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HEALTH AND ECOLOGICAL CRITERIA DIVISION
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OFFICE OF WATER
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FOREWORD

Section 1412 (b)(3)(A) of the Safe Drinking Water Act, as amended in 1986, requires the Administrator of the Environmental Protection Agency to publish maximum contaminant level goals (MCLGs) and promulgate National Primary Drinking Water Regulations for each contaminant, which, in the judgment of the Administrator, may have an adverse effect on public health and which is known or anticipated to occur in public water systems. The MCLG is nonenforceable and is set at a level at which no known or anticipated adverse health effects in humans occur and which allows for an adequate margin of safety. Factors considered in setting the MCLG include health effects data and sources of exposure other than drinking water.

This document provides the health effects basis to be considered in establishing the MCLG. To achieve this objective, data on pharmacokinetics, human exposure, acute and chronic toxicity to animals and humans, epidemiology and mechanisms of toxicity are evaluated. Specific emphasis is placed on literature data providing dose-response information. Thus, while the literature search and evaluation performed in support of this document has been comprehensive, only the reports considered most pertinent in the derivation of the MCLG are cited in the document. The comprehensive literature data base in support of this document includes information published up to 1987; however, more recent data may have been added during the review process. Editorial changes were also made in 1991 when this document was finalized.

When adequate health effects data exist, Health Advisory values for less than lifetime exposures (1-day, 10-day and longer-term, ~10% of an individual's lifetime) are included in this document. These values are not used in setting the MCLG, but serve as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur.

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LIST OF ABBREVIATIONS

ATP	Adenosine triphosphate
bw	Body weight
CCl_4	Carbon tetrachloride
CNS	Central nervous system
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
dw	Dry weight
DWEL	Drinking Water Equivalent Level
EC	Electron capture
EEG	Electroencephalogram
GABA	Gamma-aminobutyric acid
GC	Gas chromatography
GI	Gastrointestinal
HA	Health advisory
i.p.	Intraperitoneal
i.v.	Intravenous
LD_{50}	Dose Lethal to 50% of the recipients
LD_{90}	Dose lethal to 90% of the recipients
LDH	Lactic dehydrogenase
LOAEL	Lowest-observed-adverse-effect level
LOEL	Lowest-observed-effect level
MEL	Minimal effect level
MS	Mass spectroscopy
NADPH	Nicotinamide adenine dinucleotide phosphate (reduced form)
NAPH	Nicotinamide adenine dinucleotide (reduced form)
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PCAA	Polychlorocycloalkane
ppm	Parts per million
RfD	Reference dose

SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
ST_{50}	Survival time of 50% of the recipients
TBPS	t-Butylbicyclophosphorothionate
TLC	Thin-layer chromatography
TLV	Threshold limit value
TWA	Time-weighted average
ww	Wet weight

I. SUMMARY

Endrin is an organochlorine alicyclic pesticide first introduced into the United States in 1951. It is produced by the epoxidation of isodrin obtained from the reaction of hexachlorocycloheptadiene and cyclopentadiene. It has been produced in the United States by the Velsicol Chemical Corporation. Endrin currently has limited uses (1979 usage: 176 megagram) in the cotton growing regions of western Oklahoma, western Texas, New Mexico, Arizona and California. It controls pale-western and army-cutworms and grasshoppers, as well as eastern pine voles, western meadow voles, sugar cane beetle and is used to treat conifer seeds. Endrin is no longer commercially available in the United States.

Endrin is a compound of low solubility in water, high solubility in non-polar organic solvents, low vapor pressure (2.7×10^{-7} mm Hg at 25°C), high adsorptive potential in high organic-content soils, and a large octanol/water coefficient (2.18×10^{5}).

The major analytical methods for endrin include extraction, column chromatography, gas chromatography/electron capture (GC/ECD) and gas chromatography/mass spectrometry (GC/MS). Acidification or high temperatures will decompose endrin. Endrin has low recoveries from waters at pH 2 (23%), but >80% recoveries at pHs >7. In contrast, its acid decomposition product, endrin ketone, is well recovered from waters at all pHs. The photodecomposition product, the half-cage ketone, has also been found in environmental media. Spills of endrin in the environment have been detoxified by reaction with acidified zinc dust. Standard U.S. EPA and NIOSH analytical methods are used for measuring endrin.

Endrin has occasionally been found in drinking water and in food; measurable levels of endrin have not been detected in adipose tissue or the blood of the general population. Endrin is absorbed through the skin, by the lungs and by the gut, but no quantitative rates are known. Animals, birds and humans who have been exposed to large amounts of endrin have shown residues. In all warm-blooded species studied thus far, endrin is quickly metabolized and its metabolites quickly eliminated. Endrin deposition in tissues, especially fat, does occur at high doses in experimental animals and in birds. Residues have been detected in liver, brain, kidneys and fat. Endrin has a weighted average bioconcentration factor (BCF) of 3970 for the edible portion of all freshwater and estuarine fish and shellfish consumed by United States residents.

Poisoning incidents have occurred in animals and man; convulsions in man are known to occur above doses of 0.2 mg endrin/kg bw. Blood residues have been found in humans grossly exposed to endrin in occupational and poisoning incidents. Endrin poisoning incidents have been documented in Wales, the United Arab Republic, Qatar, Pakistan and Saudi Arabia. The major toxicant in mammals is considered to be the metabolite, 12-ketoendrin, but endrin itself is considered the toxicant in birds; residues in brains are also supportive of these hypotheses. Modes of elimination are species dependent, but in mammals the measured and calculated half-lives of endrin derived material are between 1 and 4 days. The major metabolite in mammals is anti-12-hydroxyendrin glucuronide. Hydroxylation at the 3-position, epoxide hydration and production of 12-ketoendrin also occur.

Endrin has been shown to penetrate the placental barrier in rats, mice and hamsters. In rats, >50% of endrin-derived material is eliminated within 1 day in the bile as glucuronides, which after enterobacterial degradation and enterohepatic circulation are eliminated as aglycones in the feces. Excretion occurs slower in females than in males. Cows excrete free anti-12-hydroxyendrin conjugated in the urine as the sulfate. This also occurs in hens. The anti-12-hydroxyendrin has been detected as the glucuronide in the urine and feces of humans. Hens appear to eliminate endrin faster than other birds; with endrin itself being excreted. Endrin accumulates more in birds than in mammals.

Exposure to endrin in humans causes CNS effects, convulsions, and in some cases, death. In endrin poisoning cases, electroencephalograms show paroxysms of predominantly bilateral synchronous theta waves. In mild poisoning, recovery is usually rapid and there have been no permanent effects. This is consistent with short half-lives for elimination. Epidemiology studies have corroborated the existence of convulsions and other CNS effects in endrin-exposed workers.

The acute oral LD_{50} to mammals ranges from 2.3-43.4 mg endrin/kg bw. After dermal exposure LD_{50} values range from 11-92 mg endrin/kg bw and are vehicle-dependent. Inhalation exposure to 5.62 µg endrin/m² for 7 hours over 130 days is not lethal to rats, hamsters and guinea pigs. Young animals are more sensitive than adult animals to the effects of endrin. In acute studies, sublethal endrin exposures elicited CNS effects including convulsions and behavioral changes. Depressed body weight gain was reported during somewhat longer exposures (<1 month). In subchronic and chronic

studies, dietary exposure of rats and dogs to endrin concentrations >1 ppm reportedly elicited depressed body weight gain, elevated organ-to-body weight ratios and/or early mortality.

Prenatal exposure to endrin caused adverse reproductive outcomes in rats, mice and hamsters. In the latter two species, these outcomes included terata, reduced neonatal weight or fetal weight gain and mortality. Further, evidence of altered behavioral development was reported in all three species following prenatal endrin exposure.

Endrin was not mutagenic in bacterial systems with or without metabolic activation. There are four carcinogenicity bioassays for endrin which are reported by their authors as negative. An NCI rat bioassay, however, upon further analysis shows some evidence of tumorigenicity. Overall the animal studies are regarded as inadequate i.e. inconsistent to demonstrate or refute a carcinogenic potential. Epidemiologic studies of which there are several are also inadequate because of mixed exposures and design limitations.

The toxic and convulsant potencies of polychlorocycloalkane pesticides (including endrin) have been correlated with inhibition of GABA-mediated functions in the CNS, particularly chloride ion transport. Binding of endrin or endrin metabolites to the GABA receptor may therefore be involved in the mechanism of acute endrin toxicity. The mechanism(s) mediating toxicity following chronic endrin exposure is not known.

The occurrence of convulsions is believed to be related to blood-brain permeability changes or to direct effects on the CNS. Although inhibition of membrane ATPases and mitochondrial ATPases from brain tissues have been detected, which were species-dependent, succinyl choline has prevented convulsions in all species tested. Concentrations of cytochrome P-450 in endrin-resistant animals (mice, pine voles) may be greater than in susceptible species (guinea pigs); gender may also be important. The conversion of endrin to anti- and syn-12-hydroxyendrins, and conversion of the syn-isomer to 12-ketoendrin may be dependent on the level and type of cytochrome P-450. The acute LD_{50} values for all these unconjugated metabolites are lower than for endrin itself. Lipid peroxidation may also play a role. The correlation of urinary D-glucaric acid with endrin exposure and the glucuronide of anti-12-hydroxyendrin in the urine in humans would support this hypothesis. D-glucaric acid has not been detected in human urine unless anti-12-hydroxyendrin levels in endrin equivalents were >0.13 mg/g creatinine.

The U.S. EPA has set an interim standard for endrin in finished drinking water of 0.0002 mg/ℓ. The present ambient water quality criteria for the protection of human health is 0.001 mg/ℓ and for the protection of both freshwater and saltwater aquatic life is 0.0023 µg/ℓ. The World Health Organization established as a guideline a maximum intake of 2 µg/kg/day, or 138.2 µg/day, for a 69.1 kg person. The proposed index Alimentarius Commission's maximum residue limit in wheat is 20 µg/kg.

The threshold limit value (8-hour TLV/TWA) recommended by the American Conference of Governmental Industrial Hygienists (ACGIH) is 0.10 mg/m³

(0.10 μg/ℓ), with a short-time exposure limit (15 minutes) of 0.30 mg/m^3. Limits set by the Occupational Safety and Health Administration are the same as those recommended by the ACGIH.

The 1-day health advisory (HA) for endrin in drinking water is 0.05 mg/ℓ for children. A NOAEL of 0.5 mg/kg bw/day based upon decreased locomotor activities in mice was used to derive the 1-day HA.

The 10-day HA for endrin is 0.02 mg/ℓ for children. A NOAEL of 0.150 mg/kg bw/day based upon depressed maternal body weight gain in rats was used to derive the 10-day HA.

The longer-term HAs are 0.003 mg/ℓ for children and 0.01 mg/ℓ for adults, based upon a NOAEL of 0.025 mg/kg/day for mild histopathologic changes in the livers of exposed dogs.

The DWEL for chronic exposure to endrin is 0.01 mg/ℓ. An RfD of 0.0003 mg/kg bw/day (verified by the U.S. EPA RfD Work Group on 4/20/88) based upon a NOAEL of 0.025 mg/kg/day for mild histopathologic changes in livers of exposed dogs was used to derive this DWEL.

Using the criteria in the U.S. EPA guidelines for classification of carcinogens, endrin is most appropriately classified in Group D (there is inadequate evidence to assess the potential carcinogenicity for humans). This classification is based on the nonpositive but suggestive results in some of the animal studies. The negative conclusions as reported by the study authors of the four bioassays do not support a Group E classification,

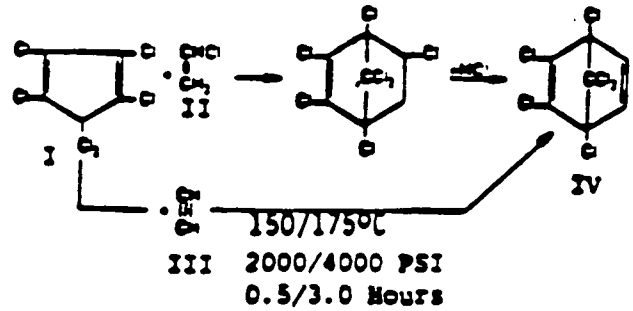
because of the inadequacies of the studies. A U.S. EPA carcinogenicity Group D weight-of-evidence classification was verified by the CRAVE Work Group on 10/19/88.

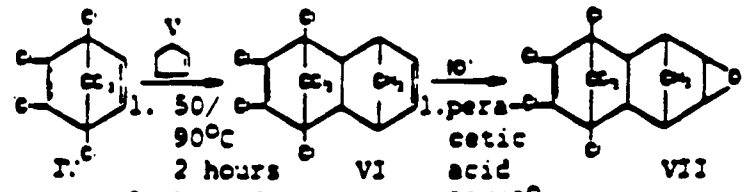
II. PHYSICAL AND CHEMICAL PROPERTIES

Endrin is an organochlorine alicyclic pesticide, introduced as an insecticide into the United States in 1951. It has an empirical formula of $C_{12}H_8Cl_6O$ and a molecular weight of 380.93. It is produced by the epoxidation of a product (isodrin) obtained from the Diels-Alder reaction of hexachlorocycloheptadiene and cyclopentadiene (Brooks, 1974a). The major synthetic pathway is shown in Figure II-1. It has been manufactured in the United States by the Velsicol Chemical Corporation. Dipicolinic acid at levels of 0.5-500 ppm relative to endrin content is often utilized to stabilize solid endrin against decomposition by metallic impurities during the epoxidation step (Sittig, 1977). The synonyms of endrin are provided in Table II-1.

