3-31-72

ENVIRONMENTAL PROTECTION AGENCY

004829 9/1113

REPLY TO ATTN OF:

DATE March 31, 1972

#174

SUBJECT: Chlordane, 1,2,4,5,6,7,8,8-octachloro-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene, insecticide, request for tolerances, as follows: At 0.04 ppm in bananas, fodder, forage, and grain of corn (field, sweet, and popcorn), rice, and eggs of poultry; at 0.06 ppm in barley, oats, rye, snap beans, sorghum (grain), soybeans, and wheat; at 0.1 ppm in or on asparagus, broccoli, brussels sprouts, cabbage, cantaloupe, cauliflower, celery, collards, cotton (seed), cucumbers, eggplant, lettuce, mustard greens, parsnips, peppers, spinach, squash, strawberries, Swiss chard, tomatoes, watermelons, and fat of cattle, sheep, goats, horses, and pigs; at 0.2 ppm on beets, flax (seed), potatoes, pumpkins, sugar beets, poultry fat, and turnips; at 0.3 ppm in fat of milk; at 0.5 ppm in crude soybean oil (food additive).

TO: Mr. Drew M. Baker, Chief
Petitions Control Branch
Pesticides Tolerances Division

Pesticide Petition No. 1F1041

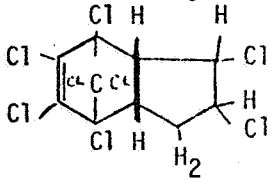
Velsicol Chemical Corp.
Washington, D. C.

Petitioner requests tolerances for chlordane, an insecticide, which are listed in title of this memo.*

Chlordane tolerances at 0.3 ppm each which presently cover a wide variety of fruits and vegetables are listed in Code of Federal Regulations, Section 420.122. Chlordane is registered on a number of crops on "extended" (former "no-residue") basis.

Proposed tolerances would either lower some of former or apply to some of latter or provide new tolerances, e.g., on animal products.

Formula of chlordane is given below.



* As revised by Petitioner in letter of September 1, 1971, this petition.

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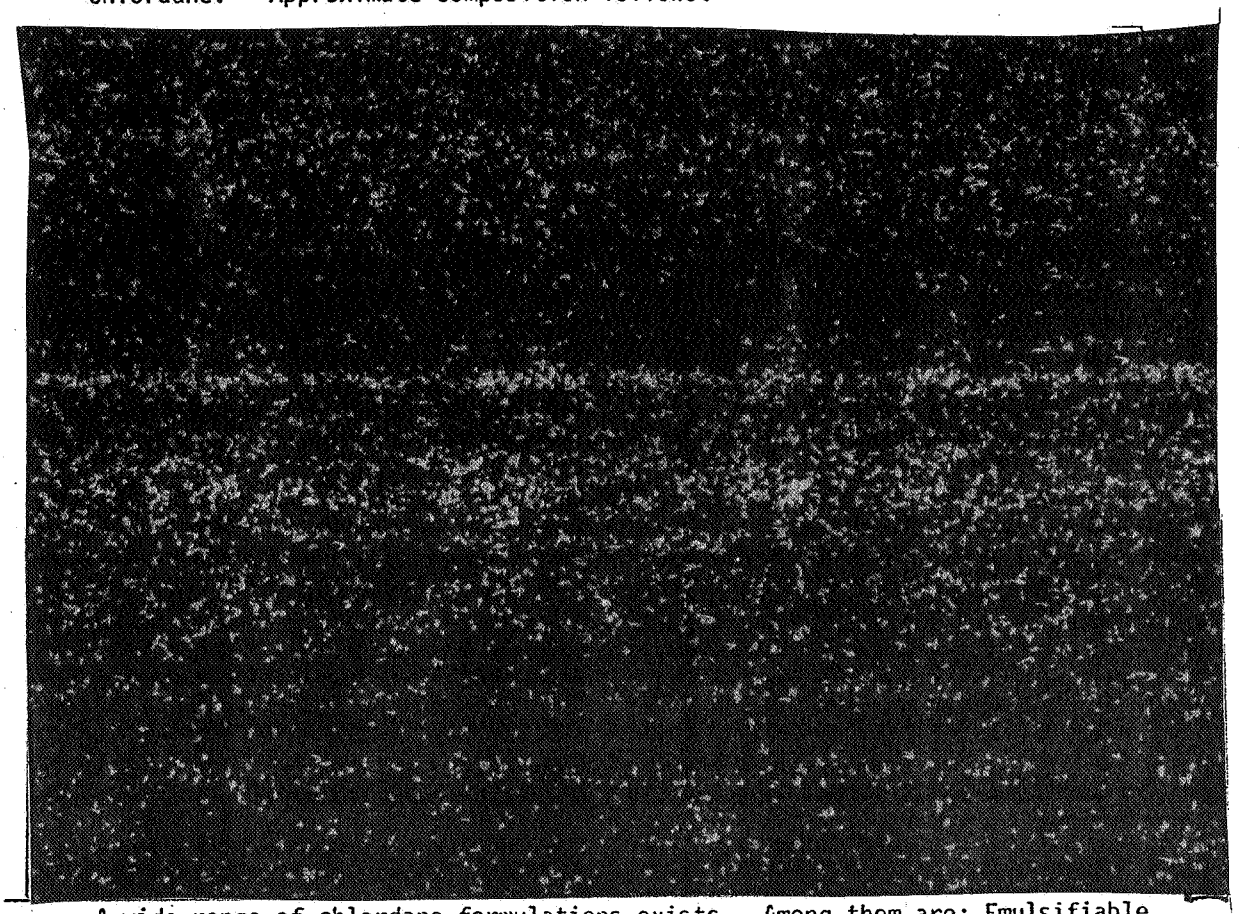
"Technical chlordane*....is a mixture of chlorinated hydrocarbons consisting of isomers of chlordane....and closely related compounds in the presence [redacted]. About one-third....consists of two major constituents, isomers of chlordane; no other individual component exceeds about one-tenth of the total product. The identity of components, their distribution ratios, and properties of the mixture must conform to those of authentic Reference Technical Chlordane." Approximate composition follows:**



