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

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CASWELL FILE

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Record No. 150980; Pre-RPAR Review of Publications and Reports Pertaining to the Carcinogenic Potential of Chlorpropham (CIPC)

Tox. Chem. No. 510A

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Due to the possibility of carcinogenic hazard resulting from the use of chlorpropham (CIPC), this chemical is being considered for Special Review. This review considers all pertinent data available on this topic. The literature submitted for this evaluation consists of the following documents (studies marked with an asterisk (*) were previously reviewed by the Toxicology Branch):

	Publication/Report	Accession Number
*1.	Journal of the National Cancer Institute - Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note	231831
*2.	British Journal of Cancer - The Production of Skin Tumours in Mice by Oral Treatment with Urethane, Isopropyl N-phenyl Carbamate or Isopropyl N-chlorophenyl Carbamate in Combination with Skin Painting with Croton Oil and Tween 60	234190
*3.	Pesticide Biochemistry and Physiology - Metabolic Studies of ^{14}C-Labeled Propham and Chlorpropham in the Female Rat	234190
*4.	Food and Cosmetics Toxicology - Long-Term Toxicity Studies of Chlorpropham and Propham in Mice and Hamsters	234190
*5.	Toxicology and Applied Pharmacology - Chronic Toxicologic Studies on Isopropyl N-(3-Chlorophenyl) Carbamate (CIPC)	234190
*6.	90-Day Rat Feeding Study of CIPC	090892

Publication/Report	Number
*7. 2-Year Rat Feeding Study of CIPC and 1-Year Dog Feeding Study of CIPC	090892
8. Report by the Public Health Council in the Hague - Investigation of the Potential Tumorigenic Properties of Chlorpropham in Comparison to Urethane	097141
9. Congressional Record - NCI Studies of Pesticides [Contains the same report as document 1.]	090892
10. U.S. Department of HEW - from the Report of the Secretary's Commission on Pesticides and Their Relationship to Environmental Health	090892

SUMMARY OF REVIEWS:

1. Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note - The incidence of hepatoma, pulmonary tumors, and lymphoma for mice dosed with CIPC was similar to the controls. Dose level - 464 mg/kg/day for 4 weeks, then 1112 ppm in the diet for 17 months.

2. The Production of Skin Tumors in Mice by Oral Treatment with Urethane, Isopropylphenyl carbamate, or N-chlorophenyl carbamate in combination with Skin Painting with Croton Oil and Tween 60 - CIPC is an initiator when dosed in conjunction with croton oil.

3. Metabolic Studies of ^{14}C-Labeled Propham and Chlorpropham in the Female Rat - Urinary excretion was the main route of elimination. Elimination was by first-order kinetics. Exhaled radioactivity in CO_2 was 35.4% for chain CIPC. Distribution was to all tissues with the greatest concentration being in the kidneys. Organ half-lives generally ranged from 3-8 hours, but half-lives for brain, fat, and muscle were double that of the other organs. CIPC and IPC were metabolized by hydrolytic and oxidative mechanisms, and the metabolites were excreted as free forms or as conjugates.

4. Long-Term Toxicity Studies of Chlorpropham and Propham in Mice and Hamsters - No toxic signs or tumors in hamsters dosed at 0.2% CIPC in feed for 33 months. Female mice dosed S.C. had reduced growth. No other toxic signs or tumors were seen in mice dosed orally or S.C. Mice were dosed orally at 0.1% CIPC in feed, or S.C. at 1 g CIPC/kg for nine injections over 17 months.

5. Chronic Toxicologic Studies on Isopropyl N-(3-Chlorophenyl) carbamate (CIPC) [in Rats and Dogs] - CIPC was nontoxic to rats and dogs at doses < 2.0% in diet. Doses of 2.0% caused decreased weight gain, male deaths, decreased hemoglobin and hematocrit values, and increased liver and spleen weights in rats. Doses of 2.0% caused initial weight losses, lower hemoglobin and hematocrit values, and increased liver and spleen weights in dogs. No lesions or tumors were seen in either species. Dose levels - 0, 0.02, 0.2, and 2.0% CIPC in feed for both species; rats were dosed for 2 years, and the dogs for 1 year.

