OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

12

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

FEB 10 1995

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Carcinogenicity Peer Review of ~~DCPA~~ (Dimethyl tetrachloroterephthalate or Dacthal)

FROM: Linda Taylor, Ph.D. Linda Taylor 1/30/95
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The Health Effects Division Carcinogenicity Peer Review Committee (CPRC) met on June 29 and Nov. 16, 1994 to discuss and evaluate the weight-of-the-evidence on DCPA with particular reference to its carcinogenic potential.

The Peer Review Committee agreed that DCPA should be classified as a Group C - possible human carcinogen and that a low-dose extrapolation methodology (Q*) be applied to the animal data. This decision was based on evidence of increased incidences of thyroid tumors in both sexes of the rat (although only at an excessive dose in the female), and liver tumors in two species: both the female rat and the female mouse, at doses which were not excessive.

SUMMARY

Administration of DCPA in the diet to Sprague Dawley rats resulted in a statistically significant increase in thyroid follicular cell adenomas and combined adenoma/carcinoma in male rats at 3 doses (50, 500 and 1000 mg/kg/day). The incidences of thyroid adenomas at these 3 doses exceeded that of historical controls. There was in males also a statistically significant increasing trend for thyroid follicular cell adenoma and combined adenoma/carcinoma.

The CPRC consensus was that in the male rat, the tumor response in the thyroid at the 2 highest doses (500 and 1000 mg/kg/day), occurred under conditions of excessive toxicity. It was agreed however, that the statistically significant increase in thyroid adenomas in the males at the next highest dose (50 mg/kg/day), was not accompanied by significant toxicity.

In female rats there was a statistically significant pairwise increase for combined thyroid follicular cell adenoma/carcinoma only and only at the highest dose tested (HDT - 1000 mg/kg/day). There was in females also a statistically significant increasing trend for thyroid follicular carcinomas, as well as for combined adenoma/carcinoma. The incidences of thyroid follicular cell adenomas and carcinomas in female rats exceeded that of historical controls.

In addition, in female rats there was a statistically significant pairwise increase in hepatocellular adenomas and combined adenoma/carcinoma/hepatocholangiocarcinoma at the 2 highest doses (500 and 1000 mg/kg/day) with a statistically significant increasing trend for each of these tumor types individually and combined. The incidence of adenomas at the two highest doses, and the incidences of carcinomas and hepatocholangiomas at the HDT exceeded that of historical controls.

In the female rat, the CPRC consensus was that the highest dose (1000 mg/kg/day) was excessively toxic, but that the doses below that were adequate.

Administration of DCPA in the diet to CD-1 mice resulted in statistically significant increases in hepatocellular adenomas alone in female mice only, and only at the HDT, with a statistically significant increasing trend for adenomas and combined adenoma/carcinoma. The incidence of adenomas at the HDT was outside the range of the historical control incidence. The dosing in this study was considered to be adequate.

The CPRC agreed that impurities (Confidential Business Information, CBI) of DCPA, associated with thyroid (and other) tumors in rodents, may have contributed to the tumor response with DCPA. The CPRC concluded, however, that the tumors seen in the DCPA study could not be solely attributed to the presence of either impurity in the administered material.

Upon consideration of a hormonal mechanism for the thyroid tumors in the rat, the CPRC concluded that the thyroid tumors associated with administration of DCPA may be due to a disruption in the thyroid-pituitary status. However, other mechanisms can not be excluded, since there were tumors in the mouse liver (at a dose which was not excessive) as well. [Details are provided in Section F. "The Weight of Evidence".]

The classification of Group C was based on increased incidences of thyroid tumors in both sexes of the rat (although only at an excessive dose in the female), and liver tumors in two species: both the female rat and the female mouse, at doses which were not excessive. Although significant increases were found only for hepatocellular adenomas and combined adenoma/carcinoma/ hepatocholangiocarcinoma, carcinomas (or combined carcinoma/hepatocholangiocarcinoma) constituted a substantial portion (38 to 45 %) of the combined tumor incidence in the female rat liver at the two highest doses. All the available evidence for genotoxicity suggest a low concern for DCPA and its 2,3,5,6,-tetrachloroterephthalate metabolite.

The CPRC agreed that these data were sufficient for the purpose of risk characterization, and that a low dose extrapolation model be applied to the animal data for the quantification of human risk (Q_1^*), based on the combined liver tumors in the female rat liver.

A. Individuals in Attendance at one or both meetings:

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

Penny Fenner-Crisp

Stephanie Irene

Reto Engler

William Burnam

Karl Baetcke

Marcia Van Gemert

Hugh Pettigrew

Esther Rinde

Richard Hill

Yin Tak Woo

Marion Copley

Kerry Dearfield

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

Linda Taylor[1]

Clark Swentzel

Lori Brunsman

Lucas Brennecke[2]
(PAI/Clement)

3. Other Attendees:

Bernice Fisher and Stanley Gross (HED), Jon Fleuchaus and Amber Aranda (OGC)

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

[2]Signature indicates concurrence with pathology report.

B. Material Reviewed

The material available for review consisted of DER's, one-liners, data from the literature and other data summaries prepared and/or supplied by Dr. Linda Taylor, and tables and statistical analysis by Lori Brunsman. The material reviewed is attached to the file copy of this report.

C. Background Information

DCPA, dimethyl tetrachloroterephthalate is an herbicide used to control a broad spectrum of weed grasses [smooth and hairy crabgrass, witchgrass, green and yellow foxtail, fall panicum, and others], certain broadleaf weeds [carpet weed, dodder, purslane, nodding/prostrate/spotted spurge, and common chickweed] when applied preemergence to germinating weed seeds. It inhibits growth by modifying cell division. It is of the chemical family: chlorinated benzoic acids, and it is known by the tradename dacthal®. Other names include 2,3,5,5-tetrachlorodimethyl-1,4-benzenedicarboxylic acid, chlorothal, chlorothal dimethyl, and dacthalor. The molecular formula is $C_{10}H_6Cl_4O_4$ (MW 332). DCPA has a vapor pressure of 0.01 mm Hg at 40° C and a solubility of < 0.5 mg/L in water and 100, 200, 170, and 140 g/L in acetone, benzene, toluene, and xylene, respectively. [See Figure 1 for structure].

