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

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Peer Review of Chlordimeform (CDM).

FROM: Reto Engler, Chief
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TO: Jay Ellenberger, Product Manager #12
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On July 23, 1985, a Peer Review Panel met to discuss and evaluate the evidence on the oncogenic potential of chlordimeform.

A. The Peer Review Panel

1. The following person constituted the voting members of the panel.

Theodore M. Farber

Donald Barnes

Herbert Lacayo

Irving Mauer

Louis Kasza

Reto Engler

Their signature indicates concurrence with the peer review unless otherwise stated.

2. The following persons who reviewed and presented portions of the data to the panel are non-voting members.

Stanley Gross

Albin Kocialski

Bertram Litt

Their signature indicates the technical accuracy of the following panel review summary report.

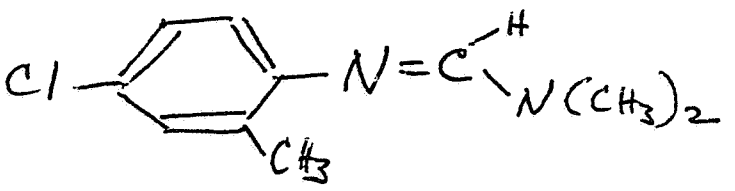
B. Material Reviewed

The material presented for review consisted of the Registration Standard Document (with attachments) and a dose-response assessment (June 14, 1985).

C. Evaluation of the Facts

1. Chemistry, Metabolism and Structure Activity Relationship

CDM is N^1-(4chloro-o-tolyl)N-N dimethyl formamidine:



Its metabolism is rather complex and the plant and animal metabolites have not been totally investigated or identified. However, the information at hand identifies at least two significant metabolites, N-formyl-4chloro-o-toluidine, and 4-chloro-o-toluidine; the latter also being called 5-CAT (5-chloro-1-amino-toluene), a substituted anilin (Note: the 4-chloro, or 5-chloro designation depends on whether the counting is started with the CH_3 or NH_2 group of the toluidine).

The metabolite 5-CAT has been identified in goats, dogs, mice, rats and humans.

The SAR for CDM is clearly evident considering that 5-CAT, a substituted aniline, is in the metabolic pathway of CDM. Anilines are in fact a class of organic chemicals which have long been identified as carcinogens. Consulting IARC Monograph Vol. 27 (April 1982) in summary provides the following information: (1) for aniline per se there is only limited evidence of carcinogenicity (2) for many of the substituted anilines however, there is sufficient evidence, e.g., o-toluidine, o-anisidine. (3) Some substituted anilines seem to be particularly oncogenic if the substituent is in the ortho position to the NH_2 group whereas meta or para substituted anilines were not carcinogenic or only marginally positive e.g., ortho versus para-anisidine 4 chloro-o-phenylenediamine versus 4 chloro-meta-phenylenediamine (4) both o-toluidine and o-anisidine have been found to be oncogenic in rats and mice.

2. Toxicity of CDM

The acute toxicity of CDM is moderate, the LD_{50} values for rats range from 160 to 400 mg/kg bw.

In subchronic and chronic tests a variety of toxic effects were noted including adverse effects on growth, liver, and kidney. The most significant effects reflected in a variety of studies, however, were seen in the hematology of treated animals (rat and dogs) i.e., decreased RCB, hematocrit and hemaglobin, in addition, methemoglobin formation was associated with CDM administration. Methemoglobin formation is often a toxic manifestation seen with aniline derivatives.

The effects of CDM on reproduction did not seem to show any serious adverse effects. CDM was not teratogenic. In a 3-generation reproduction study, the highest dose tested (500 ppm) showed a reduced lactation index and lower weight of pups, however, this study report was not sufficient for a full evaluation.

3. Mutagenicity

CDM and its metabolites have been tested in a number of mutagenicity assays; most of these assays, however, are repeats of testing the chemicals with S. typhimurium (Ames assay), with and without S-9 activation. The results of these tests are not clear cut in that some tests showed mutagenic activity and others did not. However, positive mutagenic activity was demonstrated with the parent compound, the N-formyl-4chloro-o-toluidine and the 5-CAT. (Note: The mutagenicity studies are in the process of being re-evaluated for procedural accuracy.)

The mutagenicity assays evaluated so far are listed in the following table.

Test	Parent Compound (Hcl or Base)			Metabolites "N-Formyl"			5 CAT		
	+[a]	±	-	+	±	-	+	±	-
Ames (Prokaryotes)	1[b]	1	6	1		1	2	1	1
Micronucleus Test			1						
Dom. Lethal			1						
Mouse Spot test			1			1	1		

a) Indicates positive effects (+) marginal or doubtful effect (±) or no effects (-).

b) Indicates number of studies showing the type of response.

This listing of mutagenicity assays seems to indicate that the metabolite 5-CAT may be more potent than the other two compounds studied.

4. Oncogenicity

A. Mice:

The peer review group focussed its attention on the three studies carried out at about the same time (all terminated in 1978) on CDM (study 1), N-formyl-4 chloro-o-toluidine (study 2) and 5-CAT (study 3). The studies used Tif:MAG:SPF strain of mice. In all three studies malignant hemangioendotheliomas in multiple tissues, including the liver were significantly increased by compound administration. The effect was clearly dose related and affected 70 to 85% of the treated animals at the high dose. Both sexes were affected significantly. An overall summary of the results are presented in the following table.