Chemical names and indexing terms for the major chemical degradation products of endrin are given in Table II-2, and for its major metabolites in Table II-3. The typical composition of technical grade endrin is provided in Table II-4. No other composition data were found in the literature searched.

The 1979 usage of endrin in the United States was ~175,500 kg (Anonymous, 1979). It was used as an insecticide on cotton and small grains and as a rodenticide in orchards (Eichers, 1980). With certain modifications endrin's limited use still continues although widespread resistance of many pests to it may account for further decline in its usage (Federal Register, 1979). Its use is still permitted in the cotton growing regions of western Oklahoma and western Texas, New Mexico, Arizona and California. Endrin is used on small grains to control the following insects: pale-western





I	hexachlorocyclopentadiene	II	monochloroethylene
III	acetylene	IV	hexachlorobicycloheptadiene adduct
V	cyclopentadiene	VI	isodrin
		VII	endrin

FIGURE II-1

The Major Industrial Synthetic Pathway for Endrin

(Modified from Sittig, 1977)

TABLE II-1

Nomenclature, Indexing Terms and Synonyms Currently Used for Endrin
(SANSS data base, June 1983)

CAS RN 72-20-8[a] Molecular formula: $C_{12}H_8Cl_6O$

2,7:3,6-Dimethanonaphth[2,3-b]oxirene, 3,4,5,6,8,9,9-hexachloro-1a, 2,2a,3,-6,6a,7,7a-octahydro-(1a α,2 β,2a β,3 α, 6 α,6a β,7 β,7a α)-(9CI)[b]

1,4:5,8-Dimethanonaphthalene, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,-6,7,8,8a-octahydro-endo,endo- (8CI)[c]

Compound 269

Endrex

Endricol

Endrin

Endrin isomer

Endrine (FRENCH)

Experimental Insecticide 269

EN 57 (VAN)

ENT 17,251

Hexachloroepoxyoctahydro-endo,endo-dimethanonaphthalene

Hexadrin

Mendrin

NCI-C00157

Oktanex

SD 3419

WLN: T E3 D5 C555 A A- F0 KUTJ AG AG BG JG KG LG ENDO ENDO[d]

1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo-1,4-endo-5,8-dimethanonaphthalene

1,2,3,4,10,10-Hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-1,4-endo,endo-5,8-dimethanonaphthalene

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[a]Chemical Abstracts Service Registry Number

[b]Ninth Collective Index, Chemical Abstracts

[c]Eighth Collective Index, Chemical Abstracts

[d]Wiswesser Line Notation

TABLE II-2

Chemical Information Related to Some Endrin Degradation Products

Common Chemical Names and Molecular Formula	CAS Indexing Term and CAS RN	Comment	Reference
Endrin aldehyde SD 7442 $C_{12}H_8Cl_6O$	1,2,4-Methenocyclopenta[cd]pentalene-5-carboxaldehyde, 2,2a,3,3,4,7-hexachlorodecahydro-(1 α,2 β,2a β, 4 β,4a β, 5 β, 6a β,6b β,,7R)- 7421-93-4	Stereochemical configuration of aldehyde revised; structure confirmed with ^{13}C and ^{1}H nmr spectral data. Cpd is produced by thermal or photochemical rearrangement of endrin	Bird et al., 1978 Cox and McKinney, 1978
Endrin ketone ß-ketoendrin SD 2614 $C_{12}H_8Cl_6O$	2,5,7-Metheno-3H-cyclopenta[a]pentalen-3-one, 3b, 4,5,6,6,6a-hexachlorodecahydro-(2 α,3a β,3b β,4 β, 5 β, 6a β, 7 α,7a β,8R)- 53494-70-5	Principal product of reaction of endrin with H_2SO_4 ^{13}C nmr spectra	ApSimon et al., 1982 Cox and McKinney, 1978
No common chemical name 2,3,4,5,6-hexachloro-]2-oxopentacyclo[5.4.1.1^{8,11}0^{3,10}.0^{5,9}]tridecane	6,2,3,5-[1,2]propanediyl[3]ylidene-2H-pentaleno[1,6-bc]furan, 2a,3,4,4,4a, 6b-hexachlorooctahydro- 65956-39-0	Minor product (6-8%) of acid catalyzed rearrangement of endrin; single crystal X-ray diffraction and nmr data	ApSimon et al., 1982
Endrin alcohol $C_{12}H_8Cl_6O$	1,5,2,4-Ethanediylidenecyclopenta[cd]pentalen-1(2H)-ol, 2,2a,3,3,4,8-hexachlorooctahydro- 33058-12-7	^{13}C nmr spectra	Cox and McKinney, 1978

TABLE II-3

CAS Indexing Terms and CAS RN for Endrin Metabolites
(from CHEMLINE, 1983)

Common Chemical Names and Molecular Formula	CAS Indexing Term and CAS RN
12-Ketoendrin WL 41435 $C_{12}H_6Cl_6O_2$	2,7:3,6-Dimethanonaphth(2,3-b)oxiren-8-one, 3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-,(1a α,2 β,2a β,3 α,6 α,6a β,7 β,7a α)-(9CI) 1,4:5,8-Dimethanonaphthalen-9-one, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro- (8CI) 28548-08-5
anti-12-Hydroxyendrin WL 41434 $C_{12}H_8Cl_6O_2$	2,7:3,6-Dimethanonaphth(2,3-b)oxiren-8-ol, 3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-, (1a α,2 β,2a β,3 α,6 α,6a β,7 β,7a α)- (9CI) 1,4:5,8-Dimethanonaphthalen-9-ol, 1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro- (8CI) 49748-76-7
3-Hydroxyendrin $C_{12}H_8Cl_6O_2$	2,7:3,6-Dimethanonaphth(2,3-b)oxiren-2(1aH)-ol, 3,4,5,6,9,9-hexachloro-2a,3,6,6a,7,7a-hexahydro-, (1a α,2 α,2a β,3 α,6 α,6a β,7 β,7a α)- (9CI) 57378-25-3

CI = Collective Index

TABLE II-4

Typical Composition of Technical Grade Endrin*

Component	% (by weight)
Endrin	96.6
HEOD (dieldrin)	0.42
HHDN (aldrin)	0.03
Isodrin	0.79
Heptachloronorbornadiene	0.03
Heptachloronorbornene	0.08
δ-Ketoendrin	1.57
1,2,3,4,5-pentachloro-7-oxo-1,4,5,6-tetrahydro-1,4-methanobenzene	0.09
Endrin aldehyde	<0.05
Acidity (as HCl)	0.18
Unidentified	0.12
Water content	<0.1
Xylene insoluble residue	<0.5

*Adapted from Brooks, 1974a

cutworm, army cutworm, and grasshoppers. Additionally, it is used to control the sugarcane beetle and pine voles in the eastern United States and western meadow voles in the western United States and in the treatment of conifer seeds (Federal Register, 1979). It is also used as a bird perch toxicant (Hadler, 1982). Endrin has been generally coformulated to minimize its tendency to decompose in some common formulation carriers (Brooks, 1974a). Often, up to 15% (w/w) of hexamethylene tetramine has been used for this purpose. Endrin is often coformulated with methyl parathion in emulsifiable concentrates. A selected list of pesticidal mixtures in which endrin is not the only pesticidal component is provided in Table II-5. Pure endrin appears to decompose above 245°C (Metcalf, 1981), although technical grade endrin (>92% endrin) decomposes above 200°C (Brooks, 1974a). Presently, manufacture and use has been discontinued in the United States (Merck Index, 1983).

Endrin is soluble in nonpolar solvents. The solubility of pure endrin (in g/100 ml at 25°C) is as follows: acetone, 17; benzene, 13.8; carbon tetrachloride, 3.5; xylene, 18.3; and water, 0.000023 (0.23 mg/l) (Metcalf, 1981). The equivalent solubilities for technical grade endrin (55-57% chlorine content) is as follows: acetone, 31; benzene, 51; carbon tetrachloride, 51; isopropanol, 3; methanol, 2; methyl ethyl ketone, 40; toluene, 74; and xylene, 55 (Brooks, 1974a). The specific gravity of the technical grade compound is 1.7 at 20°C. The vapor pressure of technical grade endrin is 2.7×10^{-7} mm Hg at 25°C (Brooks, 1974a). Endrin appears to obey a Freundlich adsorption isotherm in the presence of an activated carbon (200/400 mesh) aqueous slurry (U.S. EPA, 1980b). Kenaga (1980) has provided the following physical constants for endrin at 25°C: water solubility,

TABLE II-5

Some Pesticide Mixtures in which Endrin is not the Only Pesticide (Chemname, 1983)*

CAS Registry Number	Component CAS Registry Numbers	Component Chemical Names (endrin chemical name omitted)	Synonyms
53858-08-5	(50-29-3, 72-20-8, 298-00-0)	1,1'-(2,2,2-trichloroethylidene)bis(4-chlorobenzene) Phosphorothioic acid, O,O-dimethyl-O-(4-nitrophenyl) ester	DDT-endrin-methyl parathion mixture
58939-75-6	(72-20-8, 121-75-5)	Butanedioic acid, ((dimethoxyphosphinothioyl)thio)-, diethyl ester	Malathion-endrin mixture
59928-82-4	(72-20-8, 947-02-4)	Phosphoramidic acid, 1,3-dithiolan-2-ylidene-, diethyl ester	Cyolane-endrin mixture
64034-60-2	(57-13-6, 72-20-8)	urea	Endrin-urea mixture
8017-73-0	(60-57-1, 309-00-2) (72-20-8)	2,7:3,6-Dimethanonaphth(2,3-b)oxirene, mixture with (1.α.,4.α.,4a.β.,5.α., 8.α.,8a.β.)-1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene	Lepit; Aldrin-dieldrin mixture; Binarin
8066-55-5	(72-20-8, 640-15-3)	Phosphorodithioic acid, S-(2-(ethylthio)ethyl)-O,O-dimethyl ester, mixture	Veldrin EE 922:Veldrin; Ekadrin; Thiometon-endrin mixture

TABLE II-5 (cont.)

CAS Registry Number	Component CAS Registry Numbers	Component Chemical Names (endrin chemical name omitted)	Synonyms
8075-40-9	(72-20-8, 309-00-2)	Mixture with (1.α.,4.α.,4a.β.,5.α., 8.α.,8a.β)-1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro-1,4:5,8-dimethanonaphthalene	Aldrin mixture with endrin; Endional; Mauxan; Tricotin
37247-09-9	(50-29-3, 72-20-8)	Mixture with 1,1'-(2,2,2-trichloroethylidene)bis(4-chlorobenzene)	DDT-endrin mixture; Endrin-DDT mixture
37262-64-9	(72-20-8, 298-00-0)	Phosphorothioic acid, O,O-dimethyl-O-(4-nitrophenyl) ester, mixture	Endrin-methyl parathion mixture
37338-61-7	(72-20-8, 141-66-2)	Phosphoric acid, 3-(dimethylamino)-1-methyl-3-oxo-1-propenyl dimethyl ester, mixture	Endrin-bidrin; Endrin-bidrin mixture; Endrin-dicrotophos
51602-20-1	(72-20-8, 21609-90-5)	Phosphonothioic acid, phenyl-, O-(4-bromo-2,5-dichlorophenyl) O-methyl ester, mixture	Endrin-leptophos mixture
59928-83-5	(72-20-8, 950-10-7)	Phosphoramidic acid, (4-methyl-1,3-dithiolan-2-ylidene-, diethyl ester, mixture	
61912-61-6	(72-20-8, 6923-22-4)	Phosphoric acid, dimethyl-1-methyl-3-(methylamino)-3-oxo-1-propenyl ester, (E)-, mixture	

TABLE II-5 (cont.)

CAS Registry Number	Component CAS Registry Numbers	Component Chemical Names (endrin chemical name omitted)	Synonyms
62588-93-6	(56-38-2, 72-20-8)	Phosphorothioic acid, O,O-diethyl-O-(4-nitrophenyl) ester, mixture	
62815-24-1	(72-20-8, 13171-21-6)	Phosphoric acid, 2-chloro-3-(diethylamino)-1-methyl-3-oxo-1-propenyl dimethyl ester, mixture	
63952-62-5	(72-20-8, 16752-77-5)	Ethanimidothioic acid, N-(((methylamino)carbonyl)oxy)-, methyl ester, mixture	
63952-72-7	(72-20-8, 2104-64-5)	Phosphonothioic acid, phenyl-, O-ethyl, O-(4-nitrophenyl) ester, mixture	
65437-77-6	(72-20-8, 7704-34-9)		Endrin-sulfur mixture

*Dialog Information Services, Inc.

0.024 ppm (compare the 0.23 ppm value above); octanol/water partition coefficient, 2.18×10^5; and a calculated organic soil adsorption constant of 3.4×10^4. Jarvinen and Tyo (1978) reported the water solubility of endrin at 200 µg/ℓ.

