(14)	(8)
p =	0.228	0.172	0.132	0.551	0.292	0.276	0.139	0.420
Fibroadenomas	20/53	20/53	17/58	17/58	16/58	16/58	16/59	15/59
(%)	(38)	(38)	(29)	(29)	(28)	(28)	(27)	(25)
p =	0.250	0.177	0.230	0.230	0.174	0.174	0.159	0.115
Adenocarinomas	3/53	6/53	2/58	8/58	1/58	6/58	9/59	12/59
(%)	(6)	(11)	(3)	(14)	(2)	(10)	(15)	(20)
p =	0.001**	0.055	0.457	0.459	0.276	0.554	0.090	0.149
Adenomas and/or Fibroadenomas								
	20/53	22/53	23/58	20/58	19/58	17/58	21/59	19/59
(%)	(38)	(42)	(40)	(34)	(33)	(29)	(36)	(32)
p =	0.406	0.317	0.495	0.286	0.363	0.126	0.484	0.205
Adenomas and/or Adenocarcinomas and/or Fibroadenomas								
	22/53	23/53	25/58	27/58	19/58	19/58	26/59	27/59
(%)	(42)	(43)	(43)	(47)	(33)	(33)	(44)	(46)
p =	0.290	0.305	0.509	0.463	0.224	0.169	0.468	0.476

[+] = Number of tumor bearing animals/Number of animals examined;
NOTE: Significance of trend denoted at control;
Significance of pair-wise comparison with control denoted at dose level;
If *, then $p < 0.05$. If **, then $p < 0.01$

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b. Adequacy of Dosing for Assessment of Carcinogenic Potential

The dosing in the rat combined chronic/carcinogenicity study was considered by the HED CPRC to have been above an adequate dose for assessing the carcinogenic potential of cyromazine in rats, based on depressions in mean body weight gain of 22% in males, and 33% in females at doses of 3000 ppm. This rather large depression in body weight gain was not, however, accompanied by increases in mortality or signs of toxicity.

B. Additional Toxicology Data

Structure-Activity Relationships for cyromazine were considered. Cyromazine is related to the triazine class of chemicals. Most of the triazines are used as herbicides. A NLM Chemline search found 6073 triazines, of these 49 were classified as agricultural chemicals and a further reduction of these in reference to specific tumor data available in the open literature found the following pesticide chemicals: atrazine, propazine, simazine, cyanuric acid, melamine, and anilazine. The Agency has chronic toxicity data on cyanazine, hexazinone, prometryn, terbuthylazine, atrazine, terbutryn, propazine, simazine, cyanuric acid (trihydroxytriazine), and anilazine (dyrene).

The HED CPRC did not feel that the structure-activity relationship between cyromazine and the s-triazines was strong, because cyromazine does not have the chloro- group common to most of the s-triazines. It was noted, however, that six of these (atrazine, cyanazine, terbutryn, propazine, simazine, and terbuthylazine) produced the same tumor type, mammary, in rats; all of these except terbutryn contain a chloro group on the heterocyclic ring. Additionally, interstitial cell tumors resulted from terbutryn and atrazine administration in the rat, although the atrazine tumors were discounted because they were within historical control range. In the mouse carcinogenicity studies conducted with the structurally related compounds there was no evidence of any increased incidence of mammary gland tumors.

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F. Weight of Evidence Considerations

The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) on September 14, 1994 considered the following facts regarding the toxicity data on cyromazine to be of importance in a weight-of-evidence determination of the carcinogenic potential:

1. The results of the registrant's PWG [Pathology Working Group] re-examination indicate that the malignant neoplasm incidence in the mammary gland of female mice exposed to 50, 1000, and 3000 ppm cyromazine in the diet for 24 months is similar to that of the control female mice. There is no dose response in the tumor incidence in mice exposed to cyromazine.

2. The results of the re-examination by the registrant's PWG verify that there was no increase in the mammary gland benign tumor incidence in female rats and there was no dose response. There was no evidence of an increase in tumors, either benign or malignant, in female rats exposed to cyromazine as compared to control female rats; and the incidence of mammary gland tumors in treated female rats did not exceed the provided historical control ranges from the testing laboratory.

3. The HED CPRC did not feel that the structure-activity relationship between cyromazine and the s-triazines was strong, because cyromazine does not have the chloro- group common to most of the s-triazines. It was noted, however, that six of these (atrazine, cyanazine, terbutryn, propazine, simazine, and terbuthylazine) produced the same tumor type, mammary, in rats; all of these except terbutryn contain a chloro group on the heterocyclic ring. Additionally, interstitial cell tumors resulted from terbutryn and atrazine administration in the rat, although the atrazine tumors were discounted because they were within historical control range. In the mouse carcinogenicity studies conducted with the structurally related compounds there was no evidence of any increased incidence of mammary gland tumors.

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G. Classification of Carcinogenic Potential:

The Peer Review Committee considered the criteria contained in the EPA's "Guidelines for Carcinogen Risk Assessment" [FR51: 33992-34003, 1986] for classifying the weight of evidence for carcinogenicity.

Cyromazine was previously classified by the CPRC as a Group C - possible human carcinogen, with the Reference Dose (RfD) methodology recommended for estimation of human risk (Peer Review of Cyromazine, dated April 20, 1993). The registrant subsequently conducted a re-examination[4], by a reviewing pathologist and a pathology working group (PWG), of the tissues from the cyromazine chronic feeding and carcinogenicity studies in both the rat and mouse.

The consensus of the CPRC was that cyromazine should be re-classified as Group E - no evidence for carcinogenicity in humans. This decision was based on the results from the Registrant's re-examination of the tissues from the mouse and rat studies. The consensus of the CPRC was that the re-examination of mammary gland tissues in the mouse and rat was performed in an acceptable manner. Based on these revised data, there were no statistically significant increases in tumors in the treated groups, and there were no statistically significant trends. Therefore, the classification of cyromazine has been revised to Group E.

[4]The re-examination was neither requested, nor required by the Agency.

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