A wide range of chlordane formulations exists. Among them are: Emulsifiable concentrates--4 or 8 pounds per gallon; dusts--10, 6, and 5%; granules--33 1/3,

* Definition from Petitioner's letter of September 1, 1971, revised, p. 20 of Sec. A, this petition.

** Ibid., revised, p. 25 of Sec. A, this petition.

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25, 20, 10, and 5 ; wettable powders--25 and 40 ; and oil solutions--20 and 2[illegible].

Chlordane is to be used for post-cutting, soil, seed, and foliar treatments, among others, at dosage rates ranging from 1 to 2 ounces per bushel and from 0.5 to 10 pounds per acre of active ingredient.

Exhibit V (which accompanies letter of September 1, 1971) lists petroleum distillate and [redacted] in addition to technical chlordane, as ingredients of chlordane 72EC and chlordane 8EC. For chlordane 40WP, additional ingredients are [redacted]

We will need information (from PCB and/or CB) as to whether these and any other ingredients of chlordane formulations are cleared for use by regulations.

Following pages give brief history of toxicity studies; discussion; evaluation; and conclusion. Appendix is an 11-page summary and evaluation of new toxicity data.

TOXICITY:

Old data.

We (M.Q.) previously evaluated toxicity of chlordane in 1963,* after which it was recommended that chlordane tolerances be revoked (memo of Dr. O. G. Fitzhugh, August 8, 1963). As suggested by 1965 advisory committee of (of N.A.S.-N.R.C.),** which recommended retaining--but later reevaluating--then existing chlordane tolerances, Petitioner carried out dog chronic feeding and rat reproduction studies. These we evaluated (in our memo of June 20, 1968)*** and found respective "no-effect levels" to be 3 and 30 ppm. Corresponding ADI (allowable daily intake) for the human was 0.03 ppm, whole-diet basis.

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* Memo contained in F.D.A. and in personal (M. Q.) files.

** In "Report of the Food and Drug Administration's Advisory Committee Appointed to Review the Proposal to Repeal the Tolerances for Residues of Chlordane on Certain Fruits and Vegetables and Establish a Tolerance of Zero for Each Crop Listed in Pesticide Regulation Section 120.122." M. Coon, Chairman, February 21, 1965. (Cf. this petition, Section C, p. 0145.)