Spectroscopic Properties

Since endrin is not aromatic and does not contain conjugated double bonds, it has a $E_1^{1\%}$ of 148 cm^{-1} at the λ_{max} at 225 nm (Tewari and Sharma, 1978). Thus, ultraviolet/visible spectroscopy would be neither sensitive nor useful analytically.

Infrared analysis is practical when utilizing the peak at 11.76 µm and baseline points at 11.50 and 11.97 µm (Brooks, 1974b). The mass spectrum is diagnostic (Safe and Hutzinger, 1973a). The molecular ion (m/e 378) is small with successive losses of Cl (m/e 343, 308). These latter peaks are intense enough to be utilized for specific ion monitoring purposes. A Retro Diels-Alder process also occurs. Chemical ionization mass spectrometry has also been performed (Safe and Hutzinger, 1973b). Cox and McKinney (1978) measured the ^{13}C-NMR spectra of endrin, endrin aldehyde, endrin ketone and endrin alcohol.

Chemistry

Endrin decomposes at temperatures above 200°C or when stored for long periods, with endrin aldehyde and a pentacyclic aldehyde as decomposition products (Brooks, 1974a). This process is important for gas chromatographic analysis in metal columns (Phillips et al., 1962). Endrin undergoes epoxide ring opening and rearrangement in the presence of acid or of metal catalysts, i.e., iron compounds (Brooks, 1974a). Endrin ketone is the principal

product of acid decomposition (ApSimon et al., 1982). Endrin can undergo the usual addition reactions, and also complex transannular rearrangements. When exposed to wavelengths of 253.7 and 300 nm and to sunlight, endrin in hexane and cyclohexane decomposes to the following half-cage ketone, 1,8-exo-9,11,11-pentachloropentacyclo[6.2.1.$1^{3,6}$.$0^{2,7}$.$0^{4,10}$]dodecan-5-one, with 60% conversion in 8 hours. This product has been identified in environmental samples (Zabik et al., 1971). Photorearrangement is possible above 300 nm in the presence of appropriate photosensitizers, e.g., silica gel (Ivie and Casida, 1971a) and rotenone on bean leaves (Ivie and Casida, 1971b). For the latter [illegible] but not the former, endrin ketone and endrin aldehyde are the major products. The nomenclature, CAS indexing terms and CAS RNs for the major degradation products are given in Table II-2. The reaction of acidified zinc dust with endrin has been suggested as a degradation procedure in the field (Butler et al., 1981).

Analytical Methods

The most recent analytical methods for endrin in animal tissues and fluids are summarized in Table II-6. Most of the methods involve extraction to separate endrin from its matrix, then cleanup or extraction before electron capture gas chromatography (EC/GC) or gas chromatography/mass spectrometry (GC/MS). Heating above 200°C or acidification in any of the analytical steps will cause degradation of the endrin as described in the chemistry section. This may be the reason for the highly variable recoveries quoted in the literature or for residues not being detected in the majority of studies. For water analysis, if waters are already acidic, probably most of the endrin will have been degraded already to endrin ketone. In water at 25°C and pH 2, endrin recovery is 23%; at pH 7-10 its recovery is 88% (Millar et al., 1981). At 4°C and pH 2, however, the recovery is 92%; 85%

TABLE II-6

Analytical Methods for Determining Endrin or Endrin Transformation Products in Tissues or Animal Fluids

Human Tissue or Fluid	Compound Determined	Method	Reference
Human urine	anti-12-hydroxyendrin and β-glucuronide conjugate	oxidation of conjugate with meta periodate hydrolysis;hexane extraction/EC/GC	Baldwin and Hutson, 1980
Human adipose tissue	endrin	hexane extraction/gel permeation chromatography cleanup/EC/GC (100% recovery at 3.2 ppm)	MacLeod et al., 1982
		hexane extraction/gel permeation chromatography cleanup/EC/GC (105% recovery)	Tessari et al., 1980
Cow milk	endrin	extractions/Florisil cleanup/ EC/GC (80% recovery; detection limit 0.5 ppb)	Frank et al., 1979
Bird brain	endrin	sodium sulfate/milling/soxhlet extraction (diethylether and petroleum ether)/EC/GC (70±6% recovery; detection limit 0.05 ppm for a 1 g sample)	Ludke, 1976

of endrin aldehyde is recovered at pH 2, 7 or 10 at 4° or 25°C but is degraded in the presence of chlorine at pH 10 (Millar et al., 1981). Carbopack B columns have also been used to concentrate 8 ppb endrin from water (Mangani et al., 1981), as have XAD-2 resins (Rees and Au, 1979). A standard NIOSH method is available for monitoring airborne endrin in the personal sampling mode (solid sorbent/battery powered pumps) (Taylor, 1980).

Summary

Endrin is an aliphatic organochlorine insecticide with a molecular weight of 380.93, water solubility of 0.024 ppm, specific gravity of 1.7 at 20°C, vapor pressure of 2.7×10^{-7} mm Hg at 25°C and an octanol water partition coefficient of 2.18×10^{3}. It was used predominantly to control cutworms and grasshoppers, but has also been used as a rodenticide in the control of eastern pine voles and western meadow voles.

Endrin decomposes at temperatures >200°C into endrin aldehyde and a pentacyclic aldehyde. Acids or metals (iron) will also decompose endrin into endrin ketones and aldehydes. Following extraction methods, endrin levels in tissue and water analysis may be determined by EC/GC or GC/MS techniques.

III. TOXICOKINETICS

This section refers only to data relevant to warm-blooded vertebrates.

Absorption

Endrin is absorbed through the skin, by the lungs and by the gut (U.S. EPA, 1980a). Rates of absorption have not been documented. That absorption does occur is demonstrated by the data in Table III-1 concerning residue levels and biological effects after exposure.

Oral. Wild and domestic animals that have absorbed endrin through ingestion of treated foliage can show residues in fat, blood and milk (see Table III-1). Several poisoning incidents have occurred through animal feeds (Long et al., 1961; Terriere et al., 1958; Kilgemagi et al., 1958; Hunter et al., 1960; U.S. EPA, 1980a). For an early review of poisoning incidents see Brooks (1969).

Animals and birds at the top of food chains as well as humans may be particularly affected by the oral route of exposure if the chemical or its metabolites bioaccumulate. The weighted average BCF for endrin is 3970 for the edible portion of all freshwater and estuarine fish and shellfish consumed by U.S. residents (U.S. EPA, 1980a).

Humans have ingested endrin-treated agricultural products (Carey et al., 1979) as well as meat from domesticated and wild animals, birds and fish. Poisoning of humans after accidental contamination of food has been attributed to doses of 0.2 mg/kg bw (U.S. EPA, 1980a).

TABLE III-1

Evidence of Absorption Using Residue and Biological Effect Data

Route of Absorption	Applied Dose	Residues	Biological Effects	Reference
Oral	not known on pasture	up to 24 µg/g fat, 6.4-14 µg/g after 42 days	Not reported	Long et al., 1961
	510 mg over 30 days to pigs	up to 2 µg/g fat	Not reported	Hunter et al., 1960
	20 mg/day/cow	up to 0.25 µg/g milk	Not reported	U.S. EPA, 1980a
	>0.2 mg/kg bw in humans	up to 10 µg/g blood 400 µg/g fat	Poisoning symptoms in humans; convulsions	U.S. EPA, 1980a Hayes, 1963 Coble et al., 1967 Weeks, 1967 Curley et al., 1970 Tewari and Sharma, 1978; Rowley et al., 1987
Inhalation/ dermal	"grossly exposed" humans animal mortality data	residues >1 µg/g blood	Convulsions at >0.2 mg/kg bw	Jager, 1970
Dermal	Carworth Farm Strain E (CFE) rats in acute dose response experiments	not reported	Ratio of dermal to acute oral LD_{50} for 20% emulsifiable concentrate is 1.6; and for 2% dust is 13	Muir, 1968

Inhalation

Since the vapor pressure of technical endrin is 2.7×10^{-7} mm Hg at 21°C (see Chapter II), this is equivalent to a vapor density of 5.5 $\mu g/m^3$ of air. Consideration of endrin's inhalation hazard to humans led the American Conference of Governmental Industrial Hygienists (ACGIH, 1982) to set the threshold limit value, 8-hour time weighted average (TLV-TWA), to be 0.10 mg/m^3 with a short-term exposure limit (STEL) for 15 minutes of 0.30 mg/m^3 (skin). The OSHA standard based on the 1968 ACGIH TLV is 0.10 mg/m^3 (skin) (NIOSH, 1978). Dermal absorption occurs concurrently with air exposure as denoted by the "skin" designation.

Few blood residues have been found in endrin-exposed workers, except in those grossly exposed (Jager, 1970). The absence of residues may imply fast metabolism or negligible absorption. In this case, fast metabolism is responsible.

Dermal

The most significant dermal exposures to endrin in the occupational environment have occurred during field applications (Wolfe et al., 1963, 1967). Unfortunately, no residues have been reported to confirm absorption. Both inhalation and dermal exposure have occurred during endrin manufacture and distribution, but only grossly exposed workers have ever shown residues. Nevertheless, convulsions have been reported in such workers (Jager, 1970).

The dermal acute LD_{50} value for male CFE strain rats was 1.6 times that for the oral acute value (diet) when the rats were exposed to a 20%

emulsifiable concentrate (Muir, 1968). Similarly, for exposure to a 20% field strength dust, the ratio was 13 (Muir, 1968), illustrating the importance of the carrier in dermal absorption (see Chapter V). Such data demonstrate that endrin is absorbed through the skin of rats and is probably also absorbed through human skin, as the "skin" designation for the ACGIH TLV-TWA implies.

Distribution and Metabolism

In contrast to its stereoisomer dieldrin, endrin is rapidly metabolized in mammals and the metabolites are also quickly eliminated. Thus, the distribution of endrin itself in tissues even after high doses may be below detection limits. Under such conditions, distribution studies with radiolabeled endrin may not reflect endrin distribution, but that of its metabolites. However at very high doses, e.g. human poisoning cases, gross occupational exposures or in suicide cases, endrin can be detected in tissues. Endrin appears to accumulate more in birds (excluding chickens) than in mammals.

Distribution in Human Tissues. Endrin is a relatively nonpersistent pesticide in humans. Measurable levels of endrin have not been detected in adipose tissue (Kutz et al., 1979) or the blood of the general population, even in those areas where endrin was used extensively, such as India or the lower Mississippi delta area (Brooks, 1974a). Endrin also has not been found in the blood of workers who manufacture or formulate endrin (Hayes and Curley, 1968; Baldwin and Hutson, 1980) except in the case of very high levels of exposure (Jager, 1970).

Measurable tissue endrin concentrations are reached in cases of acute poisoning. The time of sample collection is important to these measurements, as endrin residues decline rapidly in tissues after cessation of exposure. Endrin concentrations as high as 10 mg/kg in blood and 400 mg/kg in fat have been reported (Hayes, 1963). In an incident involving three acutely poisoned humans in the United Arab Republic in 1967, no endrin was detected (<4 µg/kg) in cerebrospinal fluid (Coble et al., 1967). The serum, 30 minutes after one patient's convulsion, contained 53 ng endrin/mℓ. After 20 hours the serum concentration was 38 ng/mℓ, and after a further 10 hours, 21 ng/mℓ. In the same patient, the endrin level in a 24-hour urine sample after convulsion was 20 ng/mℓ. Levels of endrin much lower than 10 mg/kg tissue were obtained in autopsies of 26 Saudi Arabians poisoned by endrin-contaminated bread (Weeks, 1967; Curley et al., 1970). In the same incident 874 people were hospitalized, and another 500-750 people were also exposed. Blood from the hospitalized patients contained 7-32 ng endrin/mℓ blood. Blood and urine samples taken from patients 29-31 days after the episode contained no detectable amounts of endrin. In the Punjab province of Pakistan between July 14 and September 26, 1984, there were 192 cases of probable endrin poisoning (Rowley et al., 1987). Blood levels from 12 of 18 patients with convulsions had measurable levels of endrin ranging from 0.3-254 ppb (0.3-254 µg/kg). No endrin was detected in the urine (Rowley et al., 1987). Summary data are given in Table III-2.

Tewari and Sharma (1978) studied the concentration of endrin by TLC/ultraviolet spectrophotometry of autopsy materials of eleven cases of fatal poisoning. These results are also summarized in Table III-2. High concentrations were found in fat-containing tissues, even for a time to death of 6

TABLE III-2

Endrin Concentrations Found
in Victims of Endrin Poisoning

Sample	Endrin Concentrations		
	in Saudi Arabia[a] (mg/kg)	in Pakistan[b] (µg/kg)	in Suicides[c] (mg/kg)
Blood	0.007-0.032[d]	0.3-254	4.3-8.5
Urine	0.004-0.007[d]	0[e]	2.5-5.5
Vomitus	5.24	NA	32.5-81.2
Tissues (autopsy) from:			
Stomach	0.16	NA	10.4-145
Liver	0.685	1430	9.4-200
Kidney	0.116	1760	7.5-51.7
Spleen	NA	NA	2.4-21.7
Heart	NA	NA	5.6-19.9
Lung	NA	NA	3.8-10.8
Intestine	NA	13,690	13.1-660

[a]Curley et al., 1970 (includes first and third Dohar outbreaks and Hofuf outbreak)

[b]Rowley et al., 1987 (192 cases of endrin poisoning)

[c]Tewari and Sharma, 1978 (11 suicides)

[d]On day of onset

[e]None detected in 12 patients

NA = Not analyzed

poisoning. These results are also summarized in Table III-2. High concentrations were found in fat-containing tissues, even for a time to death of 6 hours. There was some evidence to suggest that endrin in combination with a fatty carrier, such as milk, caused death faster than when ingested with solid food. The levels quoted may be in error as endrin, 12-hydroxyendrin or 12-ketoendrin were not separated.

