CALIFORNIA DEPARTMENT OF FOOD AND AGRICULTURE
MEDICAL TOXICOLOGY BRANCH

10/24/88

SUMMARY OF TOXICOLOGY DATA

LINDANE
(Gamma Hexachlorocyclohexane)

SB 950-073, Tolerance # 133

December 11, 1986
Revised October 24, 1988

I. DATA GAP STATUS

Chronic toxicity, rat:	Data gap, no study submitted
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	Data gap, inadequate study, possible adverse effect indicated
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	Data gap, inadequate study, no adverse effect indicated
Teratology, rat:	No data gap, no adverse effect
Teratology, rabbit:	No data gap, no adverse effect
Gene mutation:	No data gap, no adverse effect
Chromosome mutation:	Data gap, inadequate studies, possible adverse effect indicated
DNA damage:	Data gap, inadequate studies, possible adverse effect indicated
Neurotoxicity:	Not required at this time

Toxicology one-liners are attached.

** indicates an acceptable study.
Bold face indicates a possible adverse effect.
File name: T881024
Revised by Shimer & Davis, 10/24/88

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II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

CHRONIC TOXICITY, RAT

A Letter of 3/31/86 from McKenna, Conner and Cuneo for Centre International d'Etudes du Lindane (Volume 033) indicates that a rat oncogenicity repeat study and a rat chronic study are due on 12/21/89.

CHRONIC TOXICITY, DOG

039 059698 "Lindane Toxicity Studies in Beagle Dogs (Initial Studies and Dietary Intake for 104 Weeks)" (Huntingdon Research Centre, 9/2/71) Lindane (purity not stated) was fed for 104 weeks to 4 beagle dogs/sex/dose level at 0, 25, 50 and 100 ppm. NOEL = 50 ppm (elevated serum alkaline phosphatase levels and macroscopic liver anomalies). [Initial report (014 910293) evaluated as "insufficient information for assessment" since alternate pages were missing (Schreider 4/24/85)]. **NO ADVERSE EFFECT; ACCEPTABLE. Shimer 5/9/88, Davis 9/9/88

039 059697 "Lindane Toxicity Studies in Beagle Dogs (Initial Studies and Dietary Intake for 50 Weeks)" Interim report for 059698. Davis 9/9/88

014 910293 Initial report submitted to CDFA, evaluated as "insufficient information for assessment" since alternate pages were missing. Schreider 4/24/85

013 910274 "Lindane Toxicity Studies in Beagle Dogs. Dietary Intake (200 ppm) for 32 Weeks" (Huntingdon Research Center, 1/22/71) Lindane tested at 200 ppm in the diet for 18 months in beagle dogs; 4 dogs/sex/dose group; a pilot study to determine if high dose (200 ppm) would result in signs of toxicity; **NO ADVERSE EFFECT; SUPPLEMENTAL.** Schreider 4/17/85

ONCOGENICITY, RAT

A Letter of 3/31/86 from McKenna, Conner and Cuneo for Centre International d'Etudes du Lindane (Volume 033) indicates that a rat oncogenicity repeat study and a rat chronic study are due on 12/21/89.

040 059702 "Bioassay of Lindane for Possible Carcinogenicity." (Gulf South Research Institute, NCI, DHEW Publication No. 77-814, 1977) Lindane (100%) from 2 suppliers was fed to 50 Osborne-Mendel rats/sex/group in the diet for 80 weeks, followed by untreated diet for 30 weeks. Ten/sex were concurrent controls. Dose levels were reduced once on study for males and twice for females to yield time-weighted averages of 236 and 472 ppm for males and of 135 and 270 ppm for females. **POSSIBLE ADVERSE EFFECT**-liver neoplastic nodules in both treated groups of both sexes, pituitary adenomas and carcinomas in both treated male groups and pituitary adenomas in both treated female groups, thyroid adenomas and carcinomas in both treated male groups and thyroid adenomas in both treated female groups. NOEL not established. **UNACCEPTABLE, CANNOT BE UPGRADED**-too few control rats, only two dose levels, dose levels changed on study, MTD not reached, dosing period too short. Shimer 5/3/88, Davis 7/26/88

