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RESEARCH AND DEVELOPMENT

EVALUATION OF THE POTENTIAL CARCINOGENICITY OF DDE (72-55-9)

IN SUPPORT OF REPORTABLE QUANTITY ADJUSTMENTS PURSUANT TO CERCLA SECTION 102

PREPARED FOR

OFFICE OF EMERGENCY AND REMEDIAL RESPONSE

OFFICE OF SOLID WASTE AND EMERGENCY RESPONSE

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PREFACE

This report summarizes and evaluates information on the potential carcinogenicity of a substance designated as hazardous under Section 101 (14) of the Comprehensive Environmental Response, Compensation and Liability Act of 1980 (CERCLA). Pertinent epidemiologic and toxicologic data were obtained through on-line searches and from hard-copy sources. On-line searches were extended as far back as the data bases would allow. Retrieval of historical data was accomplished through searches of hard-copy sources and bibliographies of relevant publications. Every attempt has been made to rely upon primary publications as opposed to data summaries or abstracts contained in secondary sources such as monographs, surveys, review articles, criteria documents, etc. The on-line data bases that were searched included CHEMLINE (National Library of Medicine [NLM]), RTECS (NLM), Toxicology Data Bank (NLM), TOXLINE (NLM), CANCERLINE (NLM), and Chemical Abstracts (DIALOG Information Services). Unpublished data were not used in this evaluation.

The Agency's Methodology for obtaining, evaluating, and ranking CERCLA potential carcinogens is described in the Technical Background Document to Support Rulemaking Pursuant to CERCLA Section 102, Volume 3, April 26, 1988 (EPA/600/8-89/053). This document revises the previous methodology document of 1986 according to the public comments received on the March 16, 1987 Notice of Proposed Rulemaking (52 FR 8140). The Methodology for Adjusting reportable quantities is described in the Technical Background Document to Support Rulemaking Pursuant to CERCLA Section 102, Volume 1, March, 1985, and is also summarized in Volume 2, August, 1986, and Volume 3, December, 1986. The EPA's Office of Emergency and Remedial Response (OERR) has considered this evaluation in adjusting reportable quantities pursuant to CERCLA Section 102. This report is consistent with the revised methodology. It draws largely on information supplied by the Syracuse Research Corporation in 1984 under EPA Contract No. 68-03-3112. Due to the amount of time elapsed between the original work performed by Syracuse Research Corporation and the present

effort to produce this document, Environmental Monitoring & Services, Inc., under EPA Contract No. 68-03-3182, has been involved in an extensive review of all the Syracuse documents. In some cases, this review involved updating the information provided but it was primarily a quality assurance effort. The present document is a result of this effort.

ABSTRACT

DDE is a probable human carcinogen, classified as weight-of-evidence Group B2 under the EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a). Evidence on potential carcinogenicity from animal studies is "Sufficient," and the evidence from human studies is "Inadequate."

The potency factor (F) for DDE is estimated to be 3.82 $(mg/kg/day)^{-1}$, placing it in potency group 2 according to the CAG's methodology for evaluating potential carcinogens (U.S. EPA, 1986b).

Combining the weight-of-evidence group and the potency group, DDE is assigned a "MEDIUM" hazard ranking for the purposes of RQ adjustment.

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1.0 WEIGHT OF EVIDENCE

1.1 ANIMAL STUDIES

In a study conducted by the NCI (1978), B6C3F1 mice were fed 148 ppm and 261 ppm 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) for 78 weeks, with 15 additional weeks of observation before termination. Thus for the 93 week study the transformed doses were 16.3 mg/kg/day and 28.7 mg/kg/day. DDE in the females caused a DDE-dependent loss in weight as early as 10 weeks; the male weights were unaffected. The mortality curve (increased deaths before termination of the experiment) in the female mice was also affected by DDE ($P<0.001$). The control male mortality was 15/20 (75%) at 70 weeks. Hepatocellular carcinomas were observed in mice of both sexes, with the strongest response occurring in the females. The incidence of carcinoma in the control, low-, and high-dose animals, respectively were as follows: females, 0/19, 19/47 and 34/48; males, 0/19, 7/41, and 17/47.

In a parallel NCI study (1978), male Osborne-Mendel rats were fed 437 ppm and 839 ppm and females were fed 242 and 462 ppm DDE for 78 weeks, and observed for an additional 15 weeks. None of the rats responded with tumors within the 2-year study period. The rats exhibited liver involvement in the form of centrilobular necrosis and fatty metamorphosis.

In a study by Tomatis (1974), CF-1 mice were fed 250 ppm DDE for 130 weeks. The female mice treated with DDE showed increased hepatomas (authors' terminology) (54/55 vs 1/90 in controls) as well as early appearance of hepatomas. Male CF-1 mice responded similarly (39/53 vs 33/98 in controls) and died earlier with hepatomas. The hepatomas were largest in size and occurred with the greatest multiplicity (hepatomas/mouse) in DDE-treated mice as compared with control mice.

