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

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JUL 20 1988

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Second Peer Review of Chlorothalonil - Reevaluation Following the Sept. 23, 1987 Science Advisory Panel Review.

FROM: Esther Rinde, Ph.D. E. Rinde 6/21/88
Scientific Mission Support Staff (TS-769c)

TO: Lois Rossi
Product Manager # 21
Registration Division (TS-767c)

The Peer Review Committee met on May 9, 1988 to examine the issues raised by the Science Advisory Panel (SAP) with respect to the classification of carcinogenicity for Chlorothalonil.

A. Individuals in Attendance:

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

Theodore M. Farber	Theodore M. Farber
William L. Burnam	
Robert Beliles	Robert Beliles
Lynnard J. Slaughter	L.J. Slaughter
Judith Hauswirth	
Richard Levy	
Kerry Dearfield	
Esther Rinde	Esther Rinde

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

David Ritter

Bruce Jaeger

3. Peer Review Members in Absentia: (Committee members who were unable to attend the discussion; signatures indicate concurrence with the overall conclusions of the Committee.)

Anne Barton

Richard Hill

Reto Engler

Diane Beal

Jack Quest

Marion Copley

4. Other Attendees:

Lois Rossi, Mario Fiol (RD) and Esther Saito (SIS) were also present.

B. Material Reviewed:

The SAP Panel response (10/1/87); Peer Review Memo (9/4/87) Toxicology Chapter of the Registration Standard (2/24/88); Reviewer's summaries of additional data (Memo, D. Ritter to L. Rossi, 4/7/88 and attached DERs); Reviewer's memo and DER for interim report of a 2-year feeding study in F344 rats (Memo to L. Rossi, 6/7/88 and DER, 6/9/88)).

A copy of the above material and the transcript of the SAP meeting (9/23/88) are attached to the file copy of this report.

C. Considerations:

The initial classification (B2) of Chlorothalonil by the Peer Review Committee was reconsidered. This B2 classification was based on increased incidences of malignant and/or combined malignant/benign tumors (both sexes) in two species: rat (2 strains) and in the CD-1 mouse (Tables 1-4). This evidence was presented to the SAP, as follows:

1. NCI Osborne-Mendel Rat Study (1978)

Chlorothalonil fed in the diet to Osborne-Mendel rats, resulted in a statistically significant increase in combined renal adenoma/carcinoma in both sexes, with a significant dose-related trend in females (in males the trend was not significant, since the tumor incidence at the low and high dose was 3 and 4, respectively) (Table 1).

2. IRDC Fischer 344 Rat Study (1985)

Chlorothalonil when fed in the diet to Fischer 344 rats, resulted in a statistically significant increase in the incidence of renal adenomas and carcinomas, with a significant dose-related trend, in both sexes (Tables 2).

In female rats, there was also a statistically significant increase in papilloma and combined papilloma/carcinoma of the forestomach with a significant dose-related trend (Table 3).

3. SDS Biotech CD-1 Mouse Study (1979)

Chlorothalonil when fed in the diet to CD-1 mice, resulted in a statistically significant increase in squamous cell carcinoma of the forestomach in both sexes, with a positive dose-related trend for combined papilloma/carcinoma in females (Table 4).

Increases in the incidence of renal tumors were statistically significant for combined adenoma/carcinoma in male mice only, but there was no positive trend, since these rare tumors were seen at all treatment levels. The renal tumor response in these mice was considered convincing, because of the rarity[1] of renal tumors, because renal tumors of the same type and location were seen in the adequate rat study, and because there were no tumors reported for concurrent controls of either sex (Table 4).

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[1]Mean historical control incidence for renal adenoma and/or carcinoma: less than 1% (1490 animals for IRDC; 815 for Bio-Dynamics).

C. Considerations (Contd.):

4. NCI B6C3F1 Mouse Study (1978)

Chlorothalonil fed in the diet to B6C3F1 mice, was not oncogenic at doses up to 20,000 ppm (nominal dose).

(Table 5 summarizes the pertinent findings in all 4 studies.)

> The SAP Panel did not comment specifically on the Agency evaluation and classification of Chlorothalonil, although they did agree that the renal tumors in the CD-1 male mouse were biologically significant at concentrations below the maximum tolerated dose. The Panel expressed concern regarding additional data which had not been reviewed at the time of the Peer Review.

