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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Aldrin/Dieldrin Mutagenicity
(Genetic Toxicity Profiles)

Caswell 012/333

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Attached are a discussion and evaluation of the mutagenicity (gene-tox) data base on aldrin* and its epoxide derivative dieldrin**. These assessments were generated from reviews of the available published literature located by our contractor, Dynamac Corporation (TB Project 1244), and by EMIC (the Environmental Mutagen Information Center at Oak Ridge National Laboratory) for evaluation in Phase I of the Gene-Tox Program (Dr. Michael D. Waters, HERL, RTP). With a few (equivocal) exceptions, these two groups independently agree in their conclusions on the same studies. There appears to have been no submissions of primary data (CBI) from Shell on either chemical in our Caswell Files (Nos. 012, 333), although a number of additional published articles not located by either Dynamac or EMIC have been submitted by Scallop Corporation in response to a DCI Notice.

*Aldrin: 1,2,3,4,10,10-hexachloro-1,4,4a,8,8a-hexahydro-1,4-endo-exo-5,8-dimethanonaphthalene (Shell).

**Dieldrin: 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-endo-exo-5,8-dimethanonaphthalene (Shell).

Both chemicals are being considered together here because of the paucity of acceptable studies (only two) on aldrin, which hinders a gene-tox assessment on this chemical However, since aldrin is readily converted both in vivo and in vitro to dieldrin, the more adequate data base on the latter (nine studies) can be used for a preliminary weight-of-evidence approach on both considered together.

In addition to the discussion according to FIFRA categories of genetic effect, summary tabulation/evaluation of results of all studies reviewed from both major sources (Dynamac, Gene-Tox Program), and recommendations to fulfill regulatory requirements ("data gaps"), several attachments are appended to this assessment, in the following order:

Attachment:

I - List of references cited
II - Overview (Dynamac)
III - Data Evaluation Records (Dynamac)
IV - Gene-Tox Profiles (EMIC/HERL)
V - Lindane

THE MUTAGENICITY OF ALDRIN/DIELDRIN

The Data Base

A total of 21 assays with aldrin and 42 with dieldrin in 33 published articles were located for review, distributed according to genetic endpoint as follows:

Genetic Endpoint	Test System	Chemical	
		Aldrin	Dieldrin
Gene Mutation	Bacterial	8	19
	Mammalian cell	-	1
	in vivo	1	2
Chromosome Aberration	in vitro	1	1
	in vivo	4	7
DNA Damage/ Repair	in vitro	6	7
	in vivo	-	1
Other Mechanisms	in vitro	-	2
	in vivo	1	2

The majority (65%) of these reports (14 on aldrin and 27 on dieldrin) are inadequate (judged UNACCEPTABLE) to support the negative results reported, because of one or more of the following deficiencies:

- No data presented, or only qualitative assessments (+/-);
- Preliminary screening surveys or new techniques, with insufficient details and/or procedures;
- Only one dose or insufficient (nontoxic) doses tested in incomplete assays;
- Assays with no positive controls to assure sensitivity of the test system to respond;
- Inappropriate procedures and/or test systems.

However, these studies were considered to corroborate the conclusions based upon the minority of sufficiently adequate data judged either ACCEPTABLE or INCONCLUSIVE. Those assays judged "inconclusive" generally reported unconfirmed (presumptively) positive results which could not be satisfactorily interpreted, because of inadequate procedures or controls,

and/or the reporting of qualitative assessments in assays compromised by conflicting variables. Some of these studies are useful, however, in directing attention to further testing necessary to establish the mechanism(s) of action possessed by these organochlorines, discussed more fully below.

The few studies (two on aldrin, nine on dieldrin) judged fully adequate (ACCEPTABLE) preclude comprehensive assessments of the (potential) mutagenicity of either pesticide. Based on the available data, further testing is recommended (see below), in order to satisfy both the regulatory requirements for continued registration of these pesticidal chemicals and to provide approaches to risk assessments.