Little is still known of the distribution and persistence of endrin metabolites in human tissues. Baldwin and Hutson (1980) were unable to detect anti-12-hydroxyendrin or 12-ketoendrin in the blood of endrin workers at a Shell manufacturing plant in England. The method used had a detection limit of 2 ng/mℓ for both compounds.

By analogy with observations made in experimental animals, it may be speculated that endrin and its metabolites are rapidly eliminated. It is noteworthy in this regard that recovery from an acute poisoning episode is rapid, on the order of a day (Davies and Lewis, 1956), so that if toxic metabolites are formed in humans they are not persistent.

Distribution in Animal Tissues.

Birds -- Researchers agree that orally dosed endrin is absorbed from the avian gut and stored in various body tissues by both wild and domestic species (Terriere et al., 1959; Reichel et al., 1969).

After absorption of endrin, residues have been reported to be distributed among liver, brain, adipose, eggs, breast muscle and gonadal tissues.

Adipose tissues generally contained the highest concentration (Gregory, 1970; Terriere et al., 1959), while brain tissues usually contained the lowest (Reichel et al., 1969).

Terriere et al. (1959) examined the tissues and eggs of chickens exposed to levels of 0.1, 0.25 and 0.75 mg endrin/kg feed. In one experiment, 1-month-old male Delaware X New Hampshire chicks were fed the various endrin levels for 6 weeks and then sacrificed, while 6-month-old White Leghorn pullets were exposed to the endrin-fortified feed for 8 weeks and were returned to the basal diet for 4 additional weeks. A repeat of the male chick experiment using New Hampshire X Delaware chicks was also performed. In all endrin exposures, the amount of adipose tissue was found to be meager even though weight gain and feed consumption appeared to be normal. At a level of 0.25 mg/kg feed or higher, definite deposition of endrin in the egg tissue occurred within 2-4 weeks after exposure had ceased. Accumulation of endrin in adipose tissue was found in both experimental groups with even the lowest dietary level showing evidence of deposition. Analysis of breast and tibia tissue revealed endrin deposition at both the 0.25 and 0.75 mg/kg feed intake levels.

The fat tissue of the plain chachalacas, Ortalis vetula, was analyzed by Marion (1976) for pesticide residues during 1971 and 1972. In four different study areas 24 birds had an average endrin residue of 0.13 ± 0.52 mg/kg weight. There was no evidence that these birds died of endrin exposure. Only 8 of the 24 birds sampled contained detectable endrin residues.

The percentage of the dose retained by bobwhite quail appears to be dependent upon administration time and dose according to Gregory et al. (1972). Analyses of whole birds fed equal doses of endrin-contaminated beans or beetles revealed retention of ~16% of the total acute dose ingested, while 21% of the total chronic dose was retained. The residues found in the body tissues during the acute and chronic experiments differed, but not consistently. The average endrin content in adipose tissues in the acute dosage group was 0.014±0.002 mg/kg ww, as compared with 0.010±0.001 mg/kg found in the chronic dosage group. Gonadal tissues from both groups contained traces of endrin, while the concentration of liver residues in the chronic test was 0.007 mg/kg and in the acute test, 0.004 mg/kg.

Baldwin et al. (1976) fed 10 Sykes Hybrid III hens (~2 kg) 0.13 mg endrin/kg diet by capsule over 148 days. At day 148, the levels of endrin and 12-ketoendrin were measured in muscle, liver, kidney and fat (Table III-3). Levels of 12-ketoendrin, deltaketoendrin, anti- and syn-12-hydroxy-endrins were below detection. The distribution of ^{14}C-endrin provided at 0.3 µCi/day for 148 days is given in Table III-4 for day 148. These results for radioactivity essentially are for endrin distribution itself, as supported by the data in Table III-3.

Ludke (1976) determined lethal brain residues for several compounds in an investigation of associated mortality with additivity of chlordane and endrin. Twenty male and female, 14-week-old, bobwhite quail (Colinus virginianus) were fed diets containing 10 ppm chlordane for 10 weeks followed immediately by 10 ppm endrin in the diet for 10 weeks; 20 other quail received 10 ppm endrin in the diet only (duration unspecified).

TABLE III-3

Distribution of Endrin and 12-Ketoendrin at Day 148 in Sykes Hybrid III Hens (2 kg initially) Fed 0.016 mg/kg Diet by Capsule[a]

Tissue	Concentration (mg compound/kg ww)	
	Endrin[b]	12-Ketoendrin
Breast meat	<0.0032-0.0013	<0.002
Leg meat	0.017-0.095	<0.003
Liver	0.013-0.20	<0.0006
Kidney	0.035-0.13	<0.03
Fat	0.32-1.21	<0.0004

[a]Source: Baldwin et al., 1976

[b]Metabolites were considered absent if their concentrations were <10% of the detected endrin value.

TABLE III-4

Radioactivity in Tissues of Five Hens After a 148-Day Period of Treatment with 0.3 µCi/Day (as capsules)*

Tissue	Radioactive Residues (mg endrin equivalent/kg ww)
Breast meat	0.008-0.011
Leg meat	0.008-0.030
Fat	0.50-1.28
Liver	0.07-1.06
Kidney	0.13-0.23
Brain	0.017-0.050
Sciatic nerve	0.096-0.64
Bone marrow	0.14-0.58
Skin	0.13-0.39
Feathers	0.005-0.024

*Source: Baldwin et al., 1976

After 9-10 days on an uncontaminated diet, survivors were sacrificed. In a control group, eight quail given 10 ppm chlordane in their diet did not experience any mortality. All quail treated with endrin and with both endrin and chlordane had significant loss in weight. This loss of weight was associated with fat mobilization and increasing brain residues. Birds that died from endrin treatment alone had brain residues ranging from 0.34-1.84 ppm; survivors ranged from 0.28-0.62 ppm.

Birds that died from endrin exposure preceded by chlordane treatment had brain residues ranging from 0.17-1.25 ppm; survivors ranged from 0.14-0.56 ppm. Brain residues of survivors were lower than those of dead birds and approached significance ($0.05<p<0.10$). Birds treated with chlordane followed by endrin had considerably more brain residues of chlordane than did birds treated with chlordane alone. This observation prompted the author to conclude that lipid mobilization as a result of endrin intoxication resulted in increased accumulation of both endrin and chlordane residues in the brain. Mortality from endrin alone was associated "with as little as 0.34 ppm" endrin residues in the brain.

Endrin has also been detected (0-4% occurrence) in the wings of black ducks (Anas rubripes) at 0.01 mg/kg ww, and of adult mallards (Anas platyrhynchos) up to 0.02 mg/kg during the 1976-1977 National Pesticide Monitoring Program (White, 1979).

Blus et al. (1979) found endrin residues in all of the eggs of brown pelicans from Louisiana, many of which had lethal levels of residue in their

brains. The year/number/levels in eggs were as follows: 1971, 3, 0.08-0.12 mg/kg ww; 1972, 12, 0.11-0.29; 1973, 21, 0.03-0.46; 1974, 25, ND-0.73; 1975, 30, 0.29-1.06; 1976, 25, ND-1.47.

In September 1978, ducks in Montana were found to contain up to 1.2 mg/kg ww endrin in their fat resulting from endrin applied on wheat crops to destroy an infestation of Army cutworms (Anonymous, 1979).

Table III-5 shows some typical residue levels found since 1977 in wild and laboratory birds known to be exposed to endrin. These data illustrate that endrin is absorbed and then distributed throughout the body. No 12-ketoendrin was detected in the tissues of wild or domestic birds, unless the birds had ingested endrin-killed fauna (Stickel et al., 1979a). The connection of brain residues with lethality is discussed in Chapter V.

Mammals -- Little is known of the transport and distribution of endrin in mammals. No evidence of storage in any particular tissue or organ, other than fat, has been found. Residues of endrin ranging from 0.001-23.7 mg/kg ww, however, have been detected in a variety of mammalian tissues.

Brooks (1969) reviewed studies showing that steers, lambs and hogs receiving 0.1 mg endrin/kg diet for 12 weeks had little tendency to deposit endrin in body tissues. Continuous feeding of endrin at levels up to 2 mg/kg diet resulted in a maximum body fat concentration of 1 mg endrin/kg ww. Cattle with only ambient environmental endrin exposure were analyzed for the presence of endrin residues in their tissues by the U.S. Department of Agriculture in 1967 (Spaulding, 1972). Of the 2785 animals studied, 2783

TABLE III-5

Endrin Distribution in Birds in the Post-1978 Literature

Species	Exposure Type	Tissue	Concentration (number or sex) (mg/kg ww)	Reference
Heron (wild)	NR	carcass[a]	0.10-0.86 in MN (9) 0.19-0.22 in VA (3) 0.20 in FL (1) 0.30-0.42 in CA (2) 0.19-0.60 in WI (4)	Ohlendorf et al., 1981
Kestrel (wild) (Falco sparverius)	NR	carcass GI tract	0.42-0.63 (2)[b] 0.09-0.17	Stickel et al., 1979a
Broadwinged hawk (wild) (Buteo platypterus)	NR	carcass	0.07	Stickel et al., 1979a
White pelican (dead) (wild) (Pelecanus erythrorhynchos)	NR	carcass brain	1.1[b] 0.74[b]	Stickel et al., 1979a
Pelican (wild)	NR	brain	0.46-2.7 (21)	Stickel et al., 1979a
Bobwhite quail (Colinus virginianus)	5.8 µg/kg fed/ day/bird	brain	0.047-0.093 at 138 days	Kreitzer, 1980
Bullfinch	0.15% endrin (48 hours) 0.0375% endrin (24 hours) (via pear buds)	liver liver	0.56-3.65 (M/F) 0.19-1.28 (F)	Feare et al., 1978
Grackles (Quiscalus quiscula)	10 mg/kg diet	carcass brain	0.67-1.6[b] (8) 1.1-2.2[b]	Stickel et al., 1979a

TABLE III-5 (cont.)

Species	Exposure Type	Tissue	Concentration (number or sex) (mg/kg ww)	Reference
Mallard[d] (Anas platyrhynchos)	10 mg/kg diet (26 days)	carcass brain liver	1.4-1.9[b] at day 26 (2) 0.54-0.77[b] 1.1-1.9	Stickel et al., 1979a
Quail (dead) (Coturnix japonica)	50 mg/kg diet	carcass	1.1 (M)[b] on day 14-20 (4) 1.0 (F)[b] on days 13-15	Stickel et al., 1979a
Bald Eagle (dead)[c] (Hallaeetus leucocephalus)	20 mg/kg diet	carcass muscle brain	1.5 (F) 0.63 (M) 0.92-1.2 (M/F)	Stickel et al., 1979b
Eagle (wild)[c]	NR	carcass brain	0.5-2.5 (M) 0.71-1.2 (M)	Stickel et al., 1979b

[a]After head, skin, feet, wingtips and GI tract were removed

[b]12-Ketoendrin was below the detection limit

[c]The lower limit of detection was 0.10 ppm endrin

[d]The lower limit of detection was 0.05 ppm for endrin and 12-keto endrin. Used as the limit of detection for all Stickle et al. (1979a) referenced materials.

NR = Not reported

contained no endrin residues; one animal contained between 0.01 and 0.1 mg endrin/kg fat, and another contained between 0.11 and 0.5 mg/kg fat. By 1971, however, similar testing revealed that endrin incidence in tissues was increasing. Of 2403 cattle tested, 42 had levels of 0.01-0.1 mg endrin/kg fat (Spaulding, 1972).

Long et al. (1961) reported high levels of storage in the adipose tissue of six lambs using a dechlorination method of analysis. Higher levels were detected in the internal fat surrounding the stomach and thoracic cavity than in external fat deposits. Lambs were allowed to graze for 55 days on pastures treated with 2% endrin granules, applied six times in May and June at a rate of ~1.1 kg endrin/acre. The lambs were then transferred to untreated pasture; endrin in fat was measured after 0, 14 and 42 days. At the start of grazing in untreated pastures, lambs had 18.3-23.4 mg endrin/kg internal fat and 11.5-14.0 mg/kg external fat. After 14 days, endrin levels were surprisingly higher, with 20.3-23.7 mg/kg internal fat, and 14.6-20.1 mg/kg external fat. Some loss did occur after 42 days. Internal fat levels dropped to concentrations of 8.9-13.8 mg/kg fat, and external fat contained only 6.4-11.0 mg/kg. These findings seem to contradict later reports by Brooks (1969) of no storage and no retention. In the Long et al. (1961) study, however, much higher levels of endrin were fed to younger animals; younger animals have relatively more fat than adults. In addition the lambs initially were in "poor condition." Sharma and Gautam (1971) detected endrin residues in the brain and liver tissue of calves. In the domestic dog endrin was detected in the abdominal viscera (Reins et al., 1966) as well as in fat (Richardson et al., 1967).