*** Contained in F.D.A. and in personal (M. Q.) files.

Velsicol people (conference of May 14, 1968) mentioned finding a 1:1 ratio of dietary chlordane to chlordane in fat of rats fed it. If true, and if the ratio for humans is of similar magnitude, an estimate of chlordane content of the human diet could be made following assay of human fat samples for chlordane; such estimate would, of course be speculative at best.

ML 4/24/72

Mary L. Quaife, Ph.D.
Toxicology Branch
Pesticides Tolerances Division

cc:
JGCummings
PRD/EPA
Atlanta Branch (CLewis)
Perrine Branch
PP No. 1F1041
MLQuaife/ccw 4/13/72
Init: GEWhitmore
Init: CHWilliams

4/27/72

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New data.

Toxicity data in this petition comprise values for acute toxicity of some chlordane-related compounds; results of pilot subacute study on oxychlordane and of chronic rat studies on chlordane-related compounds; chlordane residue data for poultry, cattle, goats, and pigs; and miscellany, including data on inhalation toxicity and subacute toxicity to quail. A 90-day rat feeding study on oxychlordane is said to be in progress (according to Sec. C summary, this petition).

DISCUSSION:

Pertinent "no-effect levels" from new toxicity studies of this petition are summarized on first page and oral LD_{50}'s of chlordane-related compounds, including constituents of technical chlordane, on second page of appended review and evaluation of the new data.

We conclude that the technical chlordane constituents, alpha- and gamma-chlordanes, each (chronic basis in rat) roughly as toxic, and the various chlordenes, each (acutely in rat) one-tenth as toxic, as technical chlordane do not decrease safety of its presently proposed use.

Toxicity of heptachlor and its metabolite, heptachlor epoxide, is well characterized* except for possible mutagenicity and carcinogenicity. The various "photo" products of chlordane (photo-alpha-chlordane and its isomer; photo-heptachlor epoxide; and photo-heptachlor) are each, acutely, more toxic (to rat) than is chlordane. However, respective toxicities do not affect safety of presently requested chlordane tolerances if CB affirms Petitioner's claim (on pp 0130-1, this petition) of virtual absence of heptachlor and the "photo" compounds on chlordane-treated commodities.

Oxychlordane (1-exo-2-endo-4,5,6,7,8,8-octachloro-2,3-exo-epoxy-2,3,3a,4,7,7a-hexahydro-4,7-methanoindene), epoxide of either alpha- or gamma-chlordane, is known (only since 1970) to be chlordane metabolite in animal products. Acutely, it is ten (or more) times as toxic to rat as chlordane; only other direct study was 90-day feeding to four rats (only).

If CB finds oxychlordane is chief form of chlordane present in animal products, we may need more direct toxicologic information on it. Rate of its in vivo formation may be relatively slow, in which case its toxicity was not necessarily determined in feeding studies on its precursors (alpha- and gamma-chlordanes). And proposed chlordane milk tolerance could allow infants to consume more (0.0015 mg/kg BW/day) oxychlordane than ADI for chlordane previously calculated for adults (0.00075, this reviewer, or 0.001 mg/kg BW/day, FAO/WHO).**

* Cf. PP No. 0F0935. Newly submitted (Jan. 21, 1972, by Velsicol) mutagenicity study (dominant-lethal) on mice claims heptachlor is not potentially mutagenic (mixture of it and its epoxide tested). Carcinogenicity study on same, said (in letter of Jan. 18, 1972, from Velsicol) to be underway.

** Proposed milk tolerance--0.3 ppm in milk fat (=0.012 ppm in whole milk-4% butterfat)--would allow ingestion of 0.012 mg chlordane/day by 8-kg infant who consumes 1 kg milk/day. This equals 0.0015 mg/kg BW/day consumed by the infant.

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Suggested minimum, if further data are needed, is 90-day rat or dog study and two-generation reproduction study. Appropriate carcinogenicity, mutagenicity, and teratogenicity studies on oxychlordane may need to be initiated. We suggest, too, that tolerances on animal products may need to be expressed--at least partly--in terms of oxychlordane.