Discussion and Evaluation of Results (Tables 1 and 2)

ALDRIN

Although none of the individual published bacterial assays for gene (point) mutation was acceptable, collectively they indicate aldrin is probably not mutagenic in procaryotes, considering the consistently negative results reported by seven groups of investigators (Table 1). The lack of a mammalian cell assay constitutes a data gap for aldrin, which is not fully satisfied by the inconclusive, unconfirmed positive study reported for dieldrin in nonactivated Chinese hamster lung (V79) cells by Ahmed et al. (1977) (Table 2). The negative sex-linked lethal result for aldrin in Drosophila (Benes and Sram, 1969) is discounted because of the low dosage necessary in testing this organochlorine insecticide.

Only one assay for chromosomal effects contained sufficient primary data and procedures to render it adequate. In testing 174 substances for dominant lethality, Epstein and associates (1972) administered aldrin to male ICR Swiss mice in two dosage schedules: as a single ip dose of 8 or 40 mg/kg (the latter lethal for half the animals); by gavage at five consecutive daily doses of 0.5 and 1.0 mg/kg, both followed by 8 weeks of sequential matings (one male to three females/week). Analysis of the data revealed isolated increases in early fetal deaths in both experiments, but these were considered by the authors to lie within control reproductive parameters. Hence the reported conclusion that aldrin was negative in these studies is acceptable. On the other hand, two reportedly positive chromosome studies in mammalian somatic cells (non-activated human lymphocyte cultures; bone marrow cells from rats and mice treated ip) by Georgian (1975) were judged inconclusive because the increased aberration counts were observed only at excessively toxic levels and included effects not conventionally considered aberrations (e.g., gaps which may reflect nonstaining regions and not actual breaks).

Finally, the negative mouse micronucleus assay by Usha Rani et al. (1980) is unacceptable because they reported no toxicity at the single dose tested and included no positive control. The bean root tip study of Njagi and Gopalan (1981) provided no useful information.

The requirement for an acceptable chromosome study is satisfied by the germinal assay of Epstein et al.; however, to complete the testing in this category, adequate cytogenetic testing of aldrin in mammalian somatic cells (in vitro or in vivo) is recommended.

Although inadequately tested in bacterial systems, the single acceptable assay for unscheduled DNA synthesis in primary rat hepatocyte cultures performed by Probst and colleagues (1981) would appear to indicate no potential for aldrin to induce primary DNA damage in mammalian cells. However, confirmation for this conclusion is necessary in view of the presumptively positive studies reported in other mammalian test systems (Table 1). For example, both Rocchi et al. (1980) and Ahmed and associates (1977) recorded autoradiographic evidence of DNA damage/repair in established mammalian cell cultures. These studies are considered inconclusive, however, because of technical deficiencies in the former (only one dose tested under culture conditions which did not exclude the possible inclusion of replicative S-phase, i.e., "scheduled", DNA synthesis in UDS counts), and the reporting of qualitative results only ("+") at all concentrations tested in a virus-transformed cell line by the latter. The dose-related single-strand DNA breaks in primary rat hepatocytes treated in vitro (as ascertained from alkaline elution) reported by Sina et al. (1983) were found only at cytotoxic concentrations; the validity of this study was further compromised by the listing of "positive" results for a number of acknowledged noncarcinogens.

Lastly, the "positive" reported by Markaryan (1966) for mitotic spindle inhibition in bone marrow cells from male mice administered a single ip dose of aldrin (0.002 mg/g, stated to represent 4% of the LD_{50}, 50 mg/kg) could not be interpreted because it contained major technical and reporting deficiencies.

DIELDRIN

A more comprehensive data base of acceptable studies permits a preliminary assessment of the genetic toxicology profile for dieldrin (Table 2). Major data gaps, however, remain to be satisfied, in order to complete regulatory requirements.