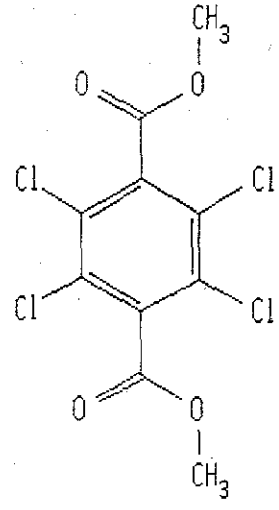

Figure 2 DCPA

The Chemical Abstracts Registry Number [CAS #] for DCPA is 1861-32-1, the CASWELL No. is 382, and the P.C. Code [Shaughnessey #] is 078701.

D. Evaluation of Carcinogenic Evidence

1. Lucas, F. and Killeen, Jr., JC. A Combined Chronic Toxicity and Tumorigenicity Study in Mice with Technical DCPA. Study #: DSK 109/88383, Huntingdon Research Centre, Ltd., England, dated October 6, 1988 [MRID # 409587-01], Document #: 008095.

Experimental Design: DCPA was administered in the diet to 60 CD-1 mice/sex/group [0, 100, 1000, 3500, or 7500 ppm which is equivalent to: ♂♂ 12, 123, 435, 930 mg/kg/day; ♀♀ 15, 150, 510, 1141 mg/kg/day, respectively] for 104 weeks. There were three interim sacrifices [♀♀/♂♂ at 26/27, 52/53, and 78/79 weeks] of an additional 10 mice/sex/dose/sacrifice.

Neoplastic Lesions: **FEMALES** - Statistically significant increasing trends in hepatocellular adenomas and combined adenomas and/or carcinomas were observed in females, and there was a significant difference in the pairwise comparison of the high-dose group with the controls for hepatocellular adenomas [Table 1, taken from the Statistics memo dated 6/20/94]. The incidence of adenomas at the high dose was outside the range of historical control data [Table 2]. **MALES** - There were no significant treatment-related tumors observed in males [Table 1], although the incidence of adenomas at the high-dose level was greater than that of the concurrent and historical control incidence [Table 2].

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Table 1. Dacthal- Hepatocellular Tumor Rates in the CD-1 Mouse+

Lesion	MALES					FEMALES				
Group Dose(ppm)	0	100	1000	3500	7500	0	100	1000	3500	7500
Adenoma (%) p=	17/68 (25) 0.150	17/75 (23) 0.447[n]	16/73 (22) 0.408[n]	11/73 (15) 0.103[n]	24[a]/77 (31) 0.262	2/74 (3) 0.001**	0/73 (0) 0.252[n]	2/71 (3) 0.674	4[g]/75 (5) 0.347	8/72 (11) 0.044*
Carcinoma (%) p=	6/68 (9) 0.129	6/75 (8) 0.548[n]	10/73 (14) 0.260	9/73 (12) 0.346	11[b]/77 (14) 0.224	1[h]/74 (1) 0.406	1/73 (1) 0.748	0/71 (0) 0.510[n]	1/75 (1) 0.748	1/72 (1) 0.745
Combined (%) p=	22[c]/68 (32) 0.062	19[d]/75 (25) 0.229[n]	24[e]/73 (33) 0.545	20/73 (27) 0.323[n]	31[f]/77 (40) 0.208	3/74 (4) 0.002**	1/73 (1) 0.315[n]	2/71 (3) 0.520[n]	5/75 (7) 0.367	9/72 (12) 0.059

\+ # of tumor-bearing mice/# of mice examined, excluding those that diet or were sacrificed before week 53.
[n] Negative change from control
[a] First male adenoma observed at week 53, dose 7500 ppm.
[b] First male carcinoma observed at week 68, dose 7500 ppm.
[c] one mouse in control had both an adenoma and a carcinoma.
[d] four mice at 100 ppm had both an adenoma and a carcinoma.
[e] two mice at 1000 ppm had both an adenoma and a carcinoma.
[f] four mice at 7500 ppm had both an adenoma and a carcinoma.
[g] First female adenoma observed at week 53, dose 3500 ppm.
[h] First female carcinoma observed at week 79, dose 0 ppm.

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

Historical control data from 9 studies in the CD-1 mouse of 97-108 weeks' duration [1981-1983] were provided [Table 2]. From the historical control data as presented, one cannot determine the combined incidence of adenoma and/or carcinoma. The highest incidence of adenoma in the historical control is 26.9% ♂♂/7.7% ♀♀.

Table 2. Historical Control Data on Liver Tumors in CD-1 Mice [# mice with tumor (%)]

Sex/lesion/study #	1	2	3	4	5	6	7	8	9
MALES									
adenomas	2(3.8)	13(12.5)	15(14.4)	6(11.5)	16(18.2)	11(21.2)	12(23.1)	14(26.9)	9(17.3)
carcinomas	12(23.1)	25(24.0)	17(16.3)	14(26.9)	25(28.4)	9(17.3)	6(11.5)	10(19.2)	20(38.5)
combined♥	14(26.7)	38(36.5)	32(30.8)	20(38.5)	41(46.6)	20(38.5)	18(34.6)	24(46.2)	29(55.8)
FEMALES									
adenomas	1(1.9)	3(2.9)	7(6.7)	4(7.7)	6(6.8)	2(3.8)	1(1.9)	2(3.8)	4(7.7)
carcinomas	1(1.9)	2(1.9)	3(2.9)	0	2(2.3)	0	0	0	1(1.9)
combined♥	2(3.8)	5(4.8)	10(9.6)	4(7.7)	8(9.1)	2(3.8)	1(1.9)	2(3.8)	5(9.6)
# mice/sex examined	52	104	104	52	88	52	52	52	52

♥ no data on whether any mice had both tumor types

Non-neoplastic Lesions: In the liver, there was a dose-related increase in the number of male mice with centrilobular hepatocyte enlargement at the 27-, 53-, and 79-week sacrifices compared to the control males, but no increase was observed at termination. Additionally, there was an increased incidence of centrilobular hepatocyte enlargement in the high-dose male mice dying on test compared to the control value. A similar effect was not observed in females. Liver weight was increased at the highest dose level [7500 ppm] in both sexes and in the 3500 ppm males at week 27, in the 3500 ppm and 7500 ppm females at week 53, and at terminal sacrifice in both sexes at 7500 ppm.