Finally, since new poultry residue study which is described below (p. 16a) suggests that heptachlor epoxide, nonachlor, and/or Compound E may occur in treated commodities in significant amounts as result of presently proposed chlordane use, we request comment from CB on the possibility.

ADDENDUM:

We strongly believe that (typical "market-basket") animal products, whether treated directly or indirectly with chlordane, should be extensively analyzed for possible occurrence of chlordane.

We further believe that human fat samples should also be surveyed for possible presence of oxychlordane. A special reason is that safety of proposed chlordane usage is frequently claimed on basis that it is absent in human tissues (fat); Petitioner so claims in this petition (on p. 1,622). He cites Ref. 14 (of Sec. D., Part V, this petition--Hoffman et al. Arch. Environ. Health 15, 758-65 (1967)), among others, in support of claim.

We (M. Q.) called attention in 1968 to possible presence of chlordane in human tissues, despite its claimed absence.* We now believe even more strongly that chlordane (as its metabolite, oxychlordane) may occur widespread in human tissues--based on same reasoning given then.* (For example, mean content in Hoffman's (Ref. 14, above) 505 human fat samples--of what we believe may be in part oxychlordane--was 0.16 $\pm$ 0.11 ppm.)

Since rats and dogs fed chlordane a year or more showed a 1:1 relation between chlordane in diet and that (as oxychlordane) in body fat,** there could have been significant amounts (up to 0.16 ppm) of chlordane in the diet of these humans.

This emphasizes need for more information on oxychlordane as to occurrence (if any) both in diet and in human tissues.

EVALUATION:

See first two pages of appended toxicity summary and evaluation for pertinent "no-effect levels" and LD_{50}'s of chlordane-related compounds.

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* On p. 9, our memo of June 20, 1968, copy appended on last page of this memo.

** This petition, Section D, pp. 1266-7.

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The new values do not change our previous estimate of human ADI for chlordane (0.03 ppm, whole-diet basis, = 0.00075 mg/kg BW/day), with possible exceptions noted under "Discussion" (above).

Present chlordane tolerances (CFR Sec. 420.122) cover about one-third of human diet at 0.3 ppm and provide theoretical maximum of 0.1 ppm, whole-diet basis. Tolerances requested in this petition would reduce this to ca. 0.073 ppm, of which 0.006 ppm--contributed by animal products--may be oxychlordane.

TB obviously prefers to lower any existing tolerances but is unable to evaluate safety either of these or of those newly requested because of reasons already cited (under "Discussion").

CONCLUSION:

TB is unable to complete safety evaluation of tolerances proposed in this petition (listed in title of this memo) pending conclusion of CB regarding (a) Petitioner's claim that heptachlor and the various possible "photo" products of technical chlordane (photo-alpha-chlordane and its isomer; photo-heptachlor epoxide; and photo-neptachlor) will be virtually absent from commodities, for which tolerances are proposed in this petition, (b) Extent of occurrence--if significant-- on these commodities of the compounds, heptachlor epoxide, nonachlor, Compound E, and (in animal products) oxychlordane, and (c) Whether petroleum distillate and other "inerts" used in chlordane formulations are cleared for use under Federal regulation; since toxicity data on above-named substances may be incomplete, in case they do occur in significant amounts on such commodities.

Summary of "No-Effect Levels" of Chlordane and Related Compounds.

Test Material	Species	Duration	"No-Effect Level"
Oxychlordane	Rat	90 days	2 mg/kg BW/day (40 ppm) (pilot study, only, with total of 4 rats used)
Chlordane, technical	Rat	2 years	25 ppm (provisional--details of study required)
Alpha-chlordane	Rat	78 weeks	15 ppm (provisional--study unfinished)

Table continued

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Gamma-chlordane	Rat	78 weeks	35 ppm (provisional--study unfinished)
Alpha- and Gamma-chlordane, 1:1 mixture	Rat	78 weeks	25 ppm (provisional--study unfinished)
Chlordane, technical	Chicken (Leghorn)	14 weeks	0.3 ppm (with respect to growth, size and hatch. of eggs and growth of progeny)
Chlordane	Quail (Coturnix)	28 days	25 ppm
Gamma-chlordane	Rat	2 years	Greater than 5 ppm and less than 75 ppm

Following were determined previously:*

Chlordane, "reference grade," presumably technical	Dog	2 years	3 ppm*
Chlordane	Rat reproduction	3 gen., 6 lit.	30 ppm*

Heptachlor epoxide, by our previous evaluation,** showed chronic "no-effect levels" in both rat and dog at 0.5 ppm, as lowest yet demonstrated (including reproduction), i.e., in most sensitive species. This is upgraded to 1 ppm in dog,*** making "no-effect" of most sensitive species = 1 ppm in dog; since different conversion factors in rat and dog (as given by Lehman, 1959) make ppm in latter equivalent to one-half ppm in former.