The negative results in bacterial screening surveys published by nine groups of investigators, although considered individually inadequate, are collectively consistent with the three acceptable negative studies provided by the Haworth (1983), Glatt (1983), and Marshall (1976) groups, who tested dieldrin in adequately controlled Ames assays using rat and/or hamster S9 for activation to the limit of toxicity and/or solubility (1000/300 ug). On the other hand, Majumdar and associates (1977) recorded dose-related increases in Salmonella reversions (in TA 1535, 98, and 100) at the two lower of three concentrations tested (1, 25, 50 ug/mL), with a greater response in the presence of S9 hepatic microsomes prepared from STS mice; a decrease in reversions was found at the HDT, which was considered evidence of cytotoxicity. This positive result is suspect because no positive controls were apparently included, and the concentration eliciting "toxicity" was well below that reported in all other studies reviewed here. Hence, the study is judged inconclusive (presumptively positive) until confirmed or refuted in repeat assays using mouse S9. The results of the Majumdar study conflict with the negative results at comparable dose levels reported by van Dijck and van der Voorde (1976) employing mouse S9. Further, it should be noted that, although judged unacceptable (because of insufficient procedural details including the absence of positive controls), Bidwell et al. (1975) also reported negative results in mouse host-mediated assays using $B_6D_2F_1$ hybrids given five consecutive oral doses of 20 mg/kg/day and the Salmonella strains TA1530, 1535, and 1538 (but not the more sensitive TA98 and 100) as indicator organisms.

Only a limited number of studies assaying dieldrin for gene mutation in eucaryotic test systems were located, none fully adequate. Two groups tested for sex-linked recessive lethals in Drosophila (Benes and Sram, 1969; Bidwell et al., 1975), and the same reservations noted above for aldrin concerning the reportedly negative results condition the validity of these studies. Only one mammalian assay was available, an inconclusive positive study reporting increased ouabain resistance in Chinese hamster (V79) cells exposed to only one concentration, 10 uM (higher levels were toxic), but conducted only in the absence of activation; further, no positive control was apparently included.

Adequate testing supporting negative results for chromosomal damage was reported in three of eight publications reviewed. In two acceptable dominant lethal assays (Dean et al., 1975; Epstein et al., 1972), male mice were administered a range of single oral or ip doses, as well as daily oral doses for 5 days (the HDT's in both schedules eliciting severe clinical toxicity, including death) with no increase recorded in fetal wastage during 8 weeks of sequential matings.

A third mouse dominant lethal (Bidwell et al. 1975), however, was inadequate since insufficient doses (HDT = 8 mg/kg, providing no evidence of toxicity) were tested.

In somatic mammalian cytogenetic assays, an acceptable study reported dose-related increases in chromosome aberrations in bone marrow cells of STS mice treated ip at single doses of 1, 30, and 50 mg/kg, all of which were reported to be cytotoxic (Majumdar et al. 1976), but a comparable assay in Chinese hamsters treated orally at comparable doses (1, 30, and 60 mg/kg) was unacceptable because neither toxicity nor positive controls were reported (Dean et al., 1975). Similarly, inadequate mouse assays for micronucleus induction and chromosome translocations were reported by Bidwell and associates (1975).

Human cells exposed to dieldrin have also been assayed for chromosomal effects. Majumdar and associates (1976) exposed unactivated Wl-38 cultures in vitro to 1, 10, and 30 ug/mL, and recorded dose-related increases in chromosome aberrations at all doses (stated to be "toxic"). This study is inconclusive because the test did not include mammalian activation (S9). Finally, in a human monitoring survey of dieldrin plant workers exposed to unstated levels, Dean et al. (1975) reported no increases in chromosomal damage compared to presumably nonexposed controls of comparable ages; this study is unacceptable because of a number of other major deficiencies.