EPA one-liner: Oncogenic NOEL > 640 ppm (HDT) (sic)
(Dosage levels = 80, 160, 320, 640 ppm) (sic)

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038 059695 "Lindane Bioassay Studies and Human Cancer Risk Assessment" by Vesselinovitch and Carlborg (Toxicologic Pathology 11:12-22, 1983; University of Chicago) This review article of both mouse and rat oncogenicity studies includes re-evaluations of histology slides from four studies, a review of six other publications, and a human cancer risk assessment. An expanded version forms the Response of the Centre International d'Etudes du Lindane to EPA's preliminary Notice of Determination and Position Document 2/3 on Lindane (CDFA Volume 009). **NO ADVERSE EFFECT**-The authors assert that 9 of the 10 studies were negative; benign liver tumors were found in males in the 10th study; risk to humans is considered insignificant. The Medical Toxicology reviews did not agree with these conclusions. **SUPPLEMENTAL STUDY.** Shimer 5/9/88, Davis 7/29/88.

ONCOGENICITY, MOUSE

SUMMARY:
Considering all of the oncogenicity studies which Medical Toxicology has reviewed as well as the Vesselinovitch documents and the EPA documents, there appears to be a pattern of liver toxicity including hepatocarcinogenicity. Although none of these studies is acceptable and a NOEL has not been established, there is no obvious benefit to conducting another study. We consider the data gap to be filled and a possible adverse effect to be identified.

040 059703 "Bioassay of Lindane for Possible Carcinogenicity." (Gulf South Research Institute, NCI, DHEW Publication No. 77-814, 1977) Lindane (100%) from 2 suppliers was fed to 50 B6C3F1 mice/sex/group in the diet at 80 or 160 ppm for 80 weeks, followed by untreated diet for 10-11 weeks. Ten/sex were concurrent controls. **POSSIBLE ADVERSE EFFECT**-liver neoplasms in both sexes. NOEL not established. **UNACCEPTABLE, CANNOT BE UPGRADED**-too few control mice, only two dose levels, MTD not clearly established. Shimer 5/3/88, Davis 7/27/88.

EPA one-liner: Oncogenic NOEL > 160 ppm (HDT)
(Dosage levels = 80, 160 ppm)

014 910386 "Carcinogenicity Study of Lindane in the Mouse" by Weisse and Herbst, Dept. Experimental Pathology and Toxicology, C. H. Boehringer Sohn, Germany; Publication (Toxicology 7:233-238, 1977) Lindane (99.5%) tested at 0, 12.5, 25, and 50 ppm (corresponding to 0, 2.1, 4.1 and 8.2 mg/kg for males and 0, 2.0, 3.9, and 7.8 mg/kg for females) in the diet for 80 weeks in NMRI (SPF) mice; 50 mice/sex/treated group and 100 mice/sex for controls; **NO ADVERSE EFFECT**-No chronic toxicity or oncogenicity; **UNACCEPTABLE**-dose levels far below MTD, no analysis of diet, incomplete study parameters. Schreider 4/25/85, Davis 8/12/88

038 59696 "Testing of the Substance Lindane for Cancerogenic Effects in Mice Using Oral Administration-Duration 80 Weeks" (C.H. Boehringer Sohn Ingelheim am Rhein, 4-75) Supplemental to 910386-protocol information, investigators signature page, test material characterization, Mean body weight and food consumption data, dates of deaths and autopsy findings, individual autopsy and microscopic findings at termination, summary of tumor findings. Shimer 5/9/88, Davis 8/12/88