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* Cf. memo (of M. Quaife) entitled, "Chlordane: Toxicological evaluation of new rat reproduction and chronic dog feeding studies in connection with assessing safety of present tolerances on chlordane," dated June 20, 1968, in personal (M.Q.) and FDA files on chlordane.

** DT memo (by M. Q.) of November 19, 1970, in PP No. 0F0935.

*** Memo of conference, April 5, 1971, in PP No. 0F0935.

Acute toxicity:

Compound	Animal and Sex	Oral LD_{50} (mg/kg)	Remarks
Chlordane, technical	Rat, M	482, 521, & 536	3 samples
" "	Rat, F	402, Ca. 530 & 649	tested
Alpha-Chlordane	Rat, M	392	99.6% pure
Gamma-Chlordane	Rat, M	327	99.8% pure
Alpha-Gamma Chlordane 1:1 Mixture of above	Rat, M	371	
Heptachlor, technical	Rat, M	60	Old (1959) data
" "	Rat, F	142	" " "
Heptachlor Epoxide	Rat, M	61	" " "
" "	Rat, F	47	" " "
" "	Rat, M & F mixed	90.5	98.4% pure
Compd. C of tech. Chlordane	Rat, F	3,800	98% pure
Chlordene	Rat, M & F mixed	>4,600	100% pure
Compound E	Rat, " "	3,000	
Gamma-Chlordene	Rat, " "	Ca. 4,600	99.4% pure
Beta-Chlordene	Rat, " "	>6,800	99.9% pure
Compound K	Rat, F	Ca. 5,700	97% pure
Oxychlordane	Rat, M & F mixed	19.1	
"	Rat, " "	43	98% pure
Photo Alpha-Chlordane	Rat, " "	305*	

* LD_{50} of alpha-chlordane (99.7% pure) determined at same time to be ca. 600 mg/kg. Similar symptoms shown by rats given the three compounds.

Table continued

Compound	Animal and Sex	Oral LD_{50} (mg/kg)	Remarks
Photo Alpha-Chlordane Isomer	Rat, M	178*	
Photo Alpha-Chlordane Isomer	Rat, F	64.5*	
Nonachlor	Rat, M & F mixed	Ca. 11,000	
Photo Heptachlor Epoxide	Rat, " "	295	92.2% pure
Photo Heptachlor	Rat, " "	7.7	
3-Chlorochlordene	Rat, " "	>4,600	99% pure
1-Hydroxychlordene	Rat, " "	>4,600	99% pure
Chlordene Epoxide	Rat, " "	>4,600	98.7% pure

Subacute Toxicity:

Oxychlordane-rat.
In a pilot study, two each male and female albino rats received, incorporated in the diet, 2 mg/kg body weight/day oxychlordane (>97% pure).

One female died from injury during collection of blood on 84th day.

No abnormalities were found in: Body weight gain; food consumption; survival and behavior; hematologic values;[1] clinical chemical values;[2] results of urinalysis;[3] gross and microscopic appearance of tissues;[4] and organ weights.[5]

* LD_{50} of alpha-chlordane (99.7% pure) determined at same time to be ca. 600 mg/kg. Similar symptoms shown by rats given the three compounds.

1 For hematocrit, R.B.C., hemoglobin level, and W.B.C.'s--total and differential.

2 For blood urea nitrogen, serum alkaline phosphatase, serum glutamic-pyruvic transaminase, and fasting blood glucose.

3 For glucose, albumin, microscopic appearance, pH, and specific gravity.

4 Including esophagus, stomach (cardia, fundus, and pylorus), small intestine (duodenum, jejunum, and ileum), cecum, colon, liver, kidney, spleen, pancreas, urinary bladder, pituitary, adrenal, testis, seminal vesicle, ovary, bone marrow, thyroid, parathyroid, salivary gland, prostate, heart, aorta, lung, lymph node (cervical and mesenteric), skeletal muscle, peripheral nerve, bone (femur), spinal cord, uterus, trachea, eye, optic nerve, and brain (cerebrum, cerebellum, and pons).