All of the available data have now been reviewed and evaluated (the supplemental data are summarized in David Ritter's memos to Lois Rossi (4/7/88 and 6/7/88) and accompanying DERs). These data included interim reports (after 1 year) for the following 2 studies:

> 1. A 2-year dietary feeding study (0, 2, 4, 15 or 175 mg/kg/d Chlorothalonil) in Fischer 344 rats, which the Registrant is conducting to determine the no-effect level for "potentially preneoplastic and tumorigenic effects in the kidney and forestomach". The interim findings included hyperplasia and karyomegaly of the renal cortex in males at 4, 15 and 175 mg/kg/d, and in females at 175 mg/kg/d; and squamous epithelia hyperplasia and hyperkeratosis of the gastric mucosa in both sexes at 15 and 175 mg/kg/d.
>
> 2. A 2-year dietary feeding study (0, 10, 40, 175 or 750 ppm Chlorothalonil) in Charles River CD-1 male mice also reports a slight increase in renal tubular hyperplasia at 175 ppm, and hyperplasia and hyperkeratosis of the squamous mucosa of the forestomach at 750 ppm.

The Registrant maintains that the "forestomach lesions associated with Chlorothalonil result from the locally irritating effects of Chlorothalonil itself" [SAP Transcript 9/23/87, pg. 73], however, it was pointed out by Dr. Slaughter that hyperplasia and/or hyperkeratosis could be caused by factors other than local irritation, such as decreased Vitamin A intake. Dr. Hauswirth also offered that she is aware of some chemical carcinogens which are known to deplete hepatic storage of Vitamin A.

C. Considerations (Contd.):

The Committee also discussed the mutagenicity data for Chlorothalonil, in light of the Registrant's claim (and the Panel's statement) that Chlorothalonil is not genotoxic. The *in vitro* data included a positive mouse lymphoma assay [as reported by NTP, Annual Report, 1986]; a positive CHO aberrations and positive CHO Sister Chromatid Exchange assays [Galloway,S. et al.: Environ. Molecular Mutagen 10:1-175, 1987]; and a positive CHO Aberration assay (data submitted to the Agency - in Peer review file). These results indicate that Chlorothalonil has at least weak clastogenic activity. Most *in vivo* studies for clastogenic activity appear negative after 1 or 2 doses; however, after 5 consecutive doses (over 5 days), there was a weak clastogenic response [Ibid]. (It was also pointed out that the protocol for the three submitted micronucleus assays, which were acceptable by standards used in the late 1970's, are unacceptable based on current guidelines).

The Committee agreed that based on the above data, it cannot be said that Chlorothalonil is devoid of genotoxic activity; however, it should be noted that these are all weak responses.

D. Classification of Oncogenic Potential:

The review of the supplemental data did not provide a basis for either increasing or decreasing the initial classification (B2) for Chlorothalonil which was based on: malignant and/or combined malignant and benign tumors (both sexes) in 2 strains of the rat and in the CD-1 mouse.

The Peer Review Committee concluded, on consideration of all of the available data for Chlorothalonil, that the evidence satisfies the criteria contained in the EPA Guidelines [FR51:33992-34003, 1986] for sufficient evidence, and reaffirmed its classification of Chlorothalonil as a Group B2 (Probable Human Carcinogen).

TABLE 1

CHLOROTHALONIL - NCI OSBORNE-MENDEL RAT STUDY

Incidence of RENAL NEOPLASMS (%)

		Control			
		0	253	506	mg/kg/day
		0	5063	10126	PPM
Carcinoma	M	0/10	1/45	3/49	
	F	0/10	1/48	2/50	
Adenoma	M	0/10	2/45	1/49	
	F	0/10	0/48	3/50	
Combined	M	0/10(0)	3/45(6.7)	4/49(8.2)*	
	F	0/10(0)**	1/48(2.1)	5/50(10.0)*	

* $p < .05$, ** $p < .01$

TABLE 2 (Revised)

CHLOROTHALONIL - IRDC Fischer 344 Rat Study
Incidence (%) of RENAL TUMORS

A. Males

	Control	Dose		
	0	40	80	175 mg/kg/day
	0	800	1600	3500 PPM
Renal Tumor Rates[1]				
Carcinomas	0/60(0)**	4/60(7)	2/60(3)	14/60(23)**
Adenomas[2]	0/60(0)*	3/60(5)	5/60(8)*	5/60(8)*
Both Carcinomas and Adenomas	0/60(0)**	7/60(12)**	7/60(12)**	19/60(32)**