Adequacy of Dose: With regard to mortality, there were no statistically significant incremental changes with increasing dose in either sex and adequate numbers of mice were available. The highest dose was approximately one gram of DCPA per kilogram of body weight, which is sufficiently high [limit dose] for assessing the carcinogenicity potential of DCPA.

2. Lucas, F., Mizens, M., and Laveglia, J. A Combined Chronic Toxicity/Oncogenicity Study in Rats with DCPA. Study # 3339-90-0005-TX-006; Ricerca, Inc., Painesville, OH; dated March 31, 1993 [MRID # 427310-01]; Document # 010513.

Experimental Design: DCPA was administered in the diet to 70 Sprague-Dawley CD rats/sex/group at dose levels of 0, 1, 10, 50, 500, or 1000 mg/kg/day for 104 weeks. There was an interim sacrifice of 10 rats/sex/dose at 52 weeks.

Neoplastic Lesions: **LIVER** - Hepatocholangiocarcinoma, which was considered with carcinoma, was described as consisting of an individual neoplasm that had cells resembling both hepatocytes and biliary epithelium and were considered to be a subtype of hepatocellular carcinoma (reference provided). **MALES** -Males did not display an increased incidence in liver tumors. **FEMALES** - Females had significant increasing trends in hepatocellular adenomas, carcinomas, hepatocholangiocarcinomas, and combined adenomas and/or carcinomas and/or hepatocholangiocarcinomas. Additionally, there were significant differences in the pair-wise comparisons of the 500 and 1000 mg/kg/day dose groups with the controls for hepatocellular adenomas and combined hepatocellular adenomas and/or carcinomas and/or hepatocholangiocarcinomas [Table 3].

Table 3. Dacthal- Sprague-Dawley CD Rats

FEMALE Hepatocellular Tumor Rates+ and (p values)

Tumor/Dose (mg/kg)	0	1	10	50	500	1000
adenoma (%) p=	0/69 (0) 0.000**	0/69 (0) 1.000	1/67 (1) 0.493	1/68 (1) 0.496	5[a]/70 (7) 0.030*	7/68 (10) 0.006**
carcinoma (%) p=	0/69 (0) 0.009**	0/69 (0) 1.000	1/67 (1) 0.493	0/68 (0) 1.000	3[b]/70 (4) 0.125	3/68 (4) 0.120
hepatocholangiocarcinomas (%) p=	0/69 (0) 0.027*	0/69 (0) 1.000	0/67 (0) 1.000	0/68 (0) 1.000	0/70 (0) 1.000	2[c]/68 (3) 0.245
combined (5) p=	0/69 (0) 0.000**	0/69 (0) 1.000	2/67 (3) 0.241	1/68 (1) 0.496	8/70 (11) 0.003**	11[d]/68 (16) 0.000**

+ # of tumor-bearing rats/# of rats examined, excluding those that died or were sacrificed before week 53.
[a] First adenoma observed at week 53, dose 500 mg/kg/day.
[b] First carcinoma observed at week 96, dose 500 mg/kg/day.
[c] First hepatocholangiocarcinoma observed at week 106, dose 1000 mg/kg/day
[d] one rat at 1000 mg/kg/day had both an adenoma and a carcinoma

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

THYROID: MALES - Males had significant increasing trends in thyroid follicular cell adenomas and combined adenomas and/or carcinomas, and there were significant differences in the pair-wise comparisons of the three highest dose levels with the controls for thyroid follicular cell adenomas and combined adenomas and/or carcinomas [Table 4]. **FEMALES** - Females had significant increasing trends in thyroid follicular cell carcinomas and combined adenomas and/or carcinomas, and there were significant differences in the pair-wise comparisons of the 1000 mg/kg/day dose group with the controls for combined thyroid follicular cell adenomas and/or carcinomas [Table 5].

Table 4. Dacthal- Sprague-Dawley CD Rats

MALE Thyroid Follicular Cell Tumor Rates+ and Peto Prevalence Test Results (p values)

Tumor/Dose (mg/kg)	0	1	10	50	500	1000
adenomas (%) p=	1/57 (2) 0.003**	2/53 (4) 0.279	2/50 (4) 0.286	8/48 (17) 0.003**	10[a]/54 (19) 0.001**	7/53 (13) 0.0104*
carcinomas (%) p=	1/67 (1) 0.740	1/63 (2) 0.377	1/63 (2) 0.453	0/63 (0) -	1[b]/68 (1) 0.499	0/68 (0) -
combined (%) p=	2/67 (3) 0.011*	3/63 (5) 0.309	3/63 (5) 0.288	8/63 (13) 0.008**	11/68 (16) 0.003**	7/68 (10) 0.024*

+ # of tumor-bearing rats/# of rats examined, excluding those that died or were sacrificed before the observation of the first tumor.

[a] First adenoma observed at week 65, dose 500 mg/kg/day.

[b] First carcinoma observed at week 51, dose 500 mg/kg/day.