5 Of liver, kidney, spleen gonad, heart, and brain.

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"No-effect level." 2 mg/kg body wt/day (40 ppm in diet) for this pilot study.

Chronic toxicity:

Chlordane-rat.

Groups of 20 M and 20 F rats each received 0, 2.5, 5, 10, 25, 50, 75, 150, or 300 ppm technical chlordane in diet for 2 years.*

Cumulative mortality of rats (only data detailed) was consistently higher among 300-ppm rats and probably somewhat increased in 150-ppm rats.

"No-effect level" may be 25 ppm, based on lack of microscopically observed changes in liver or kidney. However, we would need detailed data to confirm this.

Alpha- and gamma-chlordane-rat.

In a study by Ingle, groups of 20 M and 20 F Sprague-Dawley rats each received alpha-chlordane** at 5, 15, 25, or 35 ppm; gamma-chlordane** at 15, 25, 35, or 75 ppm; and 1:1 mixture of these two at 5, 15, 25, 35, or 50 ppm in diet for 78 weeks; a control group was included.

Observations were made on behavior, growth rate, and mortality. Animals were killed,*** autopsied, and some tissues studied histopathologically.****

Rats on alpha-chlordane at 35 ppm, on gamma-chlordane at 75 ppm, and on the mixture at 50 ppm grew less well, and more died. There was no effect on blood hematocrit (only laboratory test done) or on gross pathology of organs; no evidence of tumors, said to be seen. "Minimal" or "slight" liver changes are reported for rats on 25 and 35 ppm alpha-chlordane, on 75 ppm gamma-chlordane, and on 35 and 50 ppm of mixture.

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* Study done by Ingle sometime before 1960. Although specifications for test compound are not given, it is described as less toxic than chlordane of earlier production due to "virtual elimination of unreacted hexachlorocyclopentadiene."

** Specifications of compound, not given.

*** Number killed, not stated. It is not clear whether or not this is an interim report.

**** Including heart, lung, liver, kidney, adrenal, intestine, gonad, spleen, and urinary bladder.

Based on above, "no-effect levels" would be: Fifteen ppm alpha-chlordane, 35 ppm gamma-chlordane, and 25 ppm of 1:1 mixture of the two.

Gamma-chlordane-rat.

Study done by Ingle at University of Illinois in 1950 to 1952.

Groups of 20 M and 20 F rats each received 0, 5, 75, 150, or 300 ppm gamma-chlordane* in diet for 2 years. Only mean food consumption and mean body weight--at intervals--and cumulative mortality are detailed. Effect on behavior is mentioned. Except for autopsy and microscopic observation of some organs,** no other observations were made.

Symptoms of intoxication are described as like those due to technical chlordane, but levels at which seen are not stated. Nor did such symptoms appear if, as done on several occasions, rats were starved 36 to 48 hours.

Mortality was considerably greater in 300-ppm rats.

Organs are said to have appeared normal in size; whether they were weighed is not stated. Liver changes were not seen in 5-ppm rats but were, in a 75-ppm female. Higher-dose animals showed liver changes, consisting of considerable sinusoidal congestion, vacuolation, and hyalinization of cytoplasm, and areas of necrosis. Two controls and one 75-ppm rat had hepatomas, described as malignant.

Based on above, "no-effect level" is 5 ppm.

Residue studies on chickens, steers, dairy cows, goats, and pigs.***

Chlordane (technical) at 0.03 0.15, or 0.30 ppm in diet of mature leghorn chickens for 14 weeks did not adversely affect growth, weight or hatchability of eggs, or growth of progeny. Values for residues in chicken tissues from study are said to be unreliable due to excessive background interference.

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* Purity or specifications, not given.