6. 90-Day Rat Feeding Study (99.4%) - NOEL = 17 mg/kg/day (0.031% in feed). At doses of 0.125, 0.5, and 2.0 mg/kg/day, CIPC appeared to impose a continuous metabolic stress on the liver resulting in hepatic hypertrophy. No functional impairment was seen at these doses. Dose levels - 0.031, 0.125, 0.5, and 2.0% in feed (17, 63, 260, and 1240 mg/kg/day, respectively).

7. Two-Year Rat Feeding Study, and One-Year Dog Feeding Study of Isopropyl N-(3-Chlorophenyl) Carbamate (CIPC) - Male and female rats dosed at 2.0% in feed had decreased body weight by week 80 but the males were at normal weight by the end of the study. This group had increased mortality at week 102 relative to the controls. They had decreased hematocrit and hemoglobin values. No dose-related lesions were found. The dog NOEL = 0.2% in feed. At a dose of 2.0% in feed, dogs had anorexia, decreased weight gain, decreased hematocrit and hemoglobin values (months 1-9), and elevated spleen and liver weights. Dose levels - 0.02, 0.2, and 2.0% in feed for both species.

8. Investigation of the Potential Tumorigenic Properties of Chlorpropham in Comparison to Urethane:

   Oncogenicity Studies of Orally and Intravenously Administered CIPC and Urethane in Mice - There was no evidence that CIPC is a carcinogen when administered orally or subcutaneously. Structurally similar urethane, however, caused lung tumors in nearly all mice. Dose levels - 0.1% CIPC in feed for 116 weeks, or 1000 mg/kg/dose of CIPC S.C., 7 times over 17 months.

   Assessment of the Initiating Effect of IPC and CIPC in Combination with Croton Oil on Mice - There was no evidence that CIPC acts as an initiator when administered orally prior to dermal administration of croton oil, a promoter. Orally administered IPC, however, caused an increased incidence of papillomas and two malignancies. Dose levels - 15 mg CIPC P.O. once weekly for 10 weeks, followed by dermally dosed croton oil twice weekly for 26 weeks.

9. Congressional Record - Senate, May 1 1969, S 4112:

   Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note [This is a more extensive review of Publication 1] - CIPC and IPC allegedly did not induce tumors at the doses tested. Urethane, which is structurally similar, did induce tumors. Dose level - 464 mg/kg/day of CIPC for 4 weeks, then 1112 ppm in the diet for 17 months.

10. Report of the Secretary's Commission on Pesticides and Their Relationship to Environmental Health [Teratology] - This study was not evaluable due to the poor quality of the supplied report and the apparent contradiction in the results.

In the chronic feeding/oral studies (Publications/Reports 1, 4, 5, 7, 8, and 9), tumor incidence was not significantly increased in mice, rats, dogs, or hamsters at doses as high as 0.1, 2.0, 2.0, and 0.2% in feed, respectively. Similarly, chronic subcutaneous doses of 1000 mg/kg/day in mice did not elicit tumors (Publications/Reports 4 and 8). Most of the doses described above were toxic. Two studies of CIPC as a tumor initiator gave conflicting results. In one study (Publication 2), treatment with CIPC and croton oil resulted in significantly more tumors than in the croton oil controls. In the second study (Report 8), tumor incidence in the CIPC and croton oil group and the croton oil

controls were similar (IPC treated mice had twice as many tumors as the controls, however). This discrepancy was due to the lower tumor incidence in the Publication 2 study. This may be due to the absence of acetone (an irritant) in the croton oil formulation in this study. The second study (Report 8) appears to be more reliable, thus suggesting that CIPC is not an initiator.