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

Table 5. Dacthal- Sprague-Dawley CD Rats

FEMALE Thyroid Follicular Cell Tumor Rates+ and p values

Tumor/Dose (mg/kg)	0	1	10	50	500	1000
adenomas (%) p=	1/56 (2) 0.135	1/58 (2) 0.743	2/57 (4) 0.507	4/58 (7) 0.193	1/59 (2) 0.739	4[a]/56 (7) 0.182
carcinomas (%) p=	0/56 (0) 0.002**	0/58 (0) 1.000	1/57 (2) 0.504	0/58 (0) 1.000	1/59 (2) 0.513	4[b]/56 (7) 0.059
combined (%) p=	1/56 (2) 0.012*	1/58 (2) 0.743	3/57 (5) 0.316	4/58 (7) 0.193	2/59 (3) 0.520	7[c]/56 (12) 0.030*

+ # of tumor-bearing rats/# of rats examined, excluding those that died or were sacrificed before week 54.

[a] First adenoma observed at week 68, dose 1000 mg/kg/day.

[b] First carcinoma observed at week 84, dose 1000 mg/kg/day.

[c] One rat in the 1000 mg/kg/day dose group had both an adenoma and a carcinoma.

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

Historical control data from four 2-year studies (60 animals per study) at Ricerca, Inc. [1990-1992] were provided for liver and thyroid tumors in the Sprague Dawley rat:

> The historical control incidence of hepatocellular adenomas in female rats ranged from 0 to 3.3% with a mean of 0.8% (2/240). The historical control incidence of hepatocellular carcinomas and hepatocholangiocarcinomas in female rats was 0 in all 4 studies.
>
> The historical control incidence of thyroid follicular cell adenomas in male rats ranged from 1.7 to 5.0% with a mean of 3.3% (8/240); in female rats the range was 0 to 3.4% with a mean of 1.3% (3/239). The historical control incidence of thyroid follicular cell carcinomas in male rats was 0 to 3.3% with a mean of 2.0% (5/240); in female rats the range was 0 to 1.7% with a mean of 0.8% (2/239).

In the DCPA rat study, the incidences of hepatocellular adenomas and carcinomas in females at both the 500 and 1000 mg/kg/day (HDT) dose levels, and the hepatocholangiocarcinomas at the HDT, exceeded that of the historical controls. (There were no increased incidences in liver tumors reported for male rats.)

The incidences of thyroid follicular cell adenomas in males at the 50, 500 and 1000 mg/kg/day dose levels and in females at 50 and 1000 mg/kg/day dose levels exceeded that of the historical controls; in females the incidence of thyroid follicular cell carcinomas at the HDT was also outside that of the historical controls.

Non-neoplastic Lesions: **LIVER** There was a dose-related (statistically significant) increase in the incidence and severity of centrilobular hepatocytic swelling [hepatocytic hypertrophy] in both sexes at dose levels of 50 mg/kg and above at both the interim and terminal sacrifices and in males at 10 mg/kg at the terminal sacrifice. This lesion was characterized by an increase in cellular size, accompanied by a ground-glass appearance to the cytoplasm of the hepatocytes located in close proximity to the central vein of each hepatic lobule. As the severity of the lesion increased, larger portions of the lobule were affected, which the author points out is consistent with metabolic activation and an increase in smooth endoplasmic reticulum within the cell. Additionally, there was an increased incidence of eosinophilic foci in both sexes at dose levels of 10 mg/kg and above. It was stated that eosinophilic foci are focal areas of cellular alteration in the liver characterized by areas of hepatocytes with intensely

eosinophilic cytoplasm, enlarged hepatocytes, increases in hepatocyte numbers, and distinct lesion borders occasionally resulting in compression of the adjacent parenchyma. An increase in osmiophilic membranes and smooth endoplasmic reticulum were observed in the hepatocytes of the 3 high-dose males evaluated by electron microscopy.

THYROID - There was a dose-related, statistically significant increase in the incidence and/or severity of follicular cell hypertrophy and diffuse follicular cell hyperplasia in males at dose levels of 10 mg/kg and above and a treatment-related increase in basophilic clumped colloid at the same dose levels (statistically significant at 50 mg/kg and above) at the terminal sacrifice. In females at the 50, 500, and 1000 mg/kg dose levels, a dose-related increase in the incidence and severity of basophilic clumped colloid, diffuse follicular cell hyperplasia, and follicular cell hypertrophy were noted (statistical significance attained except for the hypertrophy at 50 mg/kg). Similar findings were reported at the interim sacrifice in males at 10 mg/kg and above and in females at 500 and 1000 mg/kg.

Other Relevant Data on the Thyroid: In the chronic study, decreased T_3 and T_4 values were observed in males, and in general, increased TSH values were observed [Table 6]. In females, decreased T_4 and increased TSH values were observed throughout the study [Table 7]. Calculation of the thyroid/pituitary hormone output ratio suggests a NOEL for males at 1 mg/kg/day and for females at 10 mg/kg/day. There were increased thyroid weights at the 1000 mg/kg dose level in males, and females at all dose levels displayed increased thyroid weights, but there was no dose response. In the 90-day rat study, follicular cell hypertrophy was observed at 1000 mg/kg in both sexes, and males also displayed clumped colloid and cystic follicles at 1000 mg/kg.

Table 6. Dacthal- Sprague-Dawley CD Rats: Thyroid/Pituitary Hormone Output Ratio - **MALES**

Parameter/Dose	0 mg/kg	1 mg/kg	10 mg/kg	50 mg/kg	500 mg/kg	1000 mg/kg
T_3 (ng/mL)						
week 52	0.857	0.824	0.839	0.730	0.704	0.659
week 83	0.833	0.951	0.872	0.865	0.877	0.783
week 104	0.742	0.847	0.786	0.792	0.730	0.728
T_4 (ng/mL)						
week 52	36.8	38.4	26.2	16.9	11.0	7.7
week 83	27.9	27.8	17.4	12.4	5.3	4.4
week 104	23.9	27.0	18.4	10.2	3.9	2.3
$T_3 + T_4$						
week 52	37.657	39.224	27.039	17.630	11.704	8.359
week 83	28.733	28.751	18.272	13.265	6.177	5.183
week 104	24.642	27.847	19.186	10.992	4.630	3.028
TSH (ng/mL)						
week 52	1.52	1.59	1.89	1.97	2.12	2.46
week 83	2.13	2.48	2.31	2.44	2.63	1.96
week 104	1.49	2.00	2.88	2.05	2.90	2.17
$T_3 + T_4$/TSH						
week 52	24.774	24.669	14.306	8.949	5.521	3.398
week 83	13.490	11.593	7.910	5.392	2.349	2.644
week 104	16.538	13.924	6.662	5.362	1.597	1.395