Residue data from autopsies performed on the CF-1 mice showed that DDE was retained in the liver to a degree second only to its rate of retention in body fat. DDE residues occurred in normal livers at about the same levels as in

tumorous livers, thereby indicating that the residual presence of DDE is not, in and of itself, a sufficient cause of carcinogenesis in mice.

DDE was also tested for carcinogenicity in the hamster (Rossi et al., 1983). At doses of 500 ppm and 1000 ppm, DDE in the diet of hamsters caused a significant increase in the incidence ($P < 0.05$) of hepatomas in males (7/30 and 8/39) and in females (4/39 and 6/39). The incidence of tumors in controls was 0/31 (males) and 0/42 (females). These hamster liver tumors had a latency period of more than 76 weeks. (DDT did not produce tumors in hamsters at the same dose levels.)

1.2 HUMAN STUDIES

Pertinent data regarding the carcinogenic effects of human exposure to DDE were not located in the available literature.

1.3 WEIGHT-OF-EVIDENCE ASSESSMENT

DDE has been shown to produce liver tumors in mice in two independent studies and liver tumors in hamsters in an additional study. The value of the NCI study was limited by the poor survival in the control male mice. Fifteen of the 20 control mice died by week 70. This limited survival could have curtailed the development of late-developing hepatomas in the controls. In all these studies, the compound was administered by inc[illegible] similar study using rats, no statistically s[illegible] of any tumors was observed in the treated a[illegible] carcinogenic effects of DDE in human[illegible] r Carcinogen Risk Assessment (U.S. EPA[illegible] weight of evidence to humans, DDE is most a[illegible] 82 chemical. Appendix A contains summa[illegible] r animal studies cited in this review.

The Appendix contains...

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Despite the quantitatively greater i[illegible] Tomatis study, relative to the NCI study, ar[illegible] e in the NCI study, the latter was chosen for potency [illegible] the NCI used 2

treated groups, compared to 1 used by Tomatis. Furthermore, the historical hepatocellular carcinoma rate in untreated female B6C3F1 mice was 67/1683, as of 12/5/88 (NTP, personal communication). The incidences of hepatocellular malignancies in both groups of treated female mice therefore appeared to exceed background levels. The appendix contains summaries of the significant human and/or animal studies cited in this review.

2.0 POTENCY

The potency factor (F) for DDE is estimated to be 3.82 $(mg/kg/day)^{-1}$, placing it in potency group 2 under the CAG's methodology for evaluating potential carcinogens (U.S. EPA, 1986b). Table 2-1 contains data from the selected study used to derive the potency factor (F) for DDE.

The U.S. EPA (1986c) used a geometric mean of similar potencies from general studies of DDT, DDE, DDD, and dicofol to estimate the potency of DDE for risk assessment purposes. For this ranking of carcinogens, however, it is considered important that all substances be ranked by the same methodology as much as possible. Therefore, the study judged most appropriate for each substance individually has been used in ranking these substances.

Table 2-1. Derivation of Potency Factor(F) Agent: DDE

REFERENCE:	NCI, 1978		
EXPOSURE ROUTE:	oral		
SPECIES:	mice		
STRAIN:	B6C3F1		
SEX:	F		
VEHICLE OR PHYSICAL STATE:	diet		
BODY WEIGHT:[a]	0.03 kg		
DURATION OF TREATMENT:	546 days		
DURATION OF STUDY:	644 days		
LIFESPAN OF ANIMAL:[a]	730 days		
TARGET ORGAN:	liver		
TUMOR TYPE:	hepatocellular carcinoma		
EXPERIMENTAL DOSES/EXPOSURE:	0.0 ppm	148 ppm	261 ppm
TRANSFORMED DOSES:[b] (mg/kg/day)	0.0	16.3	28.7
TUMOR INCIDENCE:	0/19	19/47	34/48
ANIMAL POTENCY: $(mg/kg/day)^{-1}$	0.198		
HUMAN POTENCY:[c] $(mg/kg/day)^{-1}$	3.82		

[a] Estimated

[b] To derive the transformed dose from the experimental dose data: experimental dose (ppm) x an empirically-derived food factor corresponding to the fraction of body weight that is consumed each day as food (0.13 in mice) x (duration of treatment/duration of study).

[c] Human potency = animal potency x $(70\ kg/0.03\ kg)^{1/3}$ x $(730\ days/644\ days)^{3}$ to adjust for the short study duration.