040 059701 "The Toxicology of Dieldrin (HEOD). II. Comparative Long-term Oral Toxicity Studies in Mice with Dieldrin, DDT, Phenobarbitone, beta-BHC and gamma-BHC" by Thorpe and Walker. (Fd. Cosmet. Toxicol. 11:433-442, 1973) A comparative study of the response of CF1 mice to various chemicals capable of

inducing microsomal enzymes in mammalian liver cells. Based on the result range-finding tests, groups of 30 of each sex were fed diets with 10 dieldrin (> 99%), 100 ppm DDT (> 99.5%), 500 ppm sodium phenobarbitone 98%), 200 ppm beta-BHC (> 99%), or 400 ppm gamma-BHC (> 99.5%) for 110 weeks. Negative controls were 45 mice/sex. **POSSIBLE ADVERSE EFFECT**-Elevated frequencies of hyperplastic foci and tumors in the livers of both sexes for all treated groups; for lindane (gamma-BHC) the elevations were significant at the $p < 0.01$ level; the incidences of tumors in other tissues were lower than control incidences for most treated groups including the lindane (gamma-BHC) group. **SUPPLEMENTAL STUDY.** Shimer 5/9/88, Davis 7/25/88.

040 059655 "Induction of Hepatoma in Mice by Benzene Hexachloride" by Hanada et al. (Gann 64:511-513, October, 1973, Dept. of Pathology, Osaka University School of Medicine) 10 or 11 dd mice/sex/group were fed a control diet or one of four test materials (crude BHC, alpha BHC, beta BHC, and gamma BHC = lindane) at 100, 300, and 600 ppm for 32 weeks and then returned to the basal diet for 5 or 6 weeks, at which time they were sacrificed. **POSSIBLE ADVERSE EFFECT FOR THE CRUDE EXTRACT, ALPHA ISOMER, AND GAMMA ISOMER (LINDANE)** -Liver tumors, with higher frequencies in males. NOEL = 100 ppm. **SUPPLEMENTAL STUDY.** Shimer 5/9/88, Davis 7/22/88.

040 059699 "Histologic and Ultrastructural Studies on the Hepatocarcinogenicity of Benzene Hexachloride in Mice" by Ito, N., et al., (J Natl Cancer Inst 51:817-826, 1973) Groups of 20 or 40 male strain dd mice were fed alpha, beta, gamma, or delta BHC for 24 weeks at 100, 250, and 500 ppm singly and in various combinations to test for interactions. **NO ADVERSE EFFECTS FOR LINDANE (GAMMA ISOMER)**-No compelling evidence for oncogenicity from lindane alone or in combination with other isomers (NOEL > 500 ppm). Hepatocarcinogenicity from the alpha isomer (NOEL = 250 ppm). **SUPPLEMENTAL STUDY.** Shimer 5/9/88, Davis 7/22/88

040 059700 "Carcinogenicity of Benzene Hexachloride (BHC)" by Nagasaki, H., et al. of Nara Medical University, Japan (Pages 343-353 of "Topics in Chemical Carcinogenesis", Ed. Nakahara et al. Univ. Tokyo Press, Tokyo, 1972) Twenty male dd mice per group were fed a diet with BHC (mixture of isomers) at 6.6, 66.0, and 660.0 ppm for 24 weeks. Fourteen male dd mice were fed a basal diet alone, as negative controls. **POSSIBLE ADVERSE EFFECT FOR BHC**-Liver tumors developed in all 20 high dose mice but no other mice. Alpha and beta isomers accumulated in the livers of all treated groups. Other organs were unaffected. **SUPPLEMENTAL STUDY.** Shimer 5/9/88, Davis 7/25/88.

012 910381 "Carcinogenicity Study with Lindane in Mice. Electron Microscopical Investigation of Livers" (C. H. Boehringer Sohn, 8/5/73) Liver samples from four NMRI mice/sex/group, fed 0, 12.5, 25, or 50 ppm for 80 weeks in an oncogenicity study, were examined by electron microscopy. **NO ADVERSE EFFECT-results completely negative. SUPPLEMENTAL STUDY.** Davis 9/22/88

See also 038 059695 under ONCOGENICITY, RAT.

REPRODUCTION, RAT

013 910398 "Effect of Lindane on Reproductive Function of Multiple Generations in the Rat." (Huntingdon Research Centre, Report # 4239 71/445, 2/16/72) Lindane (Batch No. 6801/403, ≥ 99.0%) tested at 0, 25, 50 and 100 ppm in the diet in a 3-generation study in Charles River CD rats; 10 male and 20 female rats/dose group for all generations; increase in liver weight in F^3 pups at 100 ppm; NOEL = 50 ppm; **NO ADVERSE EFFECT; INCOMPLETE; UNACCEPTABLE** (dose levels not high enough, insufficient histopathology and necropsy,

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unknown clinical observation intervals, and too few males). Schreider 4/22/85, Davis 9/21/88

012 910275 "Effect of Lindane on Reproductive Function of Multiple Generations in the Rat. (1) The Determination of Dietary Concentration of Lindane. (2) Residues of Lindane in Rat Tissues." (Huntingdon Research Centre, 1/27/72) Describes the methods (gas liquid chromatography) and results for lindane analyses in the rat diet and selected tissues of weanlings. Davis 9/21/88

Rebuttal in 038 provides information on test material and other questions from the original CDFA review.

COMMENTS ON THE TERATOLOGY CATEGORIES: While none of the following six studies is individually acceptable, this reviewer feels that collectively they are sufficient to fill the data gaps for both teratology categories. Each of the studies was criticized for having too few pregnant dams, but taken together they are more than adequate. Dose level selection was also questioned in five of the six studies. The study in which rabbits were dosed by gavage did not use high enough dose levels, but the injection study in rabbits did produce maternal toxicity. Similarly, the injection study in mice was criticized for inadequate dose levels but the gavage study in mice produced maternal toxicity. Both studies in rats produced maternal toxicity. The studies, done in three different laboratories, with two different routes of exposure, and three different species, were consistently negative. Further studies are unlikely to provide new information. Davis 9/22/88

TERATOLOGY, RAT

014 910388 "Teratology Study in Rats-Lindane (Gamma Benzene Hexachloride, USP)." (Hazleton Laboratories America Inc., 7/13/76) Lindane (purity unspecified) tested at 0, 5, 15 and 30 mg/kg in corn oil by subcutaneous injection on Days 6-15 of gestation in Charles River Sprague Dawley rats; 15-18 pregnant rats/dose group; toxicity observed at 30 mg/kg; decrease in food consumption (Days 6-11), body weight gains and increase in mortality (2/20) and clinical signs (tremors, excitability); extra ribs only present in the presence of maternal toxicity; **NO ADVERSE EFFECT; INCOMPLETE; UNACCEPTABLE** (purity of test compound, analysis of dose solution, not enough pregnant animals, justification of route of administration, insufficient visceral data, quality assurance statement). Schreider 4/24/85

013 910394 "Effect on Lindane on Pregnancy of the Rat." (Huntingdon Research Center, 12/3/71) Lindane (≥ 99.0%) tested at 0, 5, 10, 20 mg/kg in 0.5% aqueous carboxymethylcellulose mucilage by oral gavage on Days 6-15 of gestation in CFY rats; decrease in body weight gain and food consumption at 10 and 20 mg/kg; Maternal NOEL = 5 mg/kg; dose-related increase of 14th rib at all doses and significant at 20 mg/kg (however, within historical control range); Developmental NOEL = 10 mg/kg; **NO ADVERSE EFFECT; INCOMPLETE; UNACCEPTABLE** (not enough pregnant animals, no justification of dose levels, no dosing solution analysis, no individual fetal data, insufficient protocol information). Schreider 4/18/85, Parker 12/10/86, Davis 9/21/88

Rebuttal in 038 provides information on test material and other questions from the original CDFA review.

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TERATOLOGY, MOUSE

012 910390 "Lindane Testing for Teratogenic Effects in Mice Following Subcutaneous Injection." (E. Merck-Darmstadt, 1/28/72) Lindane (purity unspecified) tested at 0 and 6 mg/kg in 0.5% CMC-mucilage by subcutaneous injection (10 ml/kg) in two groups of NMR-EMD-SPF mice; group I injected daily on Days 6-15 and group II on Days 11-13 of gestation; 25 females/dose group; increased number of runts in group II at 6 mg/kg; **NO ADVERSE EFFECT; INCOMPLETE; UNACCEPTABLE** (purity of test compound, not enough pregnant animals in group II, justification of route of exposure, only one dose level tested, no justification of dose level, no clinical observations, incomplete necropsy/histopathology study, no soft tissue data on fetuses). Schreider 4/25/85, Davis 9/21/88

012 910392 "Lindane Testing for Teratogenic Effects in Mice Following Oral Administration." (E. Merck-Darmstadt, 5/4/72) Lindane (≥ 99.0%) tested at 0, 12, 30, 60, mg/kg in 0.5% aqueous carboxy methylcellulose mucilage by oral gavage (10 ml/kg) in two groups of NMRI-EMD-SPF mice; group I treated on Days 6-15 and group II on Days 11-13 of gestation; 25 females/dose group; toxicity observed at 60 mg/kg; decreases in activity, body weights and live fetuses; increase in mortality and abortions; **NO ADVERSE EFFECT;** no fetotoxic or teratogenic effects were observed until at high doses that caused extreme maternal toxicity; **INCOMPLETE; UNACCEPTABLE** (no dosing solution analysis, too few pregnant dams, high dose level too toxic). Schreider 4/25/85, Davis 9/21/88

Rebuttal in 038 provides information on test material and other questions from the original CDFA review.

TERATOLOGY, RABBIT

014 910389 "Teratology Study in Rabbits." (Hazleton Laboratories, 8/6/76) Lindane (purity unspecified) tested at 0, 5, 15 and 45/30 mg/kg (animals received 45 mg/kg on Days 6-9 and 30 mg/kg on Days 10-18 of gestation) in corn oil by subcutaneous injection from Days 6-18 of gestation in New Zealand white rabbits; 11-15 pregnant rabbits/dose group; high mortality at 45 mg/kg (12/13); dose related loss of body weight, decrease in food consumption and clinical signs at 15 and 45 mg/kg; embryo lethality at 45 mg/kg in presence of maternal toxicity; **NO ADVERSE EFFECT; INCOMPLETE; UNACCEPTABLE** (purity of compound, analysis of dosing solution, not enough animals, justification of dose levels, incomplete examination on fetuses for visceral and skeletal effects, no visceral effects were presented; no sex ratio was presented, excessive death at high dose, justification of route of administration, quality assurance statement). Schreider 4/24/85

013 910396 "Effect of Lindane on Pregnancy of the New Zealand Rabbit." (Huntingdon Research Center, 12/1/71) Lindane (≥ 99.0%) tested at 5, 10 and 20 mg/kg in 0.5% aqueous carboxymethylcellulose mucilage by oral gavage on Days 6-18 of gestation in New Zealand rabbits; 13 animals/dose group. Report states increase respiration and drowsiness in all doses; however, no data presented. Preimplantation loss at 20 mg/kg; however, implantation occurs prior to initiation of dosing. Maternal NOEL > 20 mg/kg (Differences in food consumption and weight gain minimal); fetal loss increased with dose but was within historical range; abortions (one per dose group) at 10 and 20 mg/kg; increase in 13th ribs in fetuses and decreased ossification of sternebrae at 10 and 20 mg/kg but these are variable and minor changes which may indicate borderline fetotoxicity; Developmental NOEL > 20 mg/kg; **NO ADVERSE EFFECT; INCOMPLETE; UNACCEPTABLE** (too few pregnant dams, dose levels not high enough, no diet analysis). Schreider 4/19/85, Parker 12/10/86, Davis 9/21/88

Rebuttal in 038 provides information on test material and other questions from the original CDFA review.

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GENE MUTATION

Microbial Systems

009 019644 (Exhibit 15 of the "Response of the Centre International d'Etudes du Lindane to EPA's preliminary Notice of Determination and Position Document 2/3 on Lindane", Volume II) "Bacterial Mutagenicity Tests of Lindane With Mouse Liver Preparations as Metabolizing Systems" (Pharmakologisches Institut Der Universitat Mainz, 8/29/80) Lindane (purity unspecified) tested at 0, 15.8, 50, 158, 500, 1580, and 5000 ug/plate with and without S9 in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and *Escherichia coli* strain WP2 uvrA; duplicate plates; S9 mixes prepared +/- Arochlor induction from NMRI and CF-1 mice; additional assays with TA98 with and without activation and with and without the drug norharman. **NO ADVERSE EFFECT-no mutagenicity with lindane under any conditions. **ACCEPTABLE.** Schreider 4/29/85, Davis 9/14/88

014 910384 "Mutagenicity Versus Carcinogenicity of Organochlorine Insecticides (Ames test on Lindane with S. typhimurium)" (Public Health Laboratory, Katholieke Universiteit Louvain, 5/4/76) Lindane (purity unspecified) tested at 0, 10, 100 and 1000 ug/plate with and without NMRI mouse liver S9 in 7 strains of *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537, TA1538, TA1950 and TA1978); **INSUFFICIENT INFORMATION FOR ASSESSMENT; INCOMPLETE; UNACCEPTABLE** (purity of compound, no statistical analysis, missing individual plate revertant data, some figures unreadable, no quality assurance statement). Schreider 4/24/85

Mammalian Systems

031 034526 "Mammalian Cell (V79) Mutagenicity Test on Lindane (Fetal Hamster Lung Cells)" (Celamerck, 5/28/84) Lindane (purity unspecified) tested at 0.5 to 500 ug/ml (10 concentrations) with Aroclor 1254 induced male CD-1 mouse S9 and 0.5 to 250 ug/ml (9 concentrations) without S9 activation in cultured Chinese Hamster lung cells (V79); 2 hours exposure time with S9 and 24 hours without S9; 10^6 cells/replicate; 6 replicates/dose; 8 days expression time; an increase of mutant frequency was observed at 2.4 and 100 ug/ml in an activated trial but was not confirmed by two subsequent activated trials; **NO ADVERSE EFFECT; COMPLETE; ACCEPTABLE. Gee 9/26/85

EPA one-liner: Negative in V79 cells for mutation to HGPRT deficiency up to levels of toxicity and/or solubility, with or without activation. However, inappropriate S9 microsomes used (from CD-1 mice) instead of sensitive CF-1 mice.

Note: A letter of 7/1/85 from the EPA Product Manager in Volume 031 indicates that the appropriate activation system was from CF-1 mice since that was the strain in which Thorpe & Walker (CDFA Record 059701) demonstrated liver oncogenicity. EPA was convinced that "CD-1" was a typographical error and that CF-1 mice were in fact used. Therefore, the CORE Grade was changed to "Acceptable".

CHROMOSOME MUTATION

031 34524 "*In Vivo* Sister Chromatid Exchange Assay in CF-1 Mouse Bone Marrow Cells with Lindane (oral application)" (Research & Consulting Company, 6/20/84) Lindane (99.8%) tested at 0, 2, 10 and 50 mg/kg in male and 0, 1.6, 8 and 40 mg/kg in female in oleum arachidis by single oral gavage (10 ml/kg) in Charles River CF-1 mice; doses were 1/75, 1/15 and 1/3 of the LD_{50}; 5 mice/sex/group; BUdR tablets implanted 2 hours after dosing; mice sacrificed

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24 hours after dosing; 30 metaphases/animal scored; the high dose male SCE frequency was statistically higher than control frequency while the high dose female SCE frequency was statistically lower than control frequency; the averaged frequency was not different from the controls; **NO ADVERSE EFFECT; UNACCEPTABLE**-dose levels not high enough. Originally considered acceptable-Gee **9/25/85;** second review considered unacceptable-Gee & Choy 12/10/86; review of C.I.E.L. rebuttal of 9/21/87, still unacceptable-Davis & Gee 9/16/88

EPA one-liner: Negative in CF-1 males and females for sister-chromatid exchanges at single oral dose up to one third of reported LD_{50}. However, insufficient dosage and sampling sizes employed; no clinical or cytotoxicity at any dose.

Note: A letter of 7/1/85 from the EPA Product Manager in Volume 031 indicates that the CORE Grade has been changed to "Acceptable".

031 34525 "*In Vivo* Sister Chromatid Exchange Assay in CF-1 Mouse Bone Marrow Cells with Lindane (i.p. injection)." (Research and Consulting Company, 7/17/84) Lindane (99.8%) tested at 0, 1.3, 6.4 and 32.1 mg/kg in oleum arachidis by a single i.p. injection (10 ml/kg) in Charles River CF-1 mice; doses were 1/75, 1/15 and 1/3 of LD_{50}; 5 mice/sex/dose group; BUdR tablets implanted 2 hours after dosing; mice sacrificed 24 hours after dosing; 30 metaphases/animal scored; increases of SCE frequency in female mice at 32.1 mg/kg (1/3 of LD_{50}); **POSSIBLE ADVERSE EFFECT; UNACCEPTABLE**-pending historical control data. Originally considered acceptable-Gee 9/25/85; second review considered unacceptable-Gee & Choy 12/10/86; review of C.I.E.L. rebuttal of 9/21/87, still unacceptable-Davis & Gee 9/16/88

DNA DAMAGE

SUMMARY:
The three submissions in this category are journal articles which are considered supplemental because they were not intended to be guideline studies. Two are unscheduled DNA synthesis assays in which lindane was tested in a battery of pesticides. The third article demonstrates covalent binding of lindane to DNA. Although the authors argue that this binding cannot explain the oncogenicity of lindane, it does pose a possible source of mutation, which is important in its own right.

045 067906 "Chemically-Induced Unscheduled DNA Synthesis in Primary Rat Hepatocyte Cultures: A Comparison With Bacterial Mutagenicity Using 218 Compounds" by Probst, McMahon, Hill, Thompson, Epp, & Neal, Lilly Research Laboratories, Indianapolis (Environmental Mutagenesis 3:11-32, 1981) **NO ADVERSE EFFECT**-Lindane was found negative in both an unscheduled DNA synthesis assay in primary rat hepatocyte cultures and a modified Ames assay. The unscheduled DNA synthesis assay was done with 100 nmoles of lindane per ml. **SUPPLEMENTAL STUDY.** Davis 9/13/88

045 067907. "The Relevance of Covalent Binding to Mouse Liver DNA to the Carcinogenic Action of Hexachlorocyclohexane Isomers" (Institute of Toxicology, ETH and University of Zurich, 1983) NMRI, CF1, and B6C3F1 male mice were dosed with alpha, beta, delta, or gamma (lindane) hexachlorocyclohexane by oral gavage. Covalent binding to liver DNA was found at equivalent levels for all isomers except beta which had little binding. Gamma isomer binding was equivalent in all three mouse strains. DNA synthesis was also stimulated. The authors conclude that the known liver oncogenicity of hexachlorocyclohexane isomers, including lindane, is best explained by a

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nongenetic mechanism. **POSSIBLE ADVERSE EFFECT**-Covalent binding of lindane to DNA. **SUPPLEMENTAL STUDY.** Davis 9/13/88

045 067908 "Pesticide Induced DNA Damage and Its Repair in Cultured Human Cells" by Ahmed, Hart, & Lewis, Ohio State University (Mutation Research 42:161-174, 1977) Lindane was one of 13 pesticides tested for unscheduled DNA synthesis (autoradiography) in SV-40 transformed human fibroblasts (cell line VA-4) +/- S9. **NO ADVERSE EFFECT**-Lindane was negative with 8 hours at 1 and 1000 uM. **SUPPLEMENTAL STUDY.** Davis 9/13/88

NEUROTOXICITY

Not required at this time.

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