Table 7. Dacthal- Sprague-Dawley CD Rats: Thyroid/Pituitary Hormone Output Ratio - **FEMALES**

Parameter/Dose	0 mg/kg	1 mg/kg	10 mg/kg	50 mg/kg	500 mg/kg	1000 mg/kg
T_3 (ng/mL)						
week 52	1.147	1.149	1.178	1.051	1.135	1.147
week 83	0.926	1.058	0.899	0.967	1.051	0.981
week 104	1.171	1.064	1.003	1.034	1.071	1.097
T_4 (ng/Ml)						
week 52	25.4	24.0	23.5	13.2	8.9	5.8
week 83	18.2	22.5	16.0	11.3	7.1	2.8
week 104	25.8	18.0	18.7	11.7	4.8	3.8
$T_3 + T_4$						
week 52	26.547	25.149	24.678	14.251	10.035	6.947
week 83	19.126	23.558	16.899	12.267	8.151	3.781
week 104	26.971	19.064	19.703	12.734	5.871	4.897
TSH (ng/mL)						
week 52	1.28	1.32	1.22	1.45	1.51	1.70
week 83	1.33	1.39	1.26	1.46	1.79	1.52
week 104	1.21	1.20	1.35	1.52	1.68	2.18
$T_3 + T_4$/TSH						
week 52	20.740	19.052	20.228	9.828	6.646	4.086
week 83	14.380	16.948	13.412	8.402	4.694	2.488
week 104	22.290	15.887	14.595	8.378	3.495	2.246

Adequacy of Dose Levels: The highest dose was 1 gram/kilogram, the limit dose. Survival was comparable among the groups for both sexes for the first year of the study. There was a significant increasing trend in mortality with increasing dose of DCPA in male rats, and males showed significant differences in the pair-wise comparisons of mortality of the controls with the high-dose [1000 mg/kg/day] group. There were also clinical signs of toxicity (signs of poor health) in male rats at the 500 and 1000 mg/kg/day doses. Females displayed comparable survival among the groups at study termination, and there were no significant incremental changes in mortality with increasing doses of DCPA. Body weights were comparable among the groups for both sexes during the first year. For the most part, males displayed comparable body-weight gains among the groups for the first year, with the highest dose level males displaying decreases during the second year of the study. Female body-weight gains were decreased in a dose-related manner from the third week on and were >15% by week 78 in the 1000 mg/kg/day dose group. The data suggest a decrease in food efficiency for both sexes at dose levels of ≥ 50 mg/kg.

The CPRC consensus was that in the male rat, the 2 highest doses (500 and 1000 mg/kg/day) were excessively toxic based on increased mortality and clinical signs, but in the female rat, only the highest dose (1000 mg/kg/day) was excessive, based on body weight gain depression.

E. Other Relevant Toxicology Information:

1. Genotoxicity

DCPA has been tested in several mutagenicity studies. Dacthal was negative in the following acceptable mutagenicity assays:

1) mouse lymphoma gene mutation assay (MRID# 41054822)
2) in vitro aberrations in Chinese hamster ovary (CHO) cells (MRID# 41054823)
3) unscheduled DNA synthesis (UDS) in primary rat hepatocytes (MRID# 41054824)
4) sister chromatid exchanges in CHO cells (MRID# 41054825)

There are no data gaps for mutagenicity testing of DCPA.

Metabolite - A metabolite of DCPA, 2,3,5,6-tetrachloro terephthalate, was shown to be at best equivocal for clastogenic activity (only in male mice) in an in vivo mouse micronucleus test. This metabolite did not induce gene mutation in the CHO/HGPRT assay, was negative in the sister chromatid exchange assay in CHO cells, and did not induce an increase in UDS. An Ames assay was negative with and without metabolic activation at dose levels up to

1500 μg/plate, but no evidence of cytotoxicity was demonstrated. Based on the available evidence for the parent compound and the metabolite, there is not a mutagenicity concern for DCPA.

2. Metabolism

The major metabolite of DCPA in the urine of rats was 4-carbomethoxy-2,3,5,6-tetrachlorobenzoic acid following single [1 and 1000 mg/kg] and multiple [1 and 1000 mg/kg] oral doses. A minor polar metabolite was identified as tetrachloroterephthalic acid. No radiolabel was excreted in the urine as the parent compound. Urine was the major excretory route in both sexes at the low dose [single and multiple] but a minor route at the high dose. Feces was the major route of elimination of radiolabel at the high dose [single and multiple]. Radiolabel was found in all tissues examined. The elimination halflife was calculated to be 22-23 hours [high dose] and ≈18 hours [low dose], based on cumulative urine excretion data. The data suggest that at the high dose, the absorption/elimination processes were saturated. There was no evidence of accumulation.

3. Structure-Activity Correlations

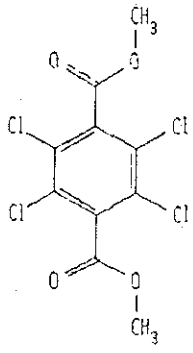
DCPA belongs to the chemical family of chlorinated benzoic acids. Dimethyl terephthalate is structurally related to DCPA and an increase [equivocal] in lung tumors in male mice has been reported. The pesticides pronamide [classified Group B_2 with a Q^*_1] and pentachloronitrobenzene [PCNB; classified Group C, no Q^*_1] have been shown to induce thyroid tumors in rats [adenomas and combined adenomas and/or carcinomas (significant trend in both sexes and significant pairwise comparison with control in males at HDT)]. These were not however considered to be appropriate structural analogs. Structures are shown in Figure 2.