Richardson et al. (1967), using three 9-month-old beagle dogs fed 0.1 mg endrin/kg bw/day and two control animals fed uncontaminated diet over the 128-day feeding period, found that endrin in jugular vein blood in each dog reached a plateau at 3-8 mg/kg after 2 days of feeding. The distribution of endrin in tissues after 128 days of feeding is provided in Table III-6. Only the levels in fat were related to levels of endrin in blood. In contrast, administered dieldrin accumulated in the blood after 114-121 days. Rats dosed at 8 µg of ^{14}C-endrin/day by the oral route achieved a steady-state in the blood in 9-10 days (Brooks, 1969), but the label was quickly eliminated after cessation of exposure.

Korte (1967) showed that conversion of endrin to metabolites was not dependent on enterobacteria but occurred in the liver, and in 1970 found that the steady-state storage level after 6 days for female rats dosed at 0.4 mg ^{14}C-endrin/kg diet (16, 64 and 128 µg endrin/kg/bw) was about twice that for males dosed similarly (27% vs. 14%, respectively) (Korte et al., 1970). After i.v. injection of 200 µg ^{14}C-endrin/kg in two doses, male rats retained 5.2% and females 12.1% after 24 hours. This illustrated that the results for different genders were probably not due to gender-dependent absorption variability. Baldwin et al. (1970) also found that concentrations of endrin metabolites in female rats were dependent on the duration of feeding (4 mg/endrin/kg feed over several weeks), whereas those in males were not. Walsh and Fink (1972) gave five Carworth Farm No. 1 adult mice 5 mg ^{14}C-endrin/kg bw by i.v. using DMSO as a vehicle. After 10 minutes the radioactivity distribution was as shown in Table III-7. Endrin was as penetrative to the blood-brain barrier as dieldrin; no endrin was found in the bile up to 2 hours after administration.

TABLE III-6

Distribution of Endrin and 12-Ketoendrin in Experimental Animals

Animal (Number)	Dose (mg/kg bw)	Tissue	Concentration (mg compound/kg tissue)		Reference
			Endrin	12-Ketoendrin	
Beagle dog (3) (9-month-old)	0.1 mg/kg bw/day over 128 days	spleen[a]	0.12-2.62		Richardson et al., 1967
		fat[a]	250-760		
		muscle[a]	120-310		
		pancreas[a]	87-280		
		heart[a]	125-170		
		liver[a]	77-84		
		kidney center[a]	30-82		
		blood[a]	1-8		
CFE rat (6) (female, 200-250 g)	2.5 in arachis oil	fat[b]	5.49±0.32	2.27±0.67	Hutson et al., 1975
		liver[b]	0.18±0.01	0.06±0.01	
		kidney[b]	0.19		
CFE rat (6) (male, 200-250 g)	2.5 in arachis oil	fat[b]	0.20±0.03	1.65±0.15	Hutson et al., 1975
		liver[b]	<0.004	0.30±0.07	
		kidneys[b]	0.19	0.04	
CFE rat (3) (male, 200-250 g)	60 in arachis oil	brain[c]	0.02-0.11	0.25-0.31	Hutson et al., 1975
Holstein cows (2) (500 kg)	0.1 mg/kg diet twice daily for 21 days	rear leg meat[d]	0.001-0.002	<0.0001	Baldwin et al., 1976
		lumbar meat[d]	0.001-0.002	<0.0001	
		liver[d]	0.008-0.011	<0.0001	
		kidney[d]	0.0005-0.0008	<0.0001	
		renal fat[d]	0.021-0.110	<0.001-0.002	
		omental fat[d]	0.050-0.060	0.003	
		subcutaneous fat[d]	0.041-0.070	0.001-0.009	
Rattus norvegicus (2) (male, 381 g, 533 g)	50 in dimethylsulfoxide	brain[e]	0.28 (533 g)	0.11-0.14	Stickel et al., 1979a
Mus musculus mouse (6)	dose not given	brain[e]	0.87-1.00	0.04-0.08	Stickel et al., 1979a
		carcass[e]	0.88-2.00	0.07-0.10	

TABLE III-6 (cont.)

Animal (Number)	Dose (mg/kg bw)	Tissue	Concentration (mg compound/kg tissue)		Reference
			Endrin	12-Ketoendrin	
Golden Syrian hamster (21)[h] (female)	1.5 day via corn oil over 11 days	liver[f] fetal tissue[f] (10)[i]	1.45 0.021±0.004	p p	Chernoff et al., 1979
	2.5 day via corn oil over 11 days	liver[f] fetal tissue[f] (7)[i]	2.55 75±36	p p	
CD rat (27)[h] (female, 175-200 g)	0.15 day	liver[g] fetal tissue[g]	0.052-0.074 <0.005	 np	Kavlock et al., 1981
(29)[h]	0.30 day	liver[g] fetal tissue[g]	0.039-0.096 <0.005	 np	
(12)[h]	0.45 day (all doses via corn oil over 13 days)	liver[g] fetal tissue[g] (6)[i]	0.261-0.323 0.013-0.042	p p	

[a]At day 120

[b]At day 3

[c]At 7-22 hours

[d]At day 21

[e]At death

[f]At day 15

[g]At day 21 of gestation

[h]Number of litters

[i]Number of fetuses

p - present but not quantified; np - not present

TABLE III-7

Distribution of Radioactivity in Various Experimental Animals After an Acute Oral Dose of Endrin

Animal Species	Admin. Route	Sex	Dose (mg/kg)	Carrier	Animal Weights (g)	Time of Analysis	Percentage of Radioactivity Administered Found in Remaining								Reference
							Urine	Feces	Liver	Kidney	Fat	Skin	Carcass	Total	
Adult rat (CFE strain)	oral	M	2.5	arachis oil (1 ml)	200-250 (6)	at day 3	2.65	66	1.2	0.60	1.7	2.3	12.2	86.9	Hutson et al., 1975
		F	2.5	arachis oil (1 ml)	200-250 (6)	at day 3	7.50	37	2.0	0.35	8.0	4.0	28.1	87.2	
Adult mice (CF No. 1)	i.v.	M	5.0	dimethyl-sulfoxide	not given (5)	at 10 minutes	NA	NA	52[a]	NA	21[a]	NA	23[a,b] 5.2[a,c]	NA	Walsh and Fink, 1972
Adult rabbit (Dutch strain)	oral	M	2.12	olive oil (10 ml)	2.2 kg (1)	at day 13	37.3	49.2	NA	NA	NA		13.5	100	Bedford et al., 1975b
Cow (Holstein)	oral	F	0.1 mg/kg diet (twice daily for 21 days)	corn oil; adminis-tered as capsule	450-650 kg	at day 21	55-57	19-21	0.6-1.5 in major organs		8.0	NA	3.7-5.3	88-91	Baldwin et al., 1976

[a]mg/kg tissue basis

[b]Brain level

[c]Blood level

NA - Not analyzed; M - male; F - female; i.v. - intravenous

Hutson et al. (1975) showed that endrin administered in the diet to 6 male and 6 female rats (200-250 g) was quickly metabolized and then eliminated as conjugates. The amount of conjugate was shown to be gender-dependent, confirming the earlier work of Korte (1967), Korte et al. (1970) and Baldwin et al. (1970). Three days after an acute oral dose of 2.5 mg endrin/kg bw in arachis oil by oral gavage, the fat, liver and kidneys of male rats contained the levels shown in Table III-6 and 31% of the administered dose was still retained by the animals. For females the corresponding levels are again provided in Table III-6; 56% of the administered dose was still retained. Female rats accumulated more endrin than male rats, but mostly in fat and skin. When 3 male rats were administered 60 mg endrin/kg bw by gavage, the brains of the dead animals (after 7-22 hours) contained 0.02-0.11 mg endrin/kg tissue and levels of 0.25-0.31 mg 12-ketoendrin/kg tissue. The brain levels of delta-ketoendrin, 3-hydroxyendrin, syn-12-hydroxyendrin and anti-12-hydroxyendrin were <5 µg/kg tissue. Distribution of radio-labeled ^{14}C-endrin in the experiments for both genders is provided in Table III-7.

Baldwin et al. (1976) dosed two Holstein cows (500 kg) with 0.1 mg ^{14}C-endrin/kg diet twice daily for 21 days. At day 21, the tissue levels of endrin and 12-ketoendrin in Table III-6 were found. Endrin constituted the vast majority of the residues in rear leg and lumbar meat, the liver, kidney and in renal, omental and subcutaneous fat. 12-Ketoendrin was detected in the fat but not the lean meat. Some anti-12-hydroxyendrin was detected (0.020 mg/kg ww) in the subcutaneous fat of one cow. Otherwise, the amounts of anti- and syn-12-hydroxyendrins and 3-hydroxyendrin were below detection limits. The distribution of radiolabeled endrin is

provided in Table III-7 for the residues 3 weeks after administration. Minor residues remained in the major organs. All of the tissue residues were essentially endrin itself (see Table III-6).

Stickel et al. (1979a), using two old, large rats (Rattus norvegicus; 381 g and 533 g), administered a dose of 50 mg endrin/kg bw in a DMSO carrier. 12-Ketoendrin was detected in the brains and carcass of both rats and endrin was also found in the carcass of the fatter animal (see Table III-6). One male (542 g) and one female (331 g) rat were also fed a diet containing 150 mg endrin/kg diet until death (16 days for the male; 24 days for the female). No endrin was detected in the brain or carcass of either animal. The levels of 12-ketoendrin in the brain and carcass were 0.18 and 0.28 m/kg tissue for the male; and 0.13 and 0.13 for the female, respectively. The number of animals in the rat experiments is too small for statistical purposes but the results do agree in general with those of Hutson et al. (1975). Stickel et al. (1979a) also found that the residues of endrin in the brains and carcasses of 6 white mice killed by eating endrin-treated pine seed, and pooled in groups of three, varied from 0.70-1.00, and 0.88-2 mg endrin/kg tissue, respectively. The corresponding figures for 12-ketoendrin were 0.04-0.08 and 0.07-0.10 mg/kg tissue. The lower limit of detection for endrin and 12-ketoendrin in homogenized duck tissue was 0.05 ppm.

Bedford et al. (1975b), in experiments on male adult rabbits (Dutch strain; 2.2 kg) involving an acute oral dose of 2.12 mg endrin/kg bw, found low levels of endrin in the carcass at day 13 (13% retention) (see Table III-7). At day 49, only 3.2% remained in the body.

Endrin and 12-ketoendrin were detected and confirmed by GC/MS in the liver and fetal tissue of the hamster (Chernoff et al., 1979). Timed pregnant Golden Syrian hamsters (LVG strain) were housed two per cage at 22-24°C under controlled lighting (16-hour light) after successful copulation. The animals were fed commercial lab chow and water ad lib. The endrin was administered at day 4 or at day 8 after copulation by gastric intubation in a corn oil vehicle. Single dose exeriments on nonpregnant and pregnant animals were at 0, 0.5, 1.5, 5.0, 7.5 and 10 mg/kg bw (the number of pregnant animals were 76, 10, 34, 50, 34 and 24, respectively). In multiple dose experiments, the doses were 0, 0.75, 1.5, 2.5 and 3.4 mg/kg/day (the number of surviving animals were 50, 19, 21, 12 and 2, respectively). At sacrifice (day 15) the 2.5 and 1.5 mg/kg/day dose groups yielded the endrin levels given in Table III-6. These results indicated that endrin crosses the placental barrier in hamsters. Although the authors stated that 12-ketoendrin crossed the placental barrier, it is uncertain whether 12-ketoendrin was formed from endrin in the fetus or penetrated the placental barrier from the mother.

A similar type of study on rats was also performed by the same group (Kavlock et al., 1981). Again 12-ketoendrin and endrin were found in maternal liver and in the fetus. Pregnant CD rats (175-200 g) were exposed, as in the Chernoff et al. (1979) study, to endrin doses of 0.450, 0.300, 0.150, 0.075 and 0 mg/kg/day on days 7-20 of gestation, and killed on day 21 of gestation. The number of pregnant animals studied for the respective doses were 12, 29, 27, 14 and 29. The results for the three highest doses are contained in Table III-6. Although 12-ketoendrin was identified, it was not quantitated. The average ratio of peak height of 12-ketoendrin to that

of endrin was 0.19 (range 0.07-0.47) for maternal livers and 0.35 (range 0.07-0.71) for the fetus. In the hamster fetus the ratio was 3.2±0.6 (10 fetuses) at a maternal dose of 1.5 mg/kg/day. Thus in the rat, passage of endrin through the placenta will occur above a critical concentration threshold in the blood produced by an oral dose between 0.300 and 0.450 mg/kg/day.