STUDY REVIEWS:

The verbatim texts of those reviews completed prior to this action are as follows (bracketed comments [ ] are for clarification or correction):

1. [Reg. No. 45-81-GGT; W. Woodrow; 10-10-78; Accession No. 231831]
Journal of the National Cancer Institute V. 42, No. 6, June, 1969. Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note. Innes, Ulland, Valerio, Petnucelli, Harat, Palotta, Bates, Falk, Gart, Klein, Mitchell, and Peters.

   120 chemicals, including controls and CIPC, were tested for tremorigenicity [tumorigenicity]. 18M and 18F/each of two mouse strains plus controls. Animals were treated daily by intubation for the first four months [weeks] with 464 mg/kg, followed by 1112 ppm mixed in diets for remaining 14 months [17 months] of the experiment.

   Results - The incidence of hepatomas, pulmonary tumors or lymphomas in test survivors (accompanied by some lithal [lethal] toxic effects) was not significantly increased above those for control animals. No significance at the $p = 0.01$ level for any type of tumor; for either of the two mouse strains used.

   Classification: Core supplementary data

   Only 18 mice/sex/dose group used, one dosage level used.

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2. [Reg. No. 45-81-GGT; W. Woodrow; 10-10-78; Accession No. 234190]
British Journal of Cancers 12 (1958). The Production of Skin Tumors in Mice by Oral Treatment with Urethane, Isopropylphenyl carbamate, or N-chlorophenyl carbamate in combination with Skin Painting with Croton Oil and Tween 80 [Tween 60]. Esch, Van Genderen, and Vink.

   Groups of 15 M and 15 F mice each were treated orally with 15 mg of CIPC, and skin tested with croton oil or Tween 80 [Tween 60] promotors for a period of 6 months. At this time animals without papillomas were sacrificed and examined; remaining animals were continued 10 months. Dosing of CIPC plus promotors:

   a. 15 mg single dose + croton oil or Tween 80 [Tween 60].
   b. 15 mg orally 10 times once/week for 10 weeks.
   c. CIPC mixed in diets at 0.1% plus croton oil or Tween 80 [Tween 60].

   Results - Control groups of mice treated with urethane or CIPC - without oil promotors did not develop papillomas. Conclusion: CIPC has the same tumor initiating property by the oral route as the

urethane control, but to a much lesser degree when administered in combination with the oncogenic promoting agents croton oil or Tween 80 [IPC and urethane were dose in conjunction with croton oil and Tween 60, but CIPC was only dosed in conjunction with croton oil]

Classification: Core minimum data

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3. [Reg. No. 45-81-GGT; W. Woodrow; 10-10-78; Accession No. 234190]
Pesticide Bio-Chemistry and Physiology V.4 1-11 (1974).
Metabolic Studies of ^{14}C-Labeled Propham and Chlorpropham in the Female Rat.
Fanz, Fallin, Montgomery, and Freed.

Labeled material - [2-^{14}C] isopropyl-m-chlorocarbanilate (chain - [^{14}C] chloropham, 2.59 mc/m mole Lot#464-067).

Also, isopropyl-ring [^{14}C] m-chloro-carbanilate (ring- [^{14}C] chloropham, 4.30 m (i/m mole Lot#464-063)

Results - Urinary excretion is the main route of elimination and is not influenced by the oral dosages used (1 mg to approx. 200 mg/kg). The average 3 day urinary excretions of radioactivity following single oral dosages were 55.9%, 82.69% [sic], 79.5%, and 85.4% of an oral dose of chain [^{14}C] chloropham, ring and [^{14}C] chloropham, [^{14}C] chain chlorpropham - 35.4 $\pm$ 7.5% of the administered radioactivity appeared in the respired air. [Correction - "The average 3-day urinary excretions of radioactivity were 55.9%, 82.6%, 79.5% and 85.4% of an oral dose of chain [^{14}C] chlorpropham, ring [^{14}C] chlorpropham, chain [^{14}C] propham, and ring [^{14}C] propham, respectively" (from publication abstract)]

The radioactivity was distributed in all tissues with highest concentration found in the kidney. The average biological half-life of ^{14}C from chlorpropham in most organs was short, ranging between 3 and 8 hours; however, in train [brain], fat, and muscle, the half-life was about twice the value for other organs.