3.0 HAZARD RANKING

Based on the weight-of-evidence Group B2 for DDE, and the potency factor (F) of 3.82 $(mg/kg/day)^{-1}$, DDE receives a hazard ranking of "MEDIUM."

4.0 REFERENCES

NCI (National Cancer Institute), 1978. Bioassays of DDT, TDE, and p,p'-DDE for Possible Carcinogenicity. Publ. No. NCI-CG-TR-131. U.S. DHEW, PHS, NIH. p. 117.

Rossi, L., O. Barbieri, M. Sanguineti, C. Marina, R.P. Jose, P. Bruzzi and L. Santi, 1983. Carcinogenicity Study with Technical-Grade Dichlorodiphenyltrichloroethane and 1,1-Dichloro-2,2-Bis(p-Chlorophenyl)Ethylene in Hamsters. Cancer Res. 43(2): 776-781.

Tomatis, L., V. Turusov, R.T. Charles and M. Boiocchi, 1974. The Effect of Long-Term Exposure to 1,1-Dichloro-2,2-Bis(p-Chlorophenyl)Ethylene (p,p'-DDE), to 1,1-Dichloro-2,2-Bis(p-Chlorophenyl)Ethane (p,p'-DDD) and to the Two Chemicals Combined, on CF-1 Mice. J. Natl. Cancer Inst. 52: 883-891.

U.S. EPA (Environmental Protection Agency), 1986a. Guidelines for Carcinogen Risk Assessment, 51 FR 33992-34003, September 24, 1986.

U.S. EPA (Environmental Protection Agency), 1986b. Methodology for Evaluating Potential Carcinogenicity in Support of Reportable Quantity Adjustments Pursuant to CERCLA Section 102, OHEA-C-073, December 1986. Available from CERCLA Docket 102RQ-273C. The public docket for RQ rulemaking is located in room M2427, U.S. Environmental Protection Agency, 401 M Street, SW, Washington, DC 20460. It is available for inspection Monday through Friday excluding Federal holidays, between the hours of 9:00 a.m. and 4:00 p.m.

U.S. EPA (Environmental Protection Agency), 1986c. The Assessment of the Carcinogenicity of Dicofol (Kelthane), DDT, DDE, and DDD (TDE), EPA-600/6-86-001, February 1986. NTIS PB87-110904/AS

U.S. EPA (Environmental Protection Agency), 1988. Technical Background Document to Support Rulemaking Pursuant to CERCLA Section 102, Volume 3, Draft, Appendix A, April 26, 1988.

APPENDIX

SUMMARY OF SIGNIFICANT HUMAN AND/OR ANIMAL STUDIES

Table A. Animal

Agent: DDE

Reference: NCI, 1978

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
oral	rat/ Osborne-Mendel	M	0.0 ppm	NA	111 wks	NA	NA	any organ	any tumor	NA
oral	rat/ Osborne-Mendel	M	437 ppm[a]	78 wks	111 wks	95%[b]	diet	any organ	any tumor	NS
oral	rat/ Osborne-Mendel	M	839 ppm[a]	78 wks	111 wks	95%[b]	diet	any organ	any tumor	NS
oral	rat/ Osborne-Mendel	F	0.0 ppm	NA	111 wks	NA	NA	any organ	any tumor	NA
oral	rat/ Osborne-Mendel	F	242 ppm[a]	78 wks	111 wks	95%[b]	diet	any organ	any tumor	NS
oral	rat/ Osborne-Mendel	F	462 ppm[a]	78 wks	111 wks	95%[b]	diet	any organ	any tumor	NS
oral	mouse/ B6C3F1	M	0.0 ppm	NA	92 wks	NA	NA	liver	hepatocellular[c] carcinoma	0/19
oral	mouse/ B6C3F1	M	148 ppm[a]	78 wks	92 wks	95%[b]	diet	liver	hepatocellular carcinoma	7/41

Table A. Animal

Agent: DDE

Reference: NCI, 1978 (cont.)

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
oral	mouse/ B6C3F1	M	261 ppm[a]	78 wks	92 wks	95%[b]	diet	liver	hepatocellular carcinoma	17/47 (P<0.001)
oral	mouse/ B6C3F1	F	0.0 ppm	NA	92 wks	NA	NA	liver	hepatocellular carcinoma	0/19
oral	mouse/ B6C3F1	F	148 ppm[a]	78 wks	92 wks	95%[b]	diet	liver	hepatocellular carcinoma	19/47 (P<0.001)
oral	mouse/ B6C3F1	F	261 ppm[a]	78 wks	92 wks	95%[b]	diet	liver	hepatocellular carcinoma	34/48 (P<0.001)

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QUALITY OF EVIDENCE

Strength of Study: Extensive histopathological examinations were performed. Two levels of exposure were used. A significant dose-response was observed in the female mice as well as the male mice.