4. Other Data

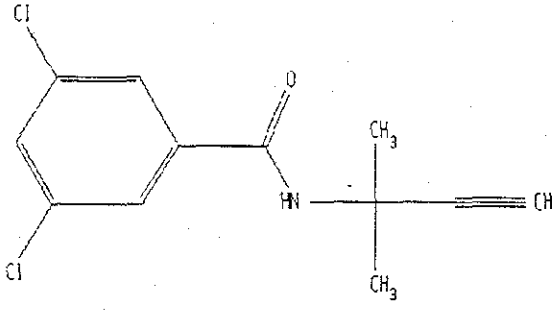
Two impurities (CBI) in DCPA have been shown to produce thyroid tumors in Syrian golden hamsters and Sprague Dawley rats; tumors at other sites (parathyroid, liver, lungs, bile duct, kidney, and adrenal) have also been observed in rat and mouse studies with these impurities. No significant genotoxicity was reported for either impurity.

IMPURITIES - THE TYPES OF TUMORS AND THE LEVELS AT WHICH TUMORS WERE OBSERVED IN THE DCPA STUDY, WERE COMPARED WITH THAT SEEN IN STUDIES WITH THE IMPURITIES. THE LEVELS AT WHICH THE IMPURITIES MIGHT HAVE BEEN PRESENT IN THE ADMINISTERED DCPA WERE CALCULATED TO ASSESS WHAT, IF ANY, CONTRIBUTION TO TUMOR INCIDENCE COULD BE ATTRIBUTED TO THESE IMPURITIES. THE FULL DISCUSSION OF THE

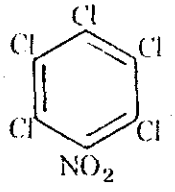
Figure 2



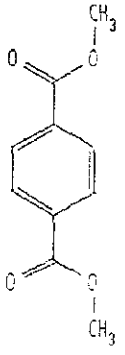
DCPA



Pronamide



PCNB



Dimethyl Terephthalate

IMPURITIES IN DCPA, AND THE LEVELS CALCULATED TO BE PRESENT, ARE CONTAINED IN AN ADDENDUM DUE TO POSSIBLE CBI CONCERNS.

The CPRC agreed that these impurities (CBI) of DCPA, associated with thyroid (and other) tumors in rodents, may have contributed to the tumor response with DCPA. The CPRC concluded, however, that the tumors seen in the DCPA study could not be attributed solely to the presence of either impurity in the administered material.

F. Weight of Evidence Considerations

The Committee considered the following facts regarding the toxicology data on DCPA in a weight-of-the-evidence determination of carcinogenic potential.

1. **Male and female CD-1 mice were fed DCPA via the diet at dose levels of 0, 100, 1000, 3500, or 7500 ppm [♂♂ 12, 123, 435, 930 mg/kg/day; ♀♀ 15, 150, 510, 1141 mg/kg/day, respectively] for 104 weeks.**

In female mice, the administration of DCPA was associated with significant increasing trends in hepatocellular adenomas and combined adenomas and/or carcinomas. There was a significant difference in the pairwise comparison of the 7500 ppm dose groups with the controls for hepatocellular adenomas.

In female mice, the incidence of hepatocellular adenomas at the 7500 ppm dose level exceeded the available historical control incidences in female mice of this strain.

In male mice, there were no significant compound-related tumors observed, although the high-dose males displayed more hepatocellular adenomas than the concurrent control, and the incidence of hepatocellular adenomas at the 7500 ppm dose level exceeded the available historical control incidences in male mice of this strain.

The doses used in both sexes of mouse were considered to be adequate.

2. **Male and female Sprague-Dawley CD rats were fed diets containing DCPA at dose levels of 0, 1, 10, 50, 500, or 1000 mg/kg/day for 104 weeks.**

In female rats, DCPA was associated with significant increasing trends in hepatocellular adenomas, carcinomas, hepatocholangiocarcinoma and combined adenomas and/or carcinomas and/or hepatocholangiocarcinomas. There were significant differences in the pairwise comparisons of the 500 and 1000 mg/kg dose females with the controls for hepatocellular adenomas and combined adenomas

and/or carcinomas and/or hepatocholangiocarcinomas.

In female rats, the incidence of hepatocellular adenomas and carcinomas at the 500 and 1000 mg/kg/day dose levels, and hepatocholangiomas at 1000 mg/kg/day, exceeded the available historical control incidences in rats of this strain.

In female rats, there were significant increasing trends in thyroid follicular cell carcinomas and combined adenomas and/or carcinomas, and there were significant differences in the pairwise comparisons of the 1000 mg/kg dose group with the controls for combined thyroid follicular cell adenomas and/or carcinomas.

In female rats, the incidences of thyroid follicular cell adenomas at 50 (but not at 500) and 1000 mg/kg/day, and thyroid follicular cell carcinomas at the 1000 mg/kg/day dose level exceeded the available historical control data.

In male rats, there were significant increasing trends in thyroid follicular cell adenomas and combined adenomas and/or carcinomas and significant differences in the pair-wise comparisons of the 50, 500, and 1000 mg/kg dose males with the control males for thyroid follicular cell adenomas and combined adenomas and/or carcinomas.

In male rats, the incidence of thyroid follicular cell adenomas at the 50, 500, and 1000 mg/kg dose levels exceeded the available historical control incidence in male rats of this strain.

The dose levels used were considered excessive at the 1000 mg/kg/day level in both sexes of the rat and at the 500 mg/kg/day dose level, as well, in males.

3. The following additional effects on the thyroid were observed in the chronic rat study [both sexes]: a dose-related increase in the incidence and/or severity of follicular cell hypertrophy, follicular cell hyperplasia, and basophilic clumped colloid at both the interim and terminal sacrifices, increased thyroid weights, decreased T_4/T_3 values, and increased TSH.

4. All the available evidence for genotoxicity suggest a low concern for DCPA and its 2,3,5,6,-tetrachloroterephthalate metabolite.