Both compounds were metabolized by hydrolytic and oxidative mechanisms; resulting metabolites were excreted either as free forms or as conjugates.

Subcellular distribution of ^{14}C in the rat liver and kidney after oral administration was dependent on the elapsed time after dosing.

Classification: Core minimum data

Both sexes should have been used. Administration by the I.V. route should have been included.

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4. [Reg. No. 45-81-GGT; W. Woodrow; 10-10-78; Accession No. 234190]
Food and Cosmetics Toxicology Vol. 10 (1972) p. 373.
Long-Term Toxicity Studies of Chlorpropham and Propham in Mice and Hamsters.
Van Esch and Krofs.

49 hamsters were fed (M & F hamsters) 0.2% CIPC for 33 months.

25 Males and 25 Females mice fed a diet of 0.1% CIPC. A similar group received SC application of CIPC in methyl pyrrolodine (0.025 ml - 1 g CIPC/kg body wt.). Nine injections over 17 months.

Results

hamsters - CIPC did not affect growth (at level tested), mortality, did not enhance tumor incidence or did not induce other histopathological findings.

mice - growth reduced in female mice treated by SC route. Mortality was not affected. No histologically determined abnormalities related to CIPC treatment found for oral or SC routes. CIPC did not show carcinogenic properties (by oral in SC routes), + control was positive.

Classification: Core-minimum data

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5. [Reg. No. 45-81-GGT; W. Woodrow; 10-10-78; Accession No. 234190]
Toxicology and Applied Pharmacology 2, 659-673 (1960).
Chronic Toxicologic Studies on Isopropyl N-(3-Chlorophenyl) carbamate (CIPC).
Larson, Crawford, Smith, Hennigar, Hanz and Finnigan.

4 groups of 25 M and 25 F rats each were maintained on 0, 0.02, 0.2, and 2.0% of CIPC [in feed] for 2 years.

4 groups of 2M and 2F Beagles were placed on the same CIPC concentration diets at age 6 months. Study spanned 1st 12 months of dogs life. [Correction- The study spanned 12 months, i.e. from months 6-18 of the dog's age]

Results - relatively low chronic toxicity to rats and dogs. No discernable adverse effects of CIPC at dietary concentrations of 0.2% or less. At a dietary concentration of 2.0% adverse effects occurred in both rats and hamsters. At the 2.0% CIPC dietary level:

rats - Wt. gains depressed. Mortality in male rats increased. Lower hemoglobin and hematocrit values. Greater liver and spleen body wt. ratios. No treatment-related lesions noted at any feeding level.

dogs - Initial wt. losses. No mortality or morbidity. Lower hemoglobin and hematocrit values. Increased liver and spleen body wt. ratios. No pathologic changes seen. Extended feeding of CIPC produced no tumors in rats or dogs.

Classification: Core-minimum data

6. [Reg. No. 748-163; R. Coberly; 8-23-68; Accession No. 090892]
90-Day Rat Feeding (99.4%)
[Industrial Hygiene Foundation of America, Inc.; 1-22-54; No report number given - Although the review did not contain any identifiers beyond the title, the above reference appears to be for this study].

10 male rats were used per dosage level of 0.031, 0.125, 0.5, and 2.0%. These levels correspond to 17, 63, 260, and 1240 mg/KG.

Results

2 animals died in the 2% group. A middle ear infection was the cause of 1 death and the other died from pneumonia after 51 days. The animals in the test groups showed a higher than average overall body weight gain when compared to the corresponding controls. The test material may be considered to be agreeable to the taste or maybe even an appetizer stimulator.

The mean liver weights as percentages of body weight of the 0.125, 0.5 and 2.0 [%] treated rats were statistically significantly increased over that of the control group.