Weaknesses of Study: The survival of both control and high dose male mice was below historical values. Survival in control female mice was also below historical values.

Overall Adequacy: Adequate for female mice, but poor survival in the control male mice (15 of 20 control mice died by week 70) limited evaluation in the male mouse.

[a] The exposure is expressed as the time-weighted average exposure calculated for the treatment period.

[b] Gas liquid chromatography was used to confirm that the compound was p,p'-DDE.

[c] The pathologist made no differentiation among the liver tumors. All were designated hepatocellular carcinomas. No adenomas were reported.

NA = Not applicable; NS = Not significant

Table A. Animal

Agent: DDE

Reference: Rossi et al., 1983

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
o	hamster/ Syrian Golden	M	500 ppm	120 weeks	120 weeks	99%	olive oil/ diet	liver	neoplastic nodules	7/30
								adrenal	adenoma	5/30
o	hamster/ Syrian Golden	F	500 ppm	120 weeks	120 weeks	99%	olive oil/ diet	liver	neoplastic nodules	4/39
								adrenal	adenoma	7/39
o	hamster/ Syrian Golden	M	1000 ppm	120 weeks	120 weeks	99%	olive oil/ diet	liver	neoplastic nodules	8/39[a]
								adrenal	adenoma	17/39
o	hamster/ Syrian Golden	F	1000 ppm	120 weeks	120 weeks	99%	olive oil/ diet	liver	neoplastic nodules	6/39[b]
								adrenal	adenoma	8/39
o	hamster/ Syrian Golden	M	0 ppm (control)	120 weeks	120 weeks	NA	olive oil/ diet	liver	neoplastic nodules	0/31
								adrenal	adenoma	8/31
o	hamster/ Syrian Golden	F	0 ppm (control)	120 weeks	120 weeks	NA	olive oil/ diet	liver	neoplastic nodules	0/42
								adrenal	adenoma	2/42
o	hamster/ Syrian Golden	M	1000 ppm DDT	120 weeks	120 weeks	technical grade	olive oil/ diet	liver	neoplastic nodules	0/35[c]
								adrenal	adenoma	14/35
o	hamster/ Syrian Golden	F	1000 ppm DDT	120 weeks	120 weeks	technical grade	olive oil/ diet	liver	neoplastic nodules	0/36[c]
								adrenal	adenoma	10/36

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Table A. Animal

Agent: DDE

Reference: Rossi et al., 1983 (cont.)

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)

QUALITY OF EVIDENCE

Strengths of Study: Histological studies were carried out on a variety of tissues and organs. Animals were treated from 8-128 weeks of age. Two levels of exposure were used.

Overall Adequacy: Adequate

Comments: DDT was also tested in this study. The authors concluded that DDE, a metabolite of DDT, plays a major role in DDT carcinogenesis.

[a] Five additional animals showed hyperplastic foci of the liver.
[b] Three additional animals showed hyperplastic foci of the liver.
NA = Not applicable

Table A. Animal

Agent: DDE

Reference: Tomatis et al., 1974

Exposure Route	Species/ Strain	Sex	Dose or Exposure	Duration of Treatment	Duration of Study	Purity of Compound	Vehicle or Physical State	Target Organ	Tumor Type	Tumor Incidence (P value)
o	mouse/ CF-1	M	0.0 ppm	NA	123 weeks	NA	NA	liver	hepatoma	33/98
o	mouse/ CF-1	M	250 ppm	123 weeks	123 weeks	NR	diet	liver	hepatoma	39/53
o	mouse/ CF-1	F	0.0 ppm	NA	123 weeks	NA	NA	liver	hepatoma	1/90
o	mouse/ CF-1	F	250 ppm	123 weeks	123 weeks	NR	diet	liver	hepatoma	54/55

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QUALITY OF EVIDENCE

Strengths of Study: Animals were treated from 7 weeks old until 130 weeks old. The incidence of lymphomas, lung tumors, and osteomas were also enumerated.

Weaknesses of Study: Only one level of exposure was used.

Overall Adequacy: Adequate

NA = Not applicable; NR = Not reported

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15. SUPPLEMENTARY NOTES

16. ABSTRACT

DDE is a probable human carcinogen, classified as weight-of-evidence Group B2 under the EPA Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a). Evidence on potential carcinogenicity from animal studies is "Sufficient," and the evidence from human studies is "Inadequate."

The potency factor (F) for DDE is estimated to be 3.82 $(mg/kg/day)^{-1}$, placing it in potency group 2 according to the CAG's methodology for evaluating potential carcinogens (U.S. EPA, 1986b).

Combining the weight-of-evidence group and the potency group, DDE is assigned a "MEDIUM" hazard ranking for the purposes of RQ adjustment.

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