Of the eight assays for primary DNA damage/repair located for review, only three were fully adequate for assessment (considered ACCEPTABLE), while a further four were inconclusive in reporting unconfirmed positive results (Table 2). Dean and associates (1975) reported negative results in adequate assays for gene conversion in D4 yeast cells in host-mediated assays. Host mice were dosed orally up to toxic levels in two experiments: an acute schedule of 25 and 50 mg/kg; and 5-day repeat administration of 5 and 10 mg/kg/day. Both Probst and colleagues (1981) and Klaunig et al. (1984) found dieldrin to be negative in rat (Probst) and in both unstimulated and phenobarbitol-stimulated mouse (Klaunig) hepatocytes cultured up to cytotoxic levels. In contrast, both Rocchi and colleagues (1980) and Ahmed et al. (1977) reported weak positive UDS results in mammalian cultures, the former using nonactivated cultures of primary human lymphocytes exposed to only one concentration (100 ug/mL), and the latter with both activated (rat S9) and nonactivated cultures of the SV-40 (virus)-transformed human VA-4 cell line. Both were considered inconclusive because of the deficiencies stated above for aldrin assays.

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Dieldrin was tested in a number of ancillary assays, all not completely interpretable. As with aldrin, Markaryan (1966) found dieldrin "positive" for "mitotic spindle inhibition" in bone marrow cells of male mice injected ip (0.0012 mg/g, stated to be 4 percent of the LD_{50}), but he included cytological effects in inappropriate technical procedures (hence an unacceptable study). Dieldrin has also been found active in preliminary studies involving newer techniques presumably providing evidence of its ability to affect cellular processes not directly involved with genotoxicity. Thus, Seiler (1977) reported dieldrin to inhibit testicular DNA synthesis in mice orally gavaged at a single dose of 50 mg/kg in uncontrolled experiments (hence unacceptable), while Wade and associates (1986) recorded dieldrin to inhibit gap-junction, cell-to-cell communication in human teratocarcinoma cells at 7 ug/mL (the only dose tested), again in poorly controlled tests.

Finally dieldrin (but not aldrin) has been tested by Styles (1978) for mammalian cell transformation in an incompletely reported survey with baby hamster kidney (BHK-21) cells, and found negative at an unstated LC_{50} dose (concentration range tested: 0.08, 0.4, 2.0, 10, 50, and 250 ug/mL, with/without rat S9).

Conclusions/Recommendations:

Although adequate studies are still required in some areas, the evaluation of the available data in published literature on aldrin and dieldrin indicates that neither directly interferes with DNA or chromosomes, i.e., not mutagenic in the sense of initiating genetic effects likely to be transmitted. Thus, sufficient evidence exists to conclude that neither possesses mutagenic activities in bacteria (at least under standard metabolic activation conditions, e.g., rat hepatic S9), but further testing is needed to assess this potential in mammalian cell systems. Additional studies are also necessary to resolve conflicting mutagenic activities under specialized activation conditions, e.g., in the presence of microsomal enzyme fractions derived from tissues and/or organs responding with tumor formation (e.g., mouse S9).

At least two adequate (dominant lethal) and one less-than-adequate (translocation) assays indicate that these organochlorine insecticides pose no serious risk of transmissible chromosomal aberrations, but the contradictory results in somatic chromosomal studies mandate further testing for this endpoint. Finally, confirmation of the negative results in repair assays with primary rat hepatocytes is required, preferably in other mammalian repair assays, in view of the presumptively positive repair activity in some in vitro assays.

On the other hand, consistent with genetic toxicology assessments prepared for other members of this class (e.g., Lindane, see ATTACHMENT V), these organochlorines probably act by epigenetic mechanisms likely to promote and/or sustain cellular processes initiated by other agencies, thus indirectly affecting primary genetic mechanisms. Such activity is indicated by inadequate but presumptively positive unconfirmed studies for mitotic spindle effects, and inhibition of both cell-to-cell communication and DNA synthesis. In order to affirm the absence of a potential for direct genotoxic activity, and to complete regulatory requirements, the following additional testing is required:

1. Mammalian cell gene mutation assays, with mouse lymphoma (L5178Y/TK), or Chinese hamster (CHO/V79/HGPRT) cells inter alia, specifically comparing activation systems (S9) derived from rat vs. mouse (or hamster) liver microsomes;

2. Somatic cell cytogenetic assays, either in vitro or in vivo;

3. Repair in mammalian cell systems, e.g., primary mouse hepatocytes or established cell lines, by autoradiographic or alkaline elution techniques.