5. DCPA is structurally related to dimethyl terephthalate. Equivocal findings have been reported regarding its carcinogenicity; lung tumors in male mice.

6. The CPRC agreed that impurities (CBI) of DCPA, associated with thyroid (and other) tumors in rodents, may have contributed to the tumor response with DCPA. The CPRC concluded, however, that the tumors seen in the DCPA study could not be solely attributed to the presence of either impurity in the administered material.

7. Carcinogenicity in animals --DCPA

After a full evaluation of all of the data and supporting information regarding animal carcinogenicity, the Committee concludes that exposure to DCPA resulted in an increased incidence of thyroid follicular cell tumors in both sexes of the rat and hepatocellular tumors in both the female Sprague-Dawley rat and in the female CD-1 mouse. The tumor response was attributable to both adenomas and combined adenoma/carcinoma/hepatocholangiocarcinoma, with carcinomas (or combined carcinoma/hepatocholangiocarcinoma) contributing a substantial portion of the total incidence in the female rat liver. The incidences of most of these tumors exceeded that of historical controls.

The relevance of the tumor data to an evaluation of DCPA's potential for human carcinogenicity is discussed elsewhere in this document.

8. **Consideration of the Use of the Threshold Model for DCPA**

In the evaluation of DCPA, the Committee considered the possibility of using the threshold model for thyroid neoplasms. The following discussion has been taken from the Amitrole Peer Review Document (dated Nov. 30, 1992) and revised for DCPA.

The following guidance is given in the Agency's DRAFT Policy Document [Thyroid Follicular Carcinogenesis: Mechanistic and Science Policy Considerations, SAB Review Draft, May 1988]:

"Studies over the last several decades in multiple laboratories and using a number of different treatment regimens (eg., iodine deficiency) have demonstrated the significance of long-term thyroid-pituitary hormonal imbalance in thyroid carcinogenesis. A consistent progression of events is noted: reduction in thyroid hormone concentrations, elevation in TSH levels, cellular hypertrophy and hyperplasia, nodular hyperplasia, and neoplasia. Hyperplasia and sometimes neoplasia of the pituitary may also be

seen. A block in any of the early steps acts as a block for subsequent steps including tumor development, and cessation of treatment at an early stage in the progression results in regression toward normal thyroid structure and function. Based on these observations..... the Agency concludes that:

a. thyroid follicular cell tumors may arise from long-term disturbances in thyroid-pituitary feedback under conditions of reduced circulating thyroid hormone and elevated TSH levels:

b. the steps leading to these tumors are expected to show thresholds, such that the risks of tumor development are minimal when thyroid-pituitary homeostasis exists; and

c. models that assume thresholds may be used to assess the risks of thyroid follicular cell tumors where there is evidence of thyroid-pituitary hormonal imbalance."

Two basic questions must be addressed before this policy is applied.

"The first is a qualitative issue which addresses whether it is reasonable to presume that the neoplasms are due to thyroid-pituitary imbalance. A corollary issue is the extent to which other carcinogenic mechanisms can be discounted. The second question concerns the procedures to be employed in estimating the risks of these agents."

"The answers to the first question allow one to assign chemicals producing thyroid tumors to one of three categories. The assignation is based on knowledge as to whether the chemical disrupts thyroid-pituitary feedback, whether tumors other than thyroid follicular cell (and relevant pituitary) tumors are found, and whether mechanisms other than thyroid-pituitary imbalance may apply to the observed tumor response."

<u>Determination of whether neoplasms are due to thyroid-pituitary imbalance</u>

The document goes on to describe the 3 factors that should be considered in making this determination (answering the first question, or "qualitative issue"). These are addressed as they apply to DCPA as follows:

<u>FACTOR I</u>. Consideration of whether the thyroid tumors associated with administration of DCPA can be attributed to disruption of the thyroid-pituitary hormonal balance. [In addressing this factor, the Policy states that 6 indicators should be considered.]

a. **Goitrogenic activity <u>in vivo</u>**: Thyroid follicular cell hyperplasia and/or hypertrophy were increased in males at the

low/mid-, mid-, mid/high-, and high-dose levels [dose-related] and in females at the three highest dose levels [dose-related] in the chronic rat study. Additionally, these effects were observed at the interim [12-month] sacrifice in the chronic rat study, and thyroid follicular cell hypertrophy was observed in the 90-day rat feeding study in both sexes at the limit dose.

b. **Clinical chemistry changes** [e.g., reduced thyroid hormone and increased TSH serum concentrations]: In the chronic toxicity/ carcinogenicity study in rats, T_4 values were decreased [dose-related] in both sexes at all but the lowest dose level. TSH values were increased in both sexes, with females showing a dose-related increase at weeks 52 and 104. A dose-related reduction of thyroid/pituitary hormone output ratio [$(T_3 + T_4)$/TSH] was observed in both sexes also.

c. **Specific evidence of reduced hormone synthesis** [e.g., inhibited iodine uptake] **or increased thyroid hormone clearance** [e.g., enhanced biliary excretion]: None of the studies available provide these types of data.

d. **Evidence of progression** [e.g., hypertrophy/hyperplasia, nodular hyperplasia - neoplasia]: There was evidence of progression [hypertrophy/hyperplasia to neoplasia] in rats. In the 90-day rat study, follicular cell hypertrophy was observed at the limit dose. In the two-year rat study, follicular cell hypertrophy and follicular cell hyperplasia were observed at the 12-month sacrifice, with one follicular cell carcinoma in a mid-high dose male. At the 104-week sacrifice, follicular cell hypertrophy/ hyperplasia, as well as increased numbers of follicular cell adenomas/carcinomas were observed.

e. **Reversibility of effects after exposure is terminated:** None of the studies contain this type of data.

f. **SAR to other thyroid tumorigens:** The pesticides pronamide and pentachloronitrobenzene [PCNB] have been shown to induce thyroid tumors in rats [↑ adenomas and combined adenomas and/or carcinomas (significant trend in both sexes and significant pairwise comparison with control in males at HDT)]. Both pesticides were negative for gene mutations, and Pronamide was negative for structural chromosomal aberrations and for other genotoxic effects. PCNB was positive for structural chromosomal aberrations and no information is available for the other genotoxic effects.