Mechanisms of Transport and Metabolism

The metabolic pathway for endrin in mammals is complex (Figure III-1) and varies from species to species. In all species the unsubstituted methylene bridge (C_{12}) in endrin (compound I in Figure III-1) is preferentially attacked to form mostly anti- and lesser amounts of syn-12-hydroxyendrin, the latter being quickly oxidized by microsomal mono-oxygenases to produce 12-ketoendrin (compound IV in Figure III-1). To a smaller extent hydroxylation at the 3-positon also probably occurs, and the epoxide functional group is probably hydrated. Syn- and anti-12-hydroxyendrin are most likely interconvertible in vivo probably by 12-ketoendrin. Hydroxylation at C-3 and C-4 is inhibited by the presence of the bulky hexachlorinated fragment (Hutson, 1981). Studies in rats (Cole et al., 1970) have indicated that ^{14}C-radiolabeled-endrin is quickly metabolized to the anti-12-hydroxyendrin (compound II in Figure III-1), which is excreted in the bile (70% within 24 hours) as the glucuronide (Hutson et al., 1975). After enterobacterial deconjugation and enterohepatic circulation, elimination occurs as the aglycone (~45%) in the feces together with two other minor metabolites, 3-hydroxyendrin (compound V in Figure III-1) and 4,5-trans-dihydroisodrindiol (compound VI in Figure III-1). The major urinary metabolite in male rats (only 1-2% of the administered dose) is 12-ketoendrin

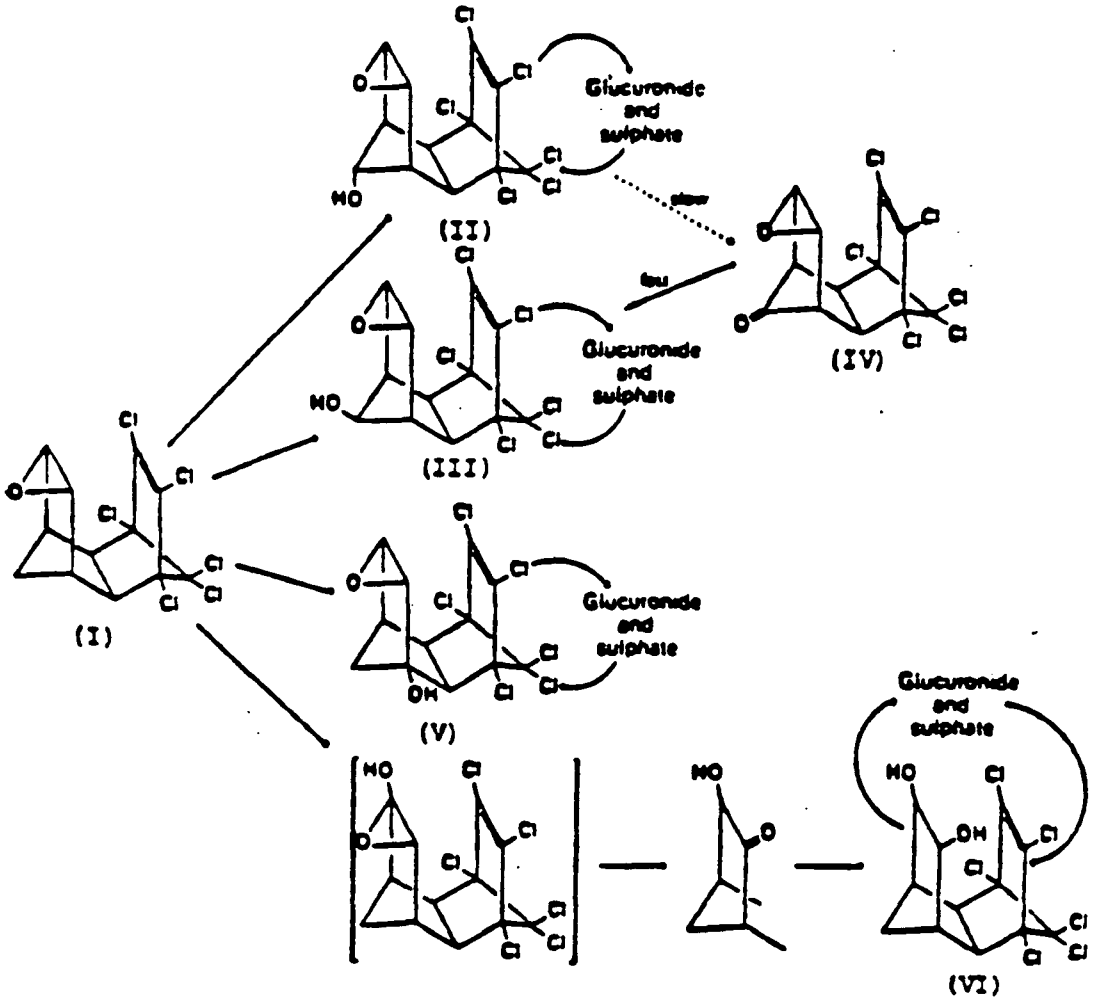

FIGURE III-1

Biotransformation of Endrin in Mammals

Source: Hutson, 1981

(compound IV in Figure III-1). This metabolite is produced by the action of microsomal mono-oxygenases on syn-12-hydroxyendrin (compound III in Figure III-1) (Hutson and Hoadley, 1974), which, in turn, is formed by attack at the unsubstituted methylene functional group of endrin. The primary hydroxylation rates in the liver for the rat and rabbit are 50:7:1.5:1 and 40:5:4:1, respectively, for anti-C-12, C-3, syn-C-12 and C-4 in that order (Bedford and Hutson, 1976). In the rabbit the major metabolite is still anti-12-hydroxyendrin, but it is conjugated with sulfate and eliminated in the urine (Bedford et al., 1975b). Some syn-12-hydroxyendrin sulfate was also found in the urine as were the glucuronide conjugates of the anti- and syn-12-hydroxyendrin, 3-hydroxyendrin, and the 4,5-trans-diol (compound VI in Figure III-1). The reason for this variability is related to the molecular weight thresholds for biliary excretion of anions in the rat and rabbit; e.g., 325±50 and 475±50, respectively (Hirom et al., 1972). The threshold for man is between these values but is closer to that of the rabbit.

The rapid metabolism has been explained in terms of the steric influence of the epoxide anion on C-12-hydroxylation in promoting anti-C-12-hydroxylation. The bulky hexachlorinated fragment inhibits attack at C-3 and C-4.

Anti-12-hydroxyendrin has been detected in the feces of factory workers and its β-glucuronide has been detected in the urine (Baldwin and Hutson, 1980). The levels of the latter appear to be dose-dependent. The toxic metabolite 12-ketoendrin was not detected in the urine and feces, neither was 3-hydroxyendrin (compound V in Figure III-1) or the diol (compound VI in Figure III-1).

These transformations are of interest because syn- and anti-12-hydroxyendrin and 12-ketoendrin all have lower LD_{50} values than endrin itself. As these metabolites are produced quickly they could be responsible for the toxic effects elicited by endrin administration. 12-Ketoendrin has been suggested as the acute toxicant (Bedford et al., 1975a).

Elimination

Endrin is rapidly eliminated both in animals and in humans. The urine is the major excretory route in cows and rabbits but is of minor importance in the rat. Endrin is both metabolized and excreted unchanged in proportions that vary with species and gender.

When ^{14}C-labeled endrin was given orally and by i.v. to rats, the keto metabolite of endrin and other hydrophilic metabolites were present in trace amounts in the urine (Klein et al., 1968). After a single i.v. dose of ^{14}C-endrin, 90% of the label was eliminated in the bile by the second day (Cole et al., 1970).

Baldwin et al. (1970) found that endrin was metabolized in the rat to at least three metabolites. One metabolite, 12-ketoendrin, was found in the urine. The other two metabolites were excreted in the feces and were not found in body tissues. The second metabolite was an isomer of 12-hydroxyendrin. This isomer had the hydroxyl group anti with respect to the epoxy group. According to Korte et al. (1970), 12-hydroxyendrin accounted for 95% of the radioactivity excreted by rats. The third metabolite was a monohydroxylated endrin, but it was not substituted at carbon 12 (Baldwin et al., 1970). The unsubstituted methylene bridge was

thus hydroxylated, and the corresponding ketone was found in adipose tissue, liver and brain.

Rabbits excreted radioactivity after i.v. administration of ^{14}C-labeled endrin mainly in the urine and only as metabolites (Korte et al., 1970). Four metabolites were found in order of decreasing polarity in the ratio of 1:1:3:1. The second most polar one was identical to the 12-hydroxyendrin, which was the main metabolite found in rats. The biological half-life of endrin in male rats receiving 0.4 mg/kg diet was 2-3 days; in females, ~4 days (Korte et al., 1970). Following i.v. injection of 200 µg of ^{14}C-labeled endrin/kg bw in two doses, male rats retained 5.2% and females 12.1% of the radioactivity after 24 hours. The radioactivity was totally excreted as metabolites (Korte et al., 1970). When ^{14}Clabeled endrin was fed to male and female rats, the males excreted 60% of it in the feces within the first 24 hours, and the females only 39%; <1% was excreted in the urine. Of the total radioactivity excreted in the feces, 70-75% occurred in the form of hydrophilic metabolites. Twenty-four hours after the last dose only metabolites were excreted (Korte et al., 1970).

The elimination and distribution of ^{14}C-labeled endrin administered acutely to rats (Hutson et al., 1975), mice (Walsh and Fink, 1972), rabbits (Bedford et al., 1975b) and cows (Baldwin et al., 1976) are provided in Table III-7.

Hutson et al. (1975) showed that 55-57% of ^{14}C-endrin was eliminated, mostly as the glucuronide of anti-12-hydroxyendrin, in the bile within 24 hours of administration to rats of 0.76-1.53 mg ^{14}C-endrin/kg bw. Other minor components (<10%) were the glucuronides of 3-hydroxy- and 12-keto-

endrin. Male rats eliminated 69% of the label within 3 days whereas female rats eliminated 45%. Feces from male and female rats fed for 2 weeks on endrin diets contained the following: endrin (11%), anti-12-hydroxyendrin (83%), syn-12-hydroxyendrin (<0.01%), 3-hydroxyendrin (5%), 12-ketoendrin (1%) and delta-ketoendrin (<0.01%). Day 1 urine samples contained 17:2:0:1:10:0 proportions for males, while those from females contained 1-2% endrin but no 12-ketoendrin, the major component being 12-hydroxyendrin-O-sulfate.

Only traces of 12-ketoendrin were found in male rabbit urine 6 days after oral dosing and none in rabbit feces (Bedford, et al., 1975b), even though 50% of ^{14}C-label was excreted in the urine. Nearly all (>99.5%) of the ^{14}C-label in feces within 24 hours was endrin itself, and endrin metabolites were excreted slowly over several days. Excretion of the label was 87% completed within 13 days. The following compounds were found in urine up to 24 hours: 12-ketoendrin (7%), the glucuronide of anti-12-hydroxyendrin (21%), anti-12-hydroxyendrin sulfate (53%), syn-12-hydroxyendrin sulfate and 3-hydroxyendrin sulfate (14%); the glucuronide of trans-4,5-dihydro-isodrin-4,5-diol glucuronide (2%), and other minor glucuronides (3%). These components accounted for 40% of the single oral intake of ^{14}C-endrin. While the bulk of endrin metabolites are excreted directly by the rat in the bile (Hutson et al., 1975), mostly as glucuronides, the rabbit excretes them directly as sulfates in the urine (Bedford et al., 1975b). This behavior is consistent with molecular weight thresholds for biliary excretion, which are 325±50 in the rat and 475±50 in the rabbit (Hirom et al., 1972).

The molecular weight threshold for biliary excretion in man lies between those of the rat and the rabbit but is closer to that of the rabbit. While metabolism of endrin in humans has not been studied systematically, anti-12-hydroxyendrin as the glucuronide has been found in both feces and urine of endrin workers (Baldwin and Hutson, 1980) (Table III-8). 12-Ketoendrin was not detected (Hutson, 1981). Thus, available information suggests that endrin is probably metabolized similarly in humans and in rats and rabbits, though the proportion and the type of conjugation products differ. Baldwin et al. (1976) showed that the sulfate conjugate of anti-12-hydroxyendrin was the major metabolite in hens. Endrin was the only other excretion product in feces, generally at levels 25-35% less than the sulfate conjugate of anti-12-hydroxyendrin, which generally was at levels of 4-20 mg of endrin equivalents/kg (Baldwin et al., 1976). Cows probably excrete the glucuronide in the bile, but after enterohepatic circulation the free metabolite is excreted in the urine and feces (see Table III-7). 12-Ketoendrin is also excreted in the urine of cows to the extent of 2-26% of the total administered ^{14}C-endrin (Baldwin et al., 1976). During daily treatment a steady-state of ^{14}C-label in the urine of cows is attained at about day 9.

A brief half-life on the order of a day for humans is consistent with the lack of persistence of endrin in human tissues (Coble et al., 1967), and with the rapidity with which plateau concentrations are reached in other mammals on chronic exposure, i.e., <1 week for blood endrin (Richardson et al., 1967). This observation suggests that the biological half-life of endrin in the dog is also on the order of 1-2 days.