Further, to confirm the potential activity of these chemicals in indirect (epigenetic) processes, the following are recommended:

1. Adequately controlled promotion assays, e.g., in cell lines already initiated (by viral transformation), or exposed to known active chemical initiators.

2. Mammalian cell transformation in systems with an established data base, e.g., C3H 10 T1/2, BALB 3T3, inter alia.

3. Assays for mitotic spindle effects (in vitro or in vivo), and/or involving other cellular mechanisms (e.g., oncogene activation), inter alia.

4. Assays which can distinguish effects on replicative S-phase (scheduled) DNA synthesis from UDS, e.g., in primary hepatocytes from several species (mouse vs. rat/hamster).

TABLE 1 MUTAGENICITY TESTING OF ALDRIN

Genetic Category	Study Type/ Test System	Range of Doses (mg/kg) or Concentrations (ug/mL)	Reference	Reported Results	Evaluation	Comment
Gene Mutation	Reversions in bacteria (Salmonella/ Ames)	Up to 5000/plate, +/- S9	Moriya et al. (1983).	Negative	Unacceptable	Survey scree
		1-10,000/plate (gradient), +/- S9	Probst et al. (1981)	Negative	Unacceptable	Survey scree
		20/disc, -S9 only	Shirasu et al. (1978)	Negative	Unacceptable	Survey scree
		1, 1000/plate, +S9 only (mouse)	Van Dijck/van der Voorde (1976)	Negative reported at 1 ug only	Unacceptable	Only one (nc toxic) dose ported; not tested -S9
	Reversions in bacteria (E. coli WP2)	Up to 5000/plate, +/- S9	Moriya et al. (1983)	Negative	Unacceptable	Survey scree
		1-10,000/plate (gradient), +/- S9	Probst et al. (1981)	Negative	Unacceptable	Survey scree
		20/disc, -S9 only	Shirasu et al. (1976)	Negative	Unacceptable	Survey scree
		1000/disc, -S9 only	Ashwood-Smith et al. (1972)	Negative	Unacceptable	Survey scree
	Sex-linked recessive lethals in Drosophila	0.001%, ip	Benes/Sram (1969)	Negative	Unacceptable	Tested at or one dose in inappropria system
Chromosome Aberration (Damage)	Root tip cells, Vicia faba	10-10,000 ppm	Njagi/Gopalan (1981)	Dose-related Positive for cytological effects	Unacceptable	Survey scre in anaphase cells only.
	Human lympho-cytes in vitro	19.125, 38.25, and 76.5, -S9	Georgian (1975)	Positive at LDT (toxic); higher doses lethal	Inconclusive	Only one do: scored at c toxic level gaps includ
	Mouse BM	1 x 2 ("0.002mg/g"), ip (4% of LD50 in males only)	Markaryan (1966)	Positive for "nuclear disturbances"	Inconclusive	Inapprop: procedur cytoto: ity in

TABLE 1 MUTAGENICITY TESTING OF ALDRIN (CONT'D)