Based on the overall judgment of the six indicators in Factor I, it may be concluded that there are sufficient data to determine whether there is suggestive evidence that the thyroid tumors in the rat associated with the administration of DCPA may be due to a disruption in the thyroid-pituitary status.

FACTOR II: Consideration of the extent to which genotoxicity may account for the observed tumor effects.

The genotoxicity data on DCPA itself are negative. There is no indication that genotoxicity plays a role in the tumorigenic activity for DCPA.

FACTOR III: Evaluation of neoplasms other than thyroid follicular cell tumors (and relevant pituitary tumors).

Female mice displayed significant increasing trends in hepatocellular adenomas and combined adenomas and/or carcinomas and a significant difference in the pair-wise comparison of the high-dose group with controls for hepatocellular adenomas. The incidence of liver adenomas at the high dose level exceeded the available historical control incidences in the strain of mouse used. Female rats showed significant increasing trends in hepatocellular adenomas, carcinomas, hepatocholangiocarcinomas, and combined adenomas and/or carcinomas and/or hepatocholangiocarcinomas, as well as significant differences in the pair-wise comparisons for hepatocellular adenomas and combined adenomas and/or carcinomas and/or hepatocholangiocarcinomas. The increased incidence of hepatocellular adenomas exceeded the available historical control data.

Based on the overall judgment of the 6 indicators in FACTOR I and adding in FACTORS II and III, sufficient data exist with which to conclude that there is suggestive evidence that the thyroid tumors in the rat associated with the administration of DCPA may be due to a disruption in the thyroid-pituitary status. All of the criteria for a threshold effect have been met except there are no data available regarding the reversibility of the thyroid effects [not tested] or reduced hormone synthesis/increased thyroid hormone clearance [not assessed] for DCPA. Nevertheless, other mechanisms of tumor induction by DCPA cannot be excluded.

Factors to be Considered in Determining Method to be Used in Estimating the Risks of DCPA

Again, this guidance was taken from the Amitrole Peer Review Document and revised for DCPA. The Committee was requested to consider these points in determining which method to use for estimating the carcinogenic risk for DCPA.

Guidance given in the EPA DRAFT policy for proceeding with the quantitation of risk is as follows:

a. "Threshold considerations should be applied in dose-response assessments for those chemical substances where (1) only thyroid tumors (and relevant pituitary tumors) have been produced; (2) the

tumors can be attributed to a disruption in thyroid-pituitary hormonal homeostasis; and (3) potential mechanisms other than thyroid-pituitary imbalance (eg., genotoxicity) can be discarded.

b. Special attention should be given to chemicals (1) that have induced thyroid tumors (and relevant pituitary tumors) that may be due to thyroid-pituitary imbalance, and (2) where there is also evidence of either a genotoxic potential or the induction of neoplasms at sites other than the thyroid (or pituitary). Generally, those cases will be approached using various principles laid out in the EPA Guidelines for Carcinogen Risk Assessment. A strong rationale must be articulated for handling these agents otherwise.

c. For those chemicals producing thyroid tumors that do not seem to be acting via thyroid-pituitary hormonal inhibition, dose-response assessments will be performed in accordance with the EPA Guidelines for Carcinogen Risk Assessment."[3]

[3]A new policy document is in process, which currently states these phrases differently: 1. "Threshold considerations will be incorporated into thyroid (and relevant pituitary) cancer dose-response assessments for chemicals that (a) cause disruption of thyroid-pituitary homeostasis and (b) are judged not to have genotoxic activity relevant to carcinogenicity. Dose-response relationships for neoplasms other than the thyroid (or pituitary) should be evaluated using mechanistic information bearing on their induction and various principles laid out in the Agency's cancer risk assessment guidelines. 2. Threshold considerations may be applied in thyroid cancer dose-response assessments on a case-by-case basis for chemicals that (a) produce thyroid-pituitary imbalance and (b) are judged to have genotoxic activity related to carcinogenicity. The implications of the genotoxic events to the thyroid carcinogenic responses need to be carefully evaluated. In some cases thyroid cancer dose-response relationships may be characterized in more than one way. 3. Threshold considerations will not be applied in thyroid cancer dose-response assessments for substances operating through mechanisms not involving thyroid-pituitary imbalance. However, case-by-case exceptions may arise, based on mode of action data."

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.

The Peer Review Committee agreed that DCPA should be classified as a Group C - possible human carcinogen and that a low-dose extrapolation methodology (Q*) be applied to the animal data. This decision was based on evidence of increased incidences of thyroid tumors in both sexes of the rat (although only at an excessive dose in the female), and liver tumors in two species: both the female rat and the female mouse, at doses which were not excessive. Although significant increases were found only for hepatocellular adenomas and combined adenoma/carcinoma/hepatocholangiocarcinoma, carcinomas (or combined carcinoma/hepatocholangiocarcinoma) constituted a substantial portion (38 to 45%) of the combined tumor incidence in the female rat liver at the two highest doses.

All the available evidence for genotoxicity suggest a low concern for DCPA and its 2,3,5,6,-tetrachloroterephthalate metabolite. DCPA is structurally related to dimethyl terephthalate, which has been associated with equivocal findings of lung tumors in the male mouse (not evaluated by the CPRC).

The CPRC recommended that a low dose extrapolation model be applied to the animal data for the quantification of human risk (Q_1^*), based on the combined liver tumors in the female rat liver.

13544

R056005

Chemical:	**DCPA (or chlorthal-dimethyl?)**
PC Code:	**078701**
HED File Code	**21200 PEER REVIEW**
Memo Date:	**02/10/95 12:00:00 AM**
File *ID*:	**00000000**
Accession Number:	**412-04-0045**

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