Micropathology-microscopic examination of the liver, kidneys, and intestines revealed that the largest dose showed no significant abnormalities.

Comments - From these data it appears that the test material at the levels of 0.125, 0.5, and 2.0 [%] impose a continuous metabolic stress on the liver resulting in hypererophy [hypertrophy] of that organ. The observations resulting from this study do not indicate that a functional impairment is evident. However this does not indicate that on a longer chronic exposure that functional impairment would not occur. On this basis we may assume the no effect level to be 17 mg/KG/day.

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7. [Reg. No. 748-163; R. Coberly; 8-23-68; Accession No. 090892]
Two-Year Rat Feeding Study, and One-Year Dog Feeding Study of Isopropyl N-(3-chlorophenyl) Carbamate (CIPC)
[Medical College of Virginia; No date or report number given - Although the review did not contain any identifiers beyond the title, the above reference appears to be for this study].

Two Year Rat Feeding

25 males and 25 females were tested per dosage level of 0.02, 0.2, and 2.0%. Hematologic studies were made at 3 month intervals on 5 or occasionally 10 rats of each sex at each dietary level.

Results

The average weekly changes indicate that the male and female animals receiving the 2.0% diet have a severe body weight loss by week 80. However by the termination of this study the weight loss in the male animals has been compensated for. However the female test animals receiving the 2.0% dietary level still exhibit a slight to moderate body weight loss.

The mortality of the various groups indicates that there is no significant difference between the test and control animals at week 80. By week 102 the male and female animals receiving the 2.0% diet do show an increase in mortality over the corresponding control animals.

The hematologic values obtained at 3 months show an indication of a relative depression in hematocrit and hemoglobin values.

The urinalysis results were normal as were the organ to body weight ratio data.

The results of a histopathologic examination did not show any consistent definite alterations due to treatment.

Comments - These data indicate that the level of 2.0% that died over 2 years does exert effects upon the animals [sic]. Lower levels did not appear to affect the animals with any degree of consistency.

One-Year Dog Feeding

2 males and 2 females were tested per dosage level of 0.02, 0.2, and 2.0%.

Results

The animals receiving the 2.0% diet showed a weight inhibition by the 52nd week of the study. The male animals of this level did consume less food than the corresponding control males.

No fatalities occurred during the study and the animals appeared to be in good general health.

The results of hematologic studies showed that from the first through the 9th month there was relatively lower hematocrit and hemoglobin values among the dogs receiving the 2.0% test material in their diet. However this effect was not present during the 12th month.

Urine samples collected at monthly intervals showed no difference between test and control dogs when analysed for sugar and protein.

The organ to body weight ratio of the spleen and liver for the dogs receiving 2.0% in their diet were higher than the corresponding controls.

These results indicate that the no effect level is in the area of 0.2%.

The preceding constitute the publications which had been previously reviewed. The following are either a more extensive description of a study (Publication 9), or the primary review of a study (Publications 8 and 10).

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8. Report by the Public Health Council in the Hague; Accession No. 097141
Investigation of the Potential Tumorigenic Properties of Chlorpropham in Comparison to Urethane;
G. J. van Esch, R. Kroes, and H. G. Verschuuren; Report No. 80/65 Tox

[Note: This study is similar to, but different from another study described in Publication 2.]

INTRODUCTION: CIPC was suspected of being a carcinogen because of its structural similarity to urethane (ethylcarbamate), a known carcinogen. Urethane induces tumors of the lungs and lymphoid system, and is a skin tumor initiator when used in conjunction with dermally applied croton oil or Tween 60. The following studies were reported:

1. Mouse feeding study of CIPC and urethane
2. Mouse toxicology study of subcutaneously injected CIPC
3. Assessment of the initiating effect of IPC and CIPC in combination with croton oil on mice
4. Mouse reproduction [teratology] study of IPC and CIPC

Studies 1 and 2 were presented together due to the similarity of the protocols. The mouse reproduction study was not relevant to this pre-RPAR review, so it was not covered in detail. The reproduction study, which was actually a teratology study, failed to show any teratogenic effect. "The conclusion of this investigation is that CIPC does not cause significant changes in the number of pregnant animals or in the number of dead fetuses. With the control animals three fetuses were exencephalous. No additional deformations were discovered miacroscopically [sic]."