Genetic Category	Study Type/ Test System	Range of Doses (mg/kg) or Concentrations (ug/mL)	Reference	Reported Results	Evaluation	Comment
Chromosome Aberration (Damage) (Cont'd)	Rat/mouse bone marrow in vivo	9.25, 19.125, 38.25, 76.5 ip once	Georgian (1978)	Positive at 38.25 (LD_{50}) and 19.125	Inconclusive	Effects only toxic levels gaps include
	Mouse micronucleus	2 X 13, 24 hours apart	Usha Rani et al. (1980)	Negative	Unacceptable	No toxicity single dose tested; no p itive contro
	Mouse dominant lethal	(1) 1 x 8 and 40, ip. (2) 5 x 0.5 and 1.0, gavage	Epstein et al. (1972)	Negative up to toxic doses	Acceptable	-
DNA damage/ repair	Differential toxicity in bacteria (B. subtilis rec)	20/disc, -S9 only	Shirasu et al. (1976)	Negative	Unacceptable	Survey scree without acti tion
	DNA strand breaks in E. coli E1 plasmid	1000, -S9 only	Griffen/Hill (1978)	Negative	Unacceptable	Survey scree without acti tion
	UDS in rat hepatocytes in vitro	0.5 - 1000 nM	Probst et al. (1981)	Negative up to cytotoxic doses	Acceptable	--
	Scheduled DNA synthesis in rat thymocytes in vitro	10, 100, 1000	Rocchi et al. (1980)	Dose related positive for S-phase inhibition	N/A	Range-findir
	UDS in human lymphocytes in vitro	100 (in presence of hydroxyurea)	Rocchi et al. (1980)	Positive, slight increase	Inconclusive	Only one dos tested.
	UDS in VA-4 cells in vitro (SV-40 transformed)	1, 10, 100, 1000 uM, +/- S9	Ahmed et al. (1977)	Positive at all doses	Inconclusive	Qualitative results in virus-trans formed cell line

TABLE 1 MUTAGENICITY TESTING OF ALDRIN (CONT'D)

Genetic Category	Study Type/ Test System	Range of Doses (mg/kg) or Concentrations (ug/mL)	Reference	Reported Results	Evaluation	Comment
DNA damage/ repair (cont'd)	DNA strand breaks in rat hepatocytes in vitro	0.03, 0.3, 3.0 mM for 3 hours	Sina et al. (1983)	Dose-related positive at 0.3, 3.0 mM (cytotoxic doses)	Inconclusive	Non-carcinog classified as "false positive" gave similar resu
Other Mechanisms	Mitotic spindle inhibition in vivo (mouse BM)	1 x 2 ("0.002 mg/g"), ip. (4% of LD_{50} in males only)	Markaryan (1966)	Positive for "nuclear disturbances" and breaks	Inconclusive	Inappropriat procedures; cytotoxic effects included.

TABLE 2 MUTAGENICITY TESTING OF DIELDRIN

Genetic Category	Study Type/ Test System	Range of Doses (mg/kg) or Concentrations (ug/mL)	Reference	Reported Results	Evaluation	Comment
Gene Mutation	Reversions in bacteria (Salmonella/ Ames)	4, 20, 100, 500, 2500/ plate, +S9 only	Anderson and Styles (1978)	Negative	Unacceptable	Survey screen
		Up to 2.6 x 10 nM, +/- S9	DeFlora (1981)	Negative	Unacceptable	Survey screen
		Up to 5000/plate, +/- S9	Moriya et al. (1983)	Negative	Unacceptable	Survey screen
		50, 1000/disc, -S9 only	Wade et al. (1979)	Negative	Unacceptable	Survey screen
		(Reported only as dilutions from solubility or toxicity limit, +/- S9)	DeFlora et al. (1984)	Negative	Unacceptable	Survey screen
		1-10,000/plate (gradient), +/- S9	Probst et al. (1981)	Negative	Unacceptable	Survey screer
		20/disc, -S9 only	Shirasu et al. (1976)	Negative	Unacceptable	Survey screer
		10-1000 nM, +/- S9	McCann et al. (1975)	Negative	Unacceptable	Survey screer
		1, 1000/plate, +S9 (mouse) only	Van Dijck/van der Voorde (1976)	Negative reported at 1 ug only	Unacceptable	Only one (nor toxic) dose reported; not tested -S9
		10-500, +/- S9	Bidwell et al. (1975)	Negative	Unacceptable	No toxicity reported
		33, 100, 330, 1000, 3333/ plate (pre-incubation) +/- S9 (rat, hamster)	Haworth et al. (1983)	Negative up to insoluble level (333 ug)	Acceptable	--