** Including lung, liver, kidney, adrenal, spleen, intestine, striated and cardiac muscle, pancreas, testis, and ovary.

*** Studies carried out at Biotoxicological Research Associates, Division of Acres, Inc., Spencerville, Ohio.

Values given for eggs are erratic. A second chicken study is said to be in progress (this petition, Sec. D, p. 1227).

In the second study,* simulated chlordane residues** at 0, 0.1, 0.3 or 1 ppm (total) in diet of mature leghorns for 17 weeks did not affect growth, food consumption, or gross pathology of parent birds or same--plus viability--of F_1 chicks. Percent eggs hatched was, in general, lower, and percent infertile eggs was, in general, higher, for all treated parental groups; higher mortality of latter, said due to various chicken diseases, which are enumerated.

Residues in poultry fat*** of all individual components fed** and of oxychlordane and Compound C show (subject to confirmation from CB) that heptachlor epoxide, Compound E, alpha-chlordane, and nonachlor each were concentrated two-fold or greater (up to twelve-fold) from dietary to body-fat level. Relative level of gamma-chlordane was much less. Both oxychlordane and nonachlor constituted significant fractions of total residues.

Above study may be first in which nonachlor residues in tissues of chlordane-fed birds (or animals) were determined.

Bovine steers (Hereford and Angus cross) fed alpha-**** or gamma-chlordane***** at 0.1 or 0.3 ppm in diet for 30 days (one steer/dose-level plus one control) did not show clinical signs of toxicity. In neither 0.3-ppm animal were there detectable residues in liver or brain. In "alpha-fed" animal, 0.01 ppm oxychlordane and 0.02 and 0.03 ppm alpha-chlordane occurred in body fat. In "gamma-fed" steer, only oxychlordane, at 0.03 ppm, was found in fat.

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* Study done at Industrial Bio-Test Laboratories, Inc.; analyses made by Velsicol Chemical Corp.; each report sent to PTD/EPA by Petitioner with letter of September 1, 1971, this petition.

** Of following composition: Alpha- and gamma-chlordanes, each 44%; Compound E, 4.5%; heptachlor, 0.5%; heptachlor epoxide, 1%; and nonachlor, 6%.

*** Cf., for example, Table I, Exhibit V, Section D, this petition, submitted on September 1, 1971.

**** Alpha-chlordane, Lot No. 82068, 99.8% active ingredient, from Velsicol.

***** Gamma-chlordane, Lot No. 82068, 99.8% active ingredient, from Velsicol.

Dairy cows (of holstein and guernsey breeds) received alpha-* or gamma-chlordane,** either separately or combined 1:1, at up to 0.3 ppm in diet for 30 days without apparent toxic effect. They showed liver, brain, or fat residues similar in amount to those of above study and none (<0.01 ppm) in milk on 30th day. We note that 0.02 ppm heptachlor epoxide, reported in the two control cows' fat samples, is ascribed to "contamination."

One holstein cow each received alpha- or gamma-chlordane (each 99.8% pure), either alone or combined 1:1, at 10 ppm for 10 days, without "visible signs of toxicity." (A control was included.) Up to 0.075 ppm residues occurred in milk, most being oxychlordane; this declined to ca. 0.01 ppm by 50 days post-test.

At 50 days, residues in body fat were about twenty times those in milk; all were oxychlordane.

The above experiment was duplicated on goats, without visible toxic effect. Body fat content of up to 0.4 ppm oxychlordane, reported for the control goat, is ascribed to either contamination or sampling error. Up to 0.5 ppm in body fat occurred in test goats, and it was all oxychlordane. Up to 0.07 ppm occurred in milk, and by 50 days, ca. 0.01 ppm remained.

Both cows and goats seemed to transfer proportionately more gamma- than alpha-chlordane to body tissues or fluids, the former apparently mostly as oxychlordane and the latter, in part, as unchanged alpha-chlordane.

Pigs (barrows) fed 300 ppm pure alpha-chlordane in diet for 90 days deposited 36 ppm oxychlordane and 9 ppm of fed compound in body fat; those similarly given gamma-chlordane had 71 ppm oxychlordane and 4 ppm of fed compound. There were "no visible gross side reactions." Several livers were noticeably enlarged (at autopsy) but of normal color and texture. On a variety of levels of chlordane in diet, dogs (after 2 years) and rats (after 1 year) showed levels of oxychlordane in body fat about equal to dietary level.