Oncogenicity Studies of Orally and Intravenously Administered CIPC and Urethane in Mice

PROTOCOL: Groups of 25 male and 25 female Swiss mice (males 25g; females 20g; 49 days old) were dosed as follows:

Group 1 - Vehicle control (feed only)
Group 2 - 0.1% CIPC mixed into the feed
Group 3 - 0.1% urethane mixed into the feed
Group 4 - Control, given feed and subcutaneous injections of methylpyrrolidone (0.025 ml)
Group 5 - Given feed and subcutaneous injections of CIPC (1000 mg/kg/dose) in methylpyrrolidone (0.025 ml)

The subcutaneous injections were given at 1 and 14 days, and at 1.5, 3, 4.5, 6, 10, 14, and 17 months. Food was available ad libitum. Body weights were determined for Groups 4 and 5 alone at irregular intervals. The length of the study was 116 weeks. Neither clinical pathology measurements nor organ weights were taken. Most of the mice were examined grossly and microscopically. Some mice from Group 1 (1), Group 2 (3), Group 3 (2), Group 4 (1), and Group 5 (5) were not examined for unspecified reasons. The following organs were examined microscopically:

liver	spleen	intestinal tract
kidney	pancreas	urinary bladder
heart	suprarenals (adrenals)	prostate
lungs	stomach	testes
		uterus

RESULTS: The Group 3 mice dosed with 1% urethane died prematurely, mostly between weeks 31 and 50. All Group 3 mice were dead by week 60. Mortality patterns in the other groups were similar. Compared to the Group 1 controls, there was a mild increase in the incidence of bronchitis, pneumonia, and lung abscesses, and liver fat vacuolation in the Group 2 mice. The Group 3 male mice had kidney lesions including a severe increase in incidence of cuboidal epithelium in the Bowman's capsules. Although this is a normal finding in this strain of mice, a compound-related effect was evident. This group also had some increases in bladder stones, hydrothorax, and hydrops ascitis. Microscopic lesions in Groups 4 and 5 were similar, although Group 4 had somewhat higher incidences of amyloidosis in the liver, spleen, and kidneys than the Group 1 controls. An unspecified number of mice had encapsulated substance at the dosing sites.

Lung tumors were seen in all groups with Group 3 being the most affected. Of the 48 mice examined in this group, 46 had "many tumors" (i.e. >10 tumors per mouse). Considering the short life-span of these mice (<60 weeks), this finding clearly confirms the carcinogenicity of urethane. Groups 1 and 2 had 10 and 15 mice with lung tumors, respectively, and an average of 2.5 and 2.0 tumors per tumored mouse, respectively. This does not indicate a carcinogenic effect. The incidence of mammary tumors and lymphomas was similar for Groups 1 and 2, but much lower in Group 3 due to the premature deaths. There was no evidence of increased tumor incidence in Groups 4 and 5.

CONCLUSIONS: There was no evidence that CIPC is a carcinogen when administered orally or subcutaneously. Structurally similar urethane, however, caused lung tumors in nearly all mice.

This study is CORE SUPPLEMENTARY. Body weights were measured for only two of the five groups at unspecified intervals. Food intake, and consequent oral doses, were not measured. No clinical pathology or organ weight measurements were taken. Gross pathology was not reported. No severities were reported for the microscopic lesions. Some of the mice were not examined for unspecified reasons; the data from these mice, particularly tumor incidence, would be valuable. The performing laboratory was not named. The date of the report was not given.