TABLE 2 MUTAGENICITY TESTING OF DIELDRIN (CONT'D)

Genetic Category	Study Type/ Test System	Range of Doses (mg/kg) on Concentrations (ug/mL)	Reference	Reported Results	Evaluation	Comment
Gene Mutation (Cont'd)	Reversions in bacteria (Salmonella/ Ames) (Cont'd)	10, 30, 100, 300, 1000, 3000/plate, +/- S9, +/- TCPO	Glatt et al. (1983)	Negative up to insoluble level (300 ug)	Acceptable	--
		50-1000/plate, +/- S9	Marshall et al. (1976)	Negative up to toxic level (1000 ug)	Acceptable	--
		1, 25, 50, +/- mouse S9	Majumdar et al. (1977)	Dose-related positive at 1, 25; decrease at 50 (toxic)	Inconclusive	No positive controls
	Host-mediated (mouse) reversions in bacteria (Salmonella TA 1530, 1535, 1538)	5x20 daily, oral	Bidwell et al. (1975)	Negative	Unacceptable	Insufficient procedural details; no positive control
	Reversions in bacteria (E. coli WP2)	Up to 5000/plate, +/- S9	Moriya et al. (1983)	Negative	Unacceptable	Survey scree
		1-10,000/plate (gradient), +/- S9	Probst et al. (1981)	Negative	Unacceptable	Survey scree
		20/disc, - S9 only	Shirasu et al. (1976)	Negative	Unacceptable	Survey scree
		1000/disc, - S9 only	Ashwood-Smith et al. (1972)	Negative	Unacceptable	Survey scree
	Sex-linked recessive lethals in Drosophila	0.001%, ip	Benes/Sram (1969)	Negative	Unacceptable	Tested at on one dose in inappropriat system.

TABLE 2 MUTAGENICITY TESTING OF DIELDRIN (CONT'D)

Genetic Category	Study Type/ Test System	Range of Doses (mg/kg) or Concentrations (ug/mL)	Reference	Reported Results	Evaluation	Comment
Gene Mutation (cont'd)	Sex-linked recessive lethals in Drosphilia (Cont'd)	10^{-2} to 10^{-10} M, "topically"	Bidwell et al. (1975)	Negative up to 10^{-4} M (higher conc.'s lethal)	Unacceptable	No data presented
	Reversion in mammalian cells in vitro (V79/oua)	10 uM, - S9 only	Ahmed et al. (1977)	Positive at 10 uM (non-toxic)	Inconclusive	Only one dose tested; no positive control.
Chromosome Aberrations (damage)	WI-38 cells (human cell line)	1, 10, and 30, - S9 only	Majumdar et al. (1976)	Dose-related positive at all doses (toxic)	Inconclusive	Not tested +
	Mouse bone marrow in vivo	1 x 1, 30, and 50, ip	Majumdar et al. (1976)	Dose-related positive at all (cyto-toxic) doses	Acceptable	--
	Chinese hamster bone marrow in vivo	1 x 30 and 60, oral (analytical grade)	Dean et al. (1975)	Negative	Unacceptable	No toxicity, positive control
	Human lympho-cytes of ex-posed workers	(No exposure levels given)	Dean et al. (1975)	Negative	Unacceptable	Monitoring screen; no exposure levels
	Mouse dominant lethal	(1) 1 x 12.5 and 25, oral (2) 1 x 12.5, 25, and 50, oral (analytical grade)	Dean et al. (1975)	Negative up to toxic doses (25, 50)	Acceptable	--
		(1) 1 x 5.2 and 26, ip. (2) 5 x 2 and 3, oral.	Epstein et al. (1972)	Negative up to toxic levels	Acceptable	--
		5 x 0.08, 0.8 and 8.0, oral	Bidwell et al. (1975)	Negative	Unacceptable	No evidence toxicity