Chlordane residues-fish.

Although relatively few values for chlordane--compared to DDT and dieldrin--in fish are reported in an extensive survey for years 1967 and 1968;*** the probability that fish--as do mammals tested--convert chlordane to oxychlordane

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* Alpha-chlordane, Lot No. 82068, 99.8% active ingredient, from Velsicol.

** Gamma-chlordane, Lot No. 82068, 99.8% active ingredient, from Velsicol.

*** "Organochlorine Insecticide Residues in Fish (National Pesticide Monitoring Program)." By C. Henderson, W. L. Johnson, and A. Inglis. Pesticides Monitoring Journal 3, 145-70 (1969). (Ref. 29, Sec. C, this petition.)

and store it as such means that little reliance can be placed on this fact as demonstrating lack of widespread occurrence of chlordane and/or metabolites in fish. Conversion of chlordane to oxychlordane in animals was not demonstrated until after the above study was completed (in 1970).*

Miscellaneous toxicity:

Chlordane inhalation-pigeons.

No ill effect was observed in pigeons continuously exposed for 60 days to vapors arising from surfaces treated with one gram per square foot of chlordane (type or degree of purity not specified). (Histopathologic studies, said to have been made, but no details, whatsoever, given.)

Chlordane, 28-day feeding-quail.

Twenty-five ppm chlordane** in diet for 28 days was without apparent harm to Coturnix quail: 100 and 200 ppm each caused pharmacotoxic signs; and 200 ppm also caused prostration and death, usually within one week.***

Chlordane acute toxicity-fish.

In various determinations of acute toxicity to fish, chlordane is variously described as less toxic,**** equally toxic;***** and more toxic****** to fish. Symptoms seen consisted of, "Excitement, jerky movements resulting from muscular spasms, loss of equilibrium, swelling of abdominal region of the body, and blanching of the integument."

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* For example, see Lawrence et al., J. Assoc. Offic. Anal. Chemists 53, 261-2 (1970).

** Described only as, "Batch 1009, light brown liquid, received from Velsicol on July 20, 1966.

*** Two-week-old unsexed quail were used--24 controls and 20 each birds at 25, 100, and 200 ppm in diet.

**** In Ref. No. 28 of Sec. C of this petition, Refs. 14 and 23.

***** " " " " " " " " " " , Refs. 15.

****** " " " " " " " " " " , Refs. 32.

COPY +
CHLORDANE

ADDENDUM:

Although no analyses of human tissues directly for chlordane are known to be extant, a recent paper* suggests the intriguing possibility that presence of chlordane in fat may have been demonstrated for a large number of human autopsy samples collected in the U.S.A.

We infer this for the following reasons:

1. A peak in the gas chromatograms (with "relative retention time" of 1.20) identical to that for heptachlor epoxide occurred in assay of over 300 samples of the authors' series of human fat samples.

2. Such peak was shown in certain samples of fat examined by thin-layer chromatography (or analyzed by colorimetric method for heptachlor epoxide) to consist only partially of heptachlor epoxide.

3. Finally, Velsicol personnel,** in analysis of tissues from chlordane-fed dogs or rats, found that a peak in gas chromatograms which was first thought to correspond to heptachlor epoxide was, in fact, chlordane, per se.

Since these fat samples analyzed by Hoffman et al. were collected in the period, 1962 through 1966, if our inference is correct, there is evidence for possible presence of chlordane in fat of humans in the U.S.A.

By extension, chlordane must occur in the diet in finite, but unknown amounts.

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* Hoffman, W., Adler, H., Fishbein, W. I., and Bauer, F. A., "Relation of Pesticide Concentrations in Fat to Pathological Changes in Tissues," Archives of Environmental Health 15, 758-65 (1967).

** Cf. memo of Conference of Bureau of Science with persons from Velsicol Chemical Corporation on May 14, 1968, by H. R. Gittes, filed in DPT folder on chlordane.

\+ Of page 9 of DPT/FDA memo by M. Quaife, June 20, 1968, entitled "Toxicological evaluation of new rat reproduction and chronic dog feeding studies in connection with assessing safety of present tolerances on chlordane."