Assessment of the Initiating Potential of IPC and CIPC in Combination with Croton Oil on Mice

PROTOCOL: Three groups of 50 male and 50 female Swiss mice were dosed as follows:

Group	Oral Dose	Dermal Dose
1	Tragacanth gum suspension [Control]	Croton oil
2	15 mg IPC in tragacanth gum suspension	Croton oil
3	15 mg CIPC in tragacanth gum suspension	Croton oil

The oral suspensions were administered by stomach tube once a week for 10 weeks. Beginning four days after the last oral dose, the rats were dermally dosed (interscapularly) twice weekly for 26 weeks with 0.1 ml of 5% croton oil mixed in equal parts of olive oil and acetone. Food and water were available ad libitum. Each rat was assessed weekly for papillomas and malignant tumors.

RESULTS: Tumor incidence in this study was as follows:

Group	Number of Rats*	Rats w/ Tumors	Total Papillomas	Papillomas Which Reversed	Malignant Tumors	Latency Period†
MALES						
1 (Control)	41	6	8	2	-	13
2 (IPC)	41	15	21	8	2	16
3 (CIPC)	43	6	7	4	-	14
FEMALES						
1 (Control)	45	15	26	9	-	12
2 (IPC)	45	18	40	16	-	13
3 (CIPC)	44	13	19	10	-	21

* Number of rats surviving at the time of the first tumor formation.
† Time in weeks for the first appearance of a papilloma.

The irritating effects of croton oil caused papillomas in all dosed and control groups, but the females were the more affected. The latency period was similar for all groups except for the females dosed with CIPC which developed papillomas 9 weeks later than the controls. In both sexes, the highest incidence of papillomas was in the rats dosed with IPC; the rats dosed with CIPC had fewer lesions than the controls. Two malignant tumors (basal cell carcinoma) were observed in the males dosed with IPC.

CONCLUSIONS: There was no evidence that CIPC acts as an initiator when administered orally prior to dermal administration of croton oil, a promoter. Orally administered IPC, however, caused an increased incidence of papillomas and two malignancies.

This study is CORE MINIMUM. The report was lacking specifics on the animals used. The performing laboratory was not named. The date of the report was not given.

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9. Congressional Record - Senate, May 1 1969, S 4112

Mr. Hart (not further identified) stated on the Senate floor that in May, 1963 the President's Science Advisory Committee filed a report on the "Use of Pesticides" and recommended that additional studies of tumorigenicity be performed using immature and adult animals. Bionetics Research Laboratories, Inc. (currently Litton Bionetics, Inc.) performed these studies using 120

chemicals and nearly 20,000 mice. The report of these studies was published in the Journal of the National Cancer Institute (Vol 42, No. 6, June 1969), and was reprinted in the Congressional Record. The title and summary from that report were as follows:

Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note

[NOTE: This review is for the same report as Publication 1.]

J. R. M. Innes, B. M. Ulland, Marion G. Valerio, L. Petrucelli, L. Fishbein, E. R. Hart, and A. J. Pallotta, Bionetics Research Laboratories, Inc. Litton Industries, 7300 Pearl Street, Bethesda, Maryland 20014

and

R. R. Bates, H. L. Falk, J. J. Gart, M. Klein, I. Mitchell, and J. Peters, National Cancer Institute, Bethesda, Maryland 20014

"SUMMARY - The tumorigenicity of selected pesticides and industrial compounds was tested by continuous oral administration to both sexes of two hybrid strains of mice, started at the age of 7 days. Maximal tolerated doses were given. Administration of 11 of the 120 test compounds induced a significantly elevated incidence of tumors, mostly hepatomas; this incidence was comparable to the mean tumor incidence of a group of positive control compounds. The 11 compounds include 5 insecticides: p,p'-DDT, Mirex, bis(2-chloroethyl)ether, Chlorobenzilate, and Strobane; the 5 fungicides PCNB, Avadex, Ethyl selenac, ethylene thiourea, and bis(2-hydroxyethyl)dithiocarbamic acid potassium salt; and the herbicide N-(hydroxethyl)hydrazine. Eighty-nine compounds gave no significant indication of tumorigenicity after oral administration. The results with the remaining 20 compounds require further evaluation. The possible relevance of these experiments to human exposure is discussed. - J Nat Cancer Inst 42:1101-1114, 1969."