B. Females

	Control	Dose		
	0	40	80	175 mg/kg/day
	0	800	1600	3500 PPM
Renal Tumor Rates[1]				
Carcinomas	0/60(0)**	1/60(2)	0/60(0)	12/60(20)**
Adenomas[2]	0/60(0)**	3/60(5)	10/60(17)**	12/60(20)**
Both Carcinomas and Adenomas	0/60(0)**	4/60(7)	10/60(17)**	24/60(40)**

[1]Number of tumor bearing animals/number of animals examined
[2]Does not include animals with Carcinoma

* $p < .05$, ** $p < .01$

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TABLE 3 (Revised)

CHLOROTHALONIL - IRDC Fischer 344 Rat Study
Incidence (%) of FORESTOMACH TUMORS
(Gastric Squamous Mucosa - Papilloma and Carcinoma)

A. Males

Fore-Stomach Tumor Rates[1]	Dose: Control 0 / 0	40 / 800	80 / 1600	175 mg/kg/day / 3500 PPM
Sq. Carcinoma	0/60(0)	0/60(0)	0/60(0)	1/60(2)
Sq. Papilloma[2]	0/60(0)	1/60(2)	1/60(2)	2/60(3)
Both Carcinoma and Papilloma	0/60(0)	1/60(2)	1/60(2)	3/60(5)

B. Females

Fore-Stomach Tumor Rates[1]	Dose: Control 0	40	80	175 mg/kg/day PPM
Sq. Carcinoma	0/60	0/60	0/60	1/60(2)
Sq. Papilloma[2]	0/60**	1/60(2)	2/60(3)	6/60(10)*
Both Carcinoma and Papilloma	0/60(0)**	1/60(2)	2/60(3)	7/60(12)**

[1]Number of tumor bearing animals/Number of animals examined
[2]Does not include animals with Carcinoma

* $p < .05$, ** $p < .01$

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TABLE 4 (Revised)

CHLOROTHALONIL - CD-1 Mice Study

A. Incidence (%) of RENAL TUBULAR TUMORS

Renal Tumor Rates[1]	Dose: Control 0 / 0	107 / 750	214 / 1500	428 mg/kg/day / 3000 PPM
	Males			
Adenomas[2]	0/60	3/60(5)	3/60(5)	4/60(7)
Carcinomas	0/60	3/60(5)	1/60(2)	1/60(2)
Both Carcinomas and Adenomas	0/60	6/60(10)*	4/60(7)	5/60(8)*

B. Incidence (%) of STOMACH TUMORS

Stomach Tumor Rates[1]	Dose: Control 0 / 0	107 / 750	214 / 1500	428 mg/kg/day / 3000 PPM
	Males			
Sq.Cell Carcinoma	0/60	2/60(3)	5/60(8)*	2/60(3)
Sq.Cell Papilloma[2]	0/60	0/60	0/60	0/60
Both Carc.and Paps.	0/60	2/60(3)	5/60(8)*	2/60(3)
Glandular Carcinoma	0/60(0)	1/60(2)	2/60(3)	0/60(0)
	Females			
Sq.Cell Carcinoma	0/60	0/60(0)	6/60(10)*	2/59(3)
Sq.Cell Papilloma[2]	0/60	2/60(3)	0/60	3/59(5)
Both Carc.and Paps.	0/60*	2/60(3)	6/60(10)*	5/59(8)*
Glandular Carcinoma	0/60	1/60(2)	1/60(2)	2/59(3)

[1]Number of tumor bearing animals/Number of animals examined
[2]Does not include animals with Carcinoma

* $p < .05$, ** $p < .01$

TABLE 5

		RENAL TUMORS			FORESTOMACH TUMORS Sq. Cell		
RAT		Carcinoma	Adenoma	Combined	Carcinoma	Papilloma	Combi
OSBORNE-MENDEL NCI	M	+	+	+*	N/R		
	F	+	+	+*T	N/R		
FISCHER 344 IRDC	M	+*T	+*T	+*T	+	+	+
	F	+*T	+*T	+*T	+	+*T	+*T
MOUSE							
CD-1 SDS Biotech	M	+	+	+*	+*	+	+*
	F	-	-	-	+*	+	+*T
B6C3F1 NCI	M	-	-	-	N/R		
	F	-	-	-	"		

\+ Positive
\- Negative
* Statistically Significant by pairwise comparison with control
T Statistically Significant Trend by Cochran Armitage
N/R Not Reported