TABLE III-8

Analysis of Urine from Endrin Plant Workers in England[a]

Worker	Concentration of Total anti-12-hydroxyendrin[b] (µg/mℓ)	12-Ketoendrin[c] (µg/mℓ)	anti-12-Acetoxyendrin after Acetylation Expressed as Alcohol (µg/mℓ)
1	0.010	NR	NR
2	0.14	0.13	0.13
3	0.098	NR	NR
4	0.040	NR	0.037
5	0.021	NR	0.024
6	0.098	0.075	NR
7	0.011	0.015	NR

[a]Source: Baldwin and Hutson, 1980

[b]Measured after β-glucuronidase cleavage

[c]Produced after oxidation

NR = Not reported

Two cows given 0.1 mg ^{14}C-endrin/kg diet twice daily for 21 days excreted the label in the milk and a steady-state was attained in 4-6 days, mostly as free endrin. The anti- and syn-12-hydroxyendrin, 3-hydroxyendrin and 12-ketoendrin were below detection limits (Baldwin et al., 1976). The estimated half-life is 2-3 days.

In August, 1976, a Canadian dairy herd was treated with endrin for control of flies; 25 animals developed poisoning symptoms, and one cow and one calf died (Frank et al., 1979). The next day after the poisoning a composite milk sample contained 0.40 ppm endrin (8.7 ppm in the milkfat). After 34 days the levels were 0.0026 ppm (0.056 ppm in the milk fat). Milk from individual cows on day 13 contained endrin levels ranging from 0.031-0.16 ppm in whole milk. The residues were analyzed by EC/GC and by TLC, or by two column EC/GC.

Estimations of the 50% disappearance time of endrin are presented in Table III-9 for a variety of animal species. These data have been estimated from the data presented in the cited references. Endrin in sheep and cattle appears to have a longer half-life than in the rest of the species.

Another study involved 50 mallard drakes (960-1360 g; 1 year old) fed 20 ppm endrin for 13 days (Heinz and Johnson, 1979). Groups of five ducks each were sacrificed at 2, 4, 6, 8, 16, 32 and 64 days after the end of dosing. Endrin was monitored in the blood and carcasses. The carcass lost 50% of its endrin in 3 days; the second half-life required an additional 8.9 days, and it took 32.9 days to lose 90% of the original amount administered. On a lipid-weight basis the first half-life of elimination was 2.2 days; the

TABLE III-9

Estimated Half-Lives in Various Species for Elimination of Endrin Administered by the Oral Route*

Species	Estimated Half-Life (dose)	Reference
Rat (M or F)	2 days (16 µg/kg) 6 days (128 µg/kg)	Korte, 1967; Korte et al., 1970
Rat (M) (i.v.) (F) (i.v.)	2-3 days (200 µg/kg) 3-4 days (200 µg/kg)	Korte, 1967; Korte et al., 1970
Rat (M) (F)	2-3 days (2.5 mg/kg) 4 days (2.5 mg/kg)	Hutson et al., 1975
Rabbit (M)	≤1 day (2.12 mg/kg) 13 days in feces alone (2.12 mg/kg) 49 days in urine alone (2.12 mg/kg)	Bedford et al., 1975b
Dog (M)	1-2 days (0.1 mg/kg/day)	Richardson et al., 1967
Man	1-2 days in blood serum	Coble et al., 1967
Sheep	1.8-8.2 weeks	Robinson, 1962
Cattle	1.8-8.2 weeks	Robinson, 1962
Mallard duck	3 days (subchronic feeding)	Heinz and Johnson, 1979
Hen	1 month from fat (chronic feeding)	Cummings et al., 1966
Cow	2-3 days	Baldwin et al., 1976

*These half-lives are based on the initial quick excretion. Acute administration was performed unless otherwise indicated.

M = male; F = female

second took an additional 6.7 days and a 90% loss of the administered amount took 24.8 days. For blood the first and second half-times and the 90% loss time on a wet weight basis were 1.7, 5.2 and 19.1 days, whereas on a lipid basis, these values were 1.4, 4.3 and 15.9 days, respectively.

Cummings et al. (1966) fed egg laying White Leghorn hens a combination of endrin, lindane, dieldrin, DDT and heptachlor epoxide at levels of 0.05, 0.15 or 0.45 ppm of each compound in the feed. After 14 weeks the birds were returned to the basal diet for 32 days. Hens in the 0.45 ppm group accumulated ~3.4 ppm endrin in the fat and required about a month to reduce the level to 50%. This increase in half-life may reflect the presence of the other pesticides. However, Baldwin et al. (1976) showed that hen eggs concentrated ^{14}C-endrin during a dosing program of 0.13 mg endrin/kg diet over a period of 148 days to the extent of 0.11-0.18 mg endrin equivalent/kg yolk. The label was identified entirely as free endrin. Thus, accumulation in eggs is a major pathway of elimination for hens.

Summary

The major route of absorption for humans appears to be through food. The average dietary intake in 1973 was 0.5 ng/kg bw/day. Special groups at risk appear to be occupational workers in the pesticide manufacturing and formulating industries. Industrial and field workers may be exposed by both dermal and respiratory routes. Several episodes of accidental and suicidal endrin poisoning in humans have occurred. Poisoning has been caused by oral doses of endrin as low as 0.2 mg/kg. Endrin levels in drinking water are usually <100 ng/ℓ. Endrin poisoning may occur in humans at blood

levels of 50-100 ng endrin/ml blood. These data indicate endrin can be absorbed in humans. Quantitative absorption rate data are not available for mammals.

Fat appears to be the major storage tissue for endrin in lambs and birds. The weighted average BCF in the edible portion of all freshwater and estuarine aquatic organisms is 3970.

The unsubstituted methylene group of endrin is preferentially and quickly attacked to form mostly anti- and lesser amounts of syn-12-hydroxy-endrin. The latter is rapidly oxidized by microsomal mono-oxygenases to produce 12-ketoendrin. Hydroxylation at the 3 position and epoxide hydration may occur to a small extent. Syn- and anti-12-hydroxyendrin are likely to be interconvertible in vivo, with 12-ketoendrin as a possible intermediary metabolite.

Endrin residues have been found in such organs as the liver, brain and kidneys and in the fat of birds, dogs, cows, rats, mice and hamsters. No 12-ketoendrin has been found in tissues of birds. Endrin appears to penetrate the blood-brain barrier in rats and hens but less readily in the cow, and the placental barrier in rats, mice and hamsters, although much less efficiently for rats. 12-Ketoendrin may also penetrate the placental barrier of these three species.

In rats >50% of the endrin metabolites are eliminated in the bile within 1 day as glucuronides that, after enterobacterial degradation and entherohepatic circulation, are eliminated as aglycones in the feces.

12-Ketoendrin is the major urinary metabolite. Females excrete endrin metabolites more slowly than males. Cows excrete free 12-hydroxyendrin after enterohepatic circulation. 12-Ketoendrin is the only other major metabolite in cow urine.

Though the major metabolite is still anti-12-hydroxyendrin in male rabbits, it is conjugated as the sulfate and excreted directly in the urine. This also occurs in hens.

The anti-12-hydroxyendrin has been detected as its glucuronide in the urine and feces of humans.

Hens appear to eliminate endrin faster than most other birds. The sulfate conjugate of anti-12-hydroxyendrin is the major metabolite in hen feces. The only other metabolite is endrin itself. Endrin does appear to accumulate more in birds than in mammals.

IV. HUMAN EXPOSURE

This chapter will be submitted by the Science and Technology Branch, Criteria and Standards Division, Office of Drinking Water.

IV. HUMAN EXPOSURE

Humans may be exposed to chemicals such as endrin from a variety of sources, including drinking water, food, ambient air, occupational settings and consumer products. This analysis of human exposure to endrin is limited to drinking water, food and ambient air because those media are considered to be sources common to all individuals. Even in limiting the analysis to these three sources, it must be recognized that individual exposure will vary widely based on many personal choices and on several factors over which there is little control. Where one lives, works and travels, what one eats, and physiologic characteristics related to age, sex and health status can all profoundly affect daily exposure and intake. Individuals living in the same neighborhood or even in the same household can experience vastly different exposure patterns.

Detailed information concerning the occurrence of and exposure to endrin in the environment is presented in another document entitled "Occurrence of Pesticides in Drinking Water, Food, and Air" (Johnston et al., 1984). This chapter summarizes the pertinent information presented in that document in order to assess the relative source contribution from drinking water, food and air.

In the Exposure Estimation section of this chapter, available information is presented on the range of human exposure and intake for endrin from drinking water, food and ambient air for the 70-kg adult male. It is not possible to provide an estimate of the number of individuals experiencing specific combined exposures from those three sources. However, the Summary

section of this chapter provides some insight into the relative contributions of the three sources, especially drinking water, to the range of intake values suggested by the available data.

Exposure Estimation

Drinking Water. Levels of endrin in drinking water vary from one location to another. The highest level of endrin monitored in the available studies was 0.008 µg/ℓ in New Orleans (U.S. EPA, 1975, as cited in Pellizzari, 1978), well below the Maximum Contaminant Level (MCL) of 0.2 µg/ℓ. Analysis of the National Screening Program for Organics in Drinking Water (NSP) (Boland, 1981) suggests that median levels of endrin in drinking water would be below 0.1 µg/ℓ, since none of 116 systems sampled contained a level of endrin above 0.1 µg/ℓ. In addition, analysis of the Rural Water Survey (RWS) (U.S. EPA, 1984) suggests that median levels of endrin in drinking water systems would be <0.008 µg/ℓ, since none of 92 systems sampled contained a level of endrin >0.008 µg/ℓ. Endrin may not be present in drinking water in some areas. The available monitoring data are not sufficient to determine regional variations in levels of exposure to endrin.

The daily intake of endrin from drinking water was estimated using the assumptions presented in Table IV-1 and the values presented above. The estimates in Table IV-1 indicate that the daily intake of endrin from drinking water ranges from 0.0-0.0028 µg/kg/day. However, the values presented do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

TABLE IV-I

Estimated Daily Intake of Endrin from Drinking Water*

Drinking water concentration (µg/ℓ)	Intake (µg/kg/day)
0.0	0.0
0.008	0.0002
0.1	0.0028

*Assumptions: 70-kg man consuming 2 ℓ of water/day.

Diet. Data are limited on the dietary intake of endrin in the United States. For fiscal year 1979, the only positive value for endrin in an FDA market basket study on toddlers (FDA, 1982a,b). In this study, an estimated dietary intake of 0.0001 µg/kg/day was calculated based on endrin levels in an oil and fat composite (FDA, 1982b).

Additional data were obtained on the estimated total dietary intake of endrin for adults in the years 1974-1979 and for infants and toddlers in the years 1975-1979 (Table IV-2). The average total intakes for adults, infants and toddlers over the years studied was 0.000008, 0.00004 and 0.00016 µg/kg/day, respectively.

Using the above data, the daily adult intake of endrin is estimated to be 0.000008 µg/kg/day. This value does not account for variances in individual exposure.

It is expected that dietary levels of endrin vary somewhat with geographical location, with higher levels occurring in foods from areas near the sources of endrin exposure. However, because of insufficient data, no estimates could be made of variations in intake by geographical region.

EPA has established a tolerance of zero for endrin in and on the following raw agricultural commodities: sugar beets, sugar beet tops, broccoli, Brussel sprouts, cabbage, cauliflower, cotton seed, cucumbers, eggplant, peppers, potatoes, summer squash and tomatoes (40 CFR 180.131, July 1, 1981).

TABLE IV-2

Estimated Total Daily Dietary Intake of Endrin
for Adult Male, Infant, and Toddler

Year	Intake (µg/kg/day)		
	Adult male[a]	Infant[b] (6 months)	Toddler[b] (2 years)
1974	ND	--	--
1975	Trace[c]	ND	ND
1976	ND	ND[d]	0.0007
1977	0.00004[c]	ND	ND
1978	ND	0.0002	ND
1979	ND	ND	0.0001
Average[e]	0.000008	0.00004	0.00016

[a]From FDA 1981, except as noted.

[b]From FDA 1980b, 1982b.

[c]Calculated based on information in Johnson and Manske 1977 and FDA 1980a.

[d]Appears to be an error since a positive value was reported in Johnson et al. 1981.

[e]Trace values were not included in the calculation; nondetected values were assumed to be equal to zero.

ND = None detected.

Air. Levels of endrin in the atmosphere also vary from one location to another. The highest level of endrin reported was 39.3 ng/m³ (0.0393 µg/m³) in the Mississippi Delta in 1972-1974 (Arthur et al., 1976). In a national study the highest level of endrin reported was 19.2 ng/m³ (0.0192 µg/m³) in Tennessee in 1971 (Kutz et al., 1976). Typical levels, however, are somewhat lower. An estimated mean level of endrin in ambient air, based on the information in Kutz et al. (1976), is 0.2 ng/m³ (0.0002 µg/m³). (However, this estimate is based on data from 1970-1972 and obtained in sampling locations with potentially high concentrations of pesticides in ambient air.) Additionally, concentrations of endrin are below the limits of detection in some areas and may be as low as 0.0 ng/m³. The available monitoring data are not sufficient to determine regional variations in levels of exposure to endrin.

The daily respiratory intake for endrin from air was estimated using the assumptions presented in Table IV-3 and the values presented above. The estimates in Table IV-3 indicate that daily endrin intake from air ranges from 0.0-0.013 µg/kg/day. These values do not account for variances in individual exposure or uncertainties in the assumptions used to estimate exposure.

Summary

This section considers the relative contribution of drinking water, food and ambient air to the total human exposure from these three sources. The data presented here indicate the potential total exposure to endrin that could occur if a population was exposed to specific combinations of endrin concentrations in drinking water, food and ambient air.

TABLE IV-3

Estimated Daily Respiratory Intake of Endrin*

Air concentration (μg/m³)	Intake (μg/kg/day)
0.0	0.0
0.0002	0.00007
0.0192	0.0063
0.0393	0.013

*Assumptions: 70-kg man inhaling 23 m³ of air/day (ICRP, 1975).

Table IV-4 presents a general view of the total amount of endrin that may be received by an adult male from air, food and drinking water. Four separate exposure levels in air, three exposure levels in drinking water, and one exposure level from foods are shown in the table.

The data in Table IV-4 have been selected from an infinite number of possible combinations of concentrations for the three sources. Whether exposure occurs at any specific combination of levels is not known; nor is it possible to determine the number of persons that would be exposed to endrin at any of the combined exposure levels. The data represent possible exposures based on the occurrence data and the estimated intake data.

A mean level for endrin in ambient air of 0.0002 $\mu g/m^3$ was estimated. Assuming a level of 0.0002 $\mu g/m^3$ in ambient air and the estimated endrin intake of 0.000008 µg/kg/day from foods, drinking water would be the predominant source of exposure to endrin for the adult male at drinking water levels >0.003 µg/ℓ.

The total estimated intake of endrin is <0.020 µg/kg/day. This value is much lower than the FAO/WHO and EPA acceptable daily intake of 0.2 µg/kg/day (FDA, 1981), but approaches a maximum safe level of 0.04 µg/kg/day calculated by EPA (U.S. EPA, 1976).

The relative source contribution data are based on estimated intake and do not account for a possible differential absorption rate for endrin by route of exposure. The relative dose received may vary with the intake. In addition, the effects of endrin on the body may vary by different routes of exposure.

TABLE IV-4

Estimated Daily Intake of Endrin from the Environment
by Adult Males

Concentration in Drinking Water (µg/ℓ	Estimated Total Intake in µg/kg/day (% From Drinking Water) Based on a Concentratiaon in Air (µg/m³) of:			
	Low (0.0)	Intermediate (0.0002)	High (0.0192)	High (0.0393)
Low (0.0)	0.000008 (0%)	0,00008 (0%)	0.0063 (0%)	0.013 (0%)
Intermediate (0.008)	0.0002 (100%)	0.0003 (67%)	0.0065 (3.1%)	0.013 (1.5%)
High (0.1)	0.0028 (100%)	0.0029 (97%)	0.0091 (31%)	0.016 (17.5%)

Intake from each source:

Drinking water:	0.0 µg/ℓ:	0.0 µg/kg/day
	0.008 µg/ℓ:	0.0002 µg/kg/day
	0.1 µg/ℓ:	0.0028 µg/kg/day
Air:	0.0 µg/m³:	0.0 µg/kg/day
	0.0002 µg/m³:	0.00007 µg/kg/day
	0.0192 µg/m³:	0.0063 µg/kg/day
	0.0393 µg/m³:	0.013 µg/kg/day
Food:	0.000008 µg/kg/day	

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V. HEALTH EFFECTS IN ANIMALS

Acute Toxicity

Experimental Lethality Studies. Endrin is acutely toxic to a number of species when administered by oral gavage in a solvent, in the diet, or applied to the skin (Table V-1). The LD_{50} varies with the species and strain of animal used. An early comprehensive study of acute toxicity in mammals included Carworth rats (male and female of two ages), 4 rabbits, 4 guinea pigs, 1 cat and 2 monkeys (Treon and Cleveland, 1955). Minimum lethal oral doses were: monkeys, 1-3 mg/kg bw; cats and female rats, <5 mg/kg; male rats, 5-7 mg/kg; rabbits, 5-7 mg/kg; and male guinea pigs, 24-36 mg/kg. These data suggest that primates are one of the most sensitive groups. Signs of intoxication included ataxia, tremors, labored breathing, diarrhea and tonic-clonic convulsions.

The oral LD_{50} of endrin for 6-month-old male Sprague-Dawley rats was reported to be 40 mg/kg bw by Speck and Maaske (1958). Groups of 8-12 rats were given single doses of endrin (20-80 mg/kg bw) in peanut oil by gastric intubation. There was a latent period of 45-60 minutes before the onset of convulsions, regardless of the dose. Deaths occurred within 24-72 hours. Gross examination at autopsy revealed contracted spleens, congested lungs, and bright red blood, along with reddened livers and viscera. No histologic changes were apparent in sections of liver tissue. Electroencephalogram recordings after acute doses showed irregular slowing, irregular spikes, and convulsive discharges. The righting reflex was not abolished during convulsions unless the attack was terminal. Pentobarbital stopped convulsions but did not prevent death. Trypan blue (2 ml of 1% solution) given with 50 mg endrin/kg bw to 30 rats prevented convulsions and lowered the death rate up

TABLE V-1

Acute Lethality of Endrin in Experimental Animals

Animal Species	Route of Administration	Formulation	LD_{50} in mg/kg bw		Reference
			Male	Female	
		MAMMALS			
Rat, young[a]	oral	peanut oil	28.8	16.8	Treon et al., 1955
Rat, adult[a]	oral	peanut oil	43.4	7.3	Treon et al., 1955
Rat, adult[a]	oral	peanut oil	40.0	NR	Speck and Maaske, 1958
Rat[a]	oral	20% e.c.[b]	6.6	3.4	Muir, 1968
Rat[a]	oral	2% f.s.d.[c]	2.5	6.6	Muir, 1968
Rat[a]	dermal	20% e.c.[b]	10.9	NR	Muir, 1968
Rat[a]	dermal	2% f.s.d.[c]	31.5	92	Muir, 1968
Rat	dermal		15-18		Gaines, 1969
Rat[a]	oral	DMSO[d]	5.6	5.3	Bedford et al., 1975a
Rat[a]	oral	arachis oil	NR	5.3	Bedford et al., 1975b
Mouse[e]	i.v.	DMSO[d]	2.3	NR	Walsh and Fink, 1972
Mouse[f]	i.p.	corn oil	5.6	NR	Graves and Bradley, 1965
Mouse	i.p.	methoxytri-glycol	8	NR	Cole and Casida, 1986
Hamster	oral	corn oil	12	17.0	Cabral et al., 1979
Hamster	oral	corn oil	NR	18.6	Chernoff et al., 1979

TABLE V-1 (cont.)

Animal Species	Route of Administration	Formulation	LD_{50} in mg/kg bw		Reference
			Male	Female	
Rabbit	oral	peanut oil	7-10	NR	Treon et al., 1955
Rabbit	dermal for 24 hours	dry, 100-mesh powder	NR	130-160	Treon et al., 1955
Guinea pig	oral	peanut oil	36[g]	16[g]	Treon et al., 1955
Dog (mongrel)	i.v.	95% ethanol	2-3[g]	NR	Reins et al., 1966
Cat	oral	peanut oil	5[h]	NR	Treon et al., 1955
Monkey	oral	peanut oil	3[g]	3[g]	Treon et al., 1955
		BIRDS			
Pigeon	i.v.	NR	1.2-2.0	1.2-2.0	Revzin, 1966
Mallard	oral	corn oil	NR	5.64	Hudson et al., 1979
Mallard	percutaneous	corn oil	>140	NR	Hudson et al., 1979

[a] CFE
[b] Emulsion concentration
[c] Field strength dust
[d] Dimethylsulfoxide
[e] Carworth Farms No. 1 strain
[f] Swiss-Webster and ICR strains of Swiss albino mice
[g] Estimated
[h] Minimum lethal dosage

NR = Not reported

to 80 hours post-treatment. All animals given endrin alone were dead at 200 hours after dosing and ~7% of the trypan blue-treated rats survived. No convulsions were seen in animals with the choroid plexus stained blue by the dye. These observations suggested that the acute reaction may involve increased blood-brain barrier permeability and that the concentration of endrin had to reach a critical level in either the blood or brain tissues before convulsions occurred.

Graves and Bradley (1965) calculated an LD_{50} of 5.6 mg/kg bw for endrin in corn oil injected into the peritoneal cavity of Swiss-Webster and ICR strains of Swiss albino mice. No mortality was seen in controls (13 mice) or at dosages of 1 mg/kg (8 mice) or 2 mg/kg (8 mice). Complete mortality was obtained with dosages $\geq$10 mg/kg (8 mice). Observations of survivors during an additional 6-day period revealed no further mortality. Similar observations have been reported for humans when individuals survived the symptomatic stage (Curley et al., 1970).

Acute i.v. LD_{50} values and median survival times (ST_{50}) of male mice (10/group) exposed to endrin were determined to be 2.3 mg/kg bw (2.0-2.6, 95% confidence limits), and 17.5 minutes (15.2-20.1, 95% confidence limits at a dose of 3 mg/kg), respectively (Walsh and Fink, 1972). Endrin was administered in DMSO. At an LD_{90} (5 mg/kg), the ST_{50} was 11 minutes. In adult male mice (CF1 strain), a latent period of no activity that followed injection ended abruptly with a first clonic convulsion. Intermittent clonic seizures ended with the beginning of hind leg tonic activity. Post-tonic activity involved continual clonic seizures, which terminated in some

cases in death. The dose that produced ataxia in 50% of the mice was 0.75 mg/kg (0.59-0.98, 95% confidence limits). The authors stated that the mechanism of toxicity may be due to effects on plasma membranes or mitochondrial ATPases in the brain or both.

When endrin was applied as a 20% emulsion, acute dermal LD_{50} values for rats were about twice the size of acute oral LD_{50} values (Muir, 1968). When endrin was applied as a field strength dust, the acute dermal LD_{50} value was more than an order of magnitude greater. However, both of these endrin preparations were more toxic than endrin administered in peanut oil, showing that LD_{50} values are vehicle dependent. Dermal administration of endrin as a dry 100-mesh powder in contact for 24 hours under a rubber sleeve with the intact skin of female rabbits yielded an acute LD_{50} between 130 and 160 mg endrin/kg bw and a minimum lethal dose between 66 and 94 mg/kg bw (Treon and Cleveland, 1955). Table V-1 summarizes these toxicity data.

Bedford et al. (1975a) determined the acute oral LD_{50} values (based on 10-day mortality) for three metabolites of endrin that have been identified in mammals (Baldwin et al., 1970; Bedford et al., 1975a). Each metabolite was more acutely toxic than the parent pesticide (Table V-2). Syn-12-hydroxyendrin and 12-ketoendrin were about 5 times more toxic than the parent compound in male rats; in females, 12-ketoendrin was 5 times and syn-12-hydroxyendrin 2 times more toxic than endrin. Anti-12-hydroxyendrin was 2 times more toxic in male rats and equitoxic to endrin in females. The most rapidly lethal compound was 12-ketoendrin; mortality was observed within 20 hours of administration for both male and female rats. Endrin and the isomers of 12-hydroxyendrin produced mortality in 4-6 days in male rats, and

TABLE V-2

Median Lethal Doses 10 Days After Oral Administration of Endrin and Its Metabolites to Rats[a]

Compound	LD_{50} (mg/kg)[b,c]	
	Male	Female
Endrin	5.6 (3.0-7.9)	5.3 (3.6-7.4)
anti-12-Hydroxyendrin	2.4 (2.0-3.0)	5.5 (4.2-7.2)
syn-12-Hydroxyendrin	1.2 (0.6-1.7)	2.8 (0.8-4.0)
12-Ketoendrin	1.1 (0.7-1.5)	0.8 (0.5-1.2)

[a]Source: Bedford et al., 1975a

[b]Administered by gavage in DMSO to CFE strain rats, 12-14 weeks of age, divided into groups of either 4 or 8 rats of each sex

[c]Numbers in parentheses are 95% confidence limits

5-8 days in female rats. The authors concluded that even though oxidative metabolism of endrin is responsible for the observed efficient elimination from rats of subacute doses, oxidative products of endrin may also be responsible for its acute toxicity.

LC_{50}s, defined as the dietary dosage (dw) required to kill 50% of the test animals in a specified period of time, have been reported for short-tail shrews and Wister rats (Table V-3).

Environmental and Accidental Poisoning. The meadow vole (Microtus pennsylvanicus) is known to be sensitive to endrin as evidenced by the virtual disappearance of the rodent population after its habitat and food supply were sprayed once with endrin (Wolfe et al., 1963). Panicum and canary seed contaminated with 2.20-4.80 ppm endrin caused the deaths of ~320 cagebirds (finches, doves, quails) in an aviary. Birds began dying 2 days after introduction of the contaminated feed, with the greatest number of mortalities occurring after 5 days of exposure. No gross or microscopic lesions were found in 12 necropsied birds (Main, 1978). Wild birds such as grackles, mallards and white pelicans have also died of endrin intoxication (Peterson and Ellarson, 1978). Two bald eagles possibly died of endrin poisoning (Kaiser et al., 1980). Brains of the eagles contained 0.71 and 1.2 mg endrin/kg ww; the known lethal range begins at ~0.6 mg endrin/kg ww. Misuse of endrin in India was responsible for the death of one bullock and symptoms of acute poisoning in three other animals (Pandey, 1978). The bullocks were treated for tick infestation with "concentrated" endrin over their