PROTOCOL: Male and female specific pathogen free mice of (C57BL/6 X C3H/Anf)F_1 and (C57BL/6 X AKR)F_1 strains were dosed by single subcutaneous injection and continuous oral administration. Only the results of the oral studies were presented. Seven carcinogens were used as positive controls. Four negative control groups and one vehicle (gelatin) control group were used. These controls were dosed in the same room(s) as the dosed groups. The mice were dosed by stomach tube between the ages of 1 and 4 weeks, then by mixing the test articles into the diet. The dosing persisted for 18 months, at which time they were necropsied and examined for gross external and visceral lesions. The abdominal and thoracic organs (specific organs were not specified) and all lesions were examined histopathologically. Craniums were not examined, and blood smears were examined for only some of the mice.

The results of the studies were subjected to statistical analysis, including chi-square test for heterogeneity of proportions after adjustment of stratification (Method of Armitage), regression analysis, and the Mantel-Haenszel procedure. It should be stressed that, "Even though nearly 20,000 mice were used in these studies, the several investigations were done as preliminary, probing experiments and were not expected to provide final definitive information on every compound."

The doses of CIPC, IPC, and urethane used in this study were as follows:

Compound	Days 7-28 mg/kg/day (Via feeding tube)	Months 1-18 ppm (Dosage in diet)
CIPC	464 in 5% gelatin	1112
IPC	215 in 5% gelatin	560
Urethane	158 in 5% gelatin	600

RESULTS: Eleven compounds were found to result in elevated tumor incidence. Twenty others required additional evaluation. The majority of compounds, including CIPC (compound #150) and IPC (compound #048), did not cause significant increases in tumor incidence. Structurally similar urethane (ethyl carbamate, compound #034) was used as a positive control, and caused adenomas of the Harderian gland, and increased incidences of hepatomas, pulmonary tumors, and lymphomas.

CONCLUSIONS: CIPC and IPC allegedly did not induce tumors at the doses tested. Urethane, which is structurally similar, did induce tumors.

This study is CORE SUPPLEMENTARY. Insufficient data were presented for an evaluation of the experiment. For example, no data were given for CIPC or IPC beyond the doses used. The tumor incidence among these mice was not given, thus making it impossible to assure that these compounds were not carcinogenic. Housing the controls and the dosed groups in the same rooms is poor procedure and makes the results of these studies suspect. Despite the defined limitations of this study, larger populations and more dose levels should have been used.

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10. Report of the Secretary's Commission on Pesticides and Their Relationship to Environmental Health
U.S. Department of Health Education and Welfare; December 1969

This report deals with a large scale teratology screening study performed by Bionetics Research Laboratories. This study bears the same contract number (NCI contracts PH 43-64-57 and PH 43-67-735) as the Tumorigenicity Bioassay described in Publications 1 and 9. It is impossible to determine whether these studies are each part of the same study (i.e. reported separately), or nonrelated studies. Unfortunately, portions of the Report of the Secretary's Commission are illegible, thus making review difficult. This report is a discussion of the teratogenic findings and not a formal study report.

The study design was either not presented or not readable. The only mention of CIPC was in Table 4 which appeared to be a list of those compounds which showed no significant increase in anomalies (the title of the table was not totally readable). IPC was also listed in Table 4 as showing no increase in anomalies, but the text described it as one of the "pesticides producing a statistically significant increase in the proportion of litters containing abnormal fetuses and in the increased incidence of abnormal fetuses within litters..." at the 0.01 level.

Because of the apparent contradiction in describing IPC effects, and the poor copy quality, further evaluation of this report was not possible.