Incidence of benign hemangiomas and malignant hemangioendothelomas in mice.

		Dose Group (ppm)				
		0	2	20	200	500
Study 1	M	2/41[(a)]	ND	1/43	17/48	39/47
	F	4/38	ND	5/43	24/37	35/41
Study 2	M	4/41	ND	7/44	18/42	40/45
	F	8/43	ND	4/44	25/41	38/46
Study 3	M	3/47	1/46	12/46	32/47	40/47
	F	3/38	1/35	11/42	31/39	34/41

(a) Numerator is sum of benign and malignant tumors denominator excludes animals which died of other causes six or more weeks before occurrence of first tumor.

In a more detailed analysis of the data (not presented here) it was also apparent that the occurrence of tumors in the high dose animals preceeded tumor formation in control animals by at least 10 weeks.

An NCI bioassay of 5-CAT (1979) was not further discussed in detail, however, it is noted that hemangiomas and hemagiosarcomas were induced in both sexes of B6C3F1 mice (NCI studies, because of their dose selection usually provide little information about dose response).

The one-liners list a 1974 Japanese mouse study with 5-CAT which was found to be invalid.

B. Rats:

Studies in rats using CDM and the two metabolites (described above) were also carried out.

The peer review committee was informed that studies on the CDM parent compound were negative; the rat studies were not further discussed.

After the meeting, one panel member noted however that the one-liners on the metabolites seemed to indicate that oncogenic response was seen in rats. The reviewer and the section head reassessed the situation and provided the following summary conclusions:

1. CDM was tested in two rat lifetime studies and was not oncogenic. Toxic effects included bile duct hyperplasia and foci of hepatic hypertrophy and hepatocytic hyper plasia.

2. The N-formyl-4chloro-o-toluidine was tested in rats and produced benign cholangiomas in females and males.

3. The 4-chloro-o-toluidine was tested in two rat studies. The one carried out at NCI was negative for oncogenic effects, a Japanese study showed effects suspect of oncogenicity but was not of sufficient quality to allow a unequivocal conclusion.

NOTE: This assessment supercedes the "classification" of the one-liner entries where the Japanese study was classified "minimum" and the study on the N-formyl metabolite as "supplementary."

4. Therefore, there is evidence that CDM per se is not oncogenic, but that its metabolite(s) are oncogenic in the rat. It, however, should be noted that in a published weight of the evidence document e.g., a PD 2/3, the rat bioassays deserve more close review especially those on CDM which showed liver hyperplasias but no tumors at the highest dose tested.

6. Dose Response Assessment

The dose response assessment was discussed in detail, i.e. the lack of monotonicity of some of the data, the omission of the high dose results and the time adjusted calculations.

1. Since the tumor response at the highest two levels of exposure is rather impressive, it was concluded that the apparent lack of monotonicity of the data simply reflects biological variations between control groups and low dose groups.

2. Omitting the high dose in modeled dose response assessments is a technique used in cases where the dose response levels off at higher doses. However, in the case of CDM this manipulation of data does not seem to apply because of the unequivocal nature of the biological evidence, i.e., clear dose response.

3. Some adjustment of the tumor response assessment in this case is probably appropriate since the treatment group animals, especially at the higher doses, were dying off early in part due to the tumor. A confounding feature of these studies, however, is that control animals were allowed to survive to 2.6 years. The question remains how to adjust potency estimates based on "time to tumor" observations.

The peer review group did not suggest which Q_1^* is the most appropriate one to be used for CDM but recommended that in future documents on CDM (e.g. PDs) the scenarios for calculating potency estimates must be discussed in detail.

D. Weight of the Evidence and Classification

The peer review committee summarized the evidence as follows:

1. CDM and two of the metabolites tested are clearly oncogenic in the mouse. The oncogenic effect (malignant hemangioendotheliomas) is dose related, the tumor response at the highest dose was 70-85% versus 10% in most controls. (One data point in study 2 control females was approximately 20%). The metabolite 5-CAT was oncogenic in two strains of mice.

2. Studies in rats with CDM and the 5-CAT metabolite were negative; the N-formyl metabolite, however, produced benign cholangiomas.

3. Mutagenicity assays showed varied results, some were positive some were negative. However, the great majority of tests were "Ames" tests thus there are data gaps concerning a comprehensive mutagenicity battery.

4. Structure activity relationship to substituted anilines supports the finding of oncogenicity.

5. The metabolite 5-CAT has been identified in the urine of exposed humans.

The committee concluded that this provides sufficient experimental evidence from animal data for CDM oncogenicity and therefore its classification in Category B. The clear evidence in mouse bioassays is further supported by the limited evidence in rat bioassays.

The panel discussed the the classification as a B_1 because of the understanding that exposed humans excrete 5-CAT. However, the identification of 5-CAT in urine is actually evidence on human exposure rather than epidemiological evidence (limited or otherwise) of oncogenicity. The conclusion thus, is that CDM is a B_2 oncogen.

E. Referral

The committee concluded that CDM is a candidate for Special Review and should be referred through the policy group. It also should be noted that data on actual residues (e.g., cotton oil) will be necessary since using tolerance levels to calculate a TMRC and a conventional "ADI" (2 ppm NOEL in the rat study and a safety factor of 100) indicates that the "ADI" is already exceeded (134%).

cc: L. Rossi
K. Barbehenn

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