TABLE 2 MUTAGENICITY TESTING OF DIELDRIN (CONT'D)

Genetic Category	Study Type/ Test System	Range of Doses (mg/kg) or Concentrations (ug/mL)	Reference	Reported Results	Evaluation	Comment
Chromosome Aberration (damage) (Cont'd)	Mouse micronucleus	5 x 0.8 and 8.0, oral	Bidwell et al. (1975)	Negative	Unacceptable	No evidence toxicity.
	Mouse translocation assay	0.008, 0.08, and 0.2 in feed for 6 weeks	Bidwell et al. (1975)	Negative	Unacceptable	No evidence toxicity.
DNA damage/ Repair	Differential toxicity in bacteria (E. coli Pol-A/ rec)	> 1000 (based on toxicity)	DeFlora et al. (1984)	Negative	Unacceptable	Survey scree
	Differential toxicity in bacteria (B. subtilis rec)	20/disc, - S9 only.	Shirasu et al. (1976)	Negative	Unacceptable	Survey scree
	Host-mediated (mouse) gene conversion in yeast (S. cerevisiae D4)	(1) 1 x 25 and 50, oral (2) 5 x 5 and 10, oral (analytical grade)	Dean et al. (1975)	Negative up to toxic levels	Acceptable	--
	DNA strand breaks in mammalian cells in vitro (V79)	0.03, 0.1, 0.3, 1.0 mM, + S9 only	Swenberg (1981)	Negative	Unacceptable	Not tested -
	UDS in rat hepatocytes in vitro	0.5-1000 nM	Probst et al. (1981)	Negative up to toxic doses	Acceptable	--
	UDS in mouse hepatocytes in vitro	(1) 10^{-4}, 10^{-5}, 10^{-6} M (2) 10^{-4}, 10^{-5}, 10^{-6} M, (phenobarb-induced)	Klaunig et al. (1984)	Negative up to toxic levels	Acceptable	--

TABLE 2 MUTAGENICITY TESTING OF DIELDRIN (CONT'D)

Genetic Category	Study Type/ Test System	Range of Doses (mg/kg) or Concentrations (ug/mL)	Reference	Reported Results	Evaluation	Comment
DNA/damage Repair (cont'd)	Scheduled DNA synthesis in rat thymocytes in vitro	10, 100, 1000	Rocchi et al. (1980)	Dose-related inhibition	N/A	Range-findin
	UDS in human lymphocytes in vitro	100, - S9 only (in presence of hydroxyurea)	Rocchi et al. (1980)	Weak positive	Inconclusive	Only one dos not tested +
	UDS in VA-4 (SV-40 transformed) cell in vitro	1, 10, 100 uM, +/- S9	Ahmed et al. (1977)	Positive at at doses	Inconclusive	Qualitative results in a virus-transformed cell line.
Other Mechanisms	Mitotic spindle inhibition in vivo (mouse BM)	1 x 1.2 ("0.0012 mg/g"), ip (4% of LD_{50} in males only)	Markaryan (1966)	Positive for "nuclear disturbances" and breaks	Inconclusive	Inappropriat procedures; cytotoxic effects included.
	Gap junction (cell-to-cell communication) inhibition in human teratocarcinoma cells in vitro	7 ug/mL	Wade et al. (1986)	Positive inhibition	Inconclusive	New techniqu for promotic at only one dose.
	Inhibition of testicular DNA synthesis in vivo (mouse)	1 x 50, oral	Seiler (1977)	Positive inhibition	Unacceptable	Only one dos in a survey screen for a new procedur
Cell Transformation	Baby Syrian hamster kidney cells (BHK-21) in vitro	0.08, 0.4, 2.0, 10, 50, and 250, +/- S9	Styles (1978)	Negative at LC_{50} (unstated)	Unacceptable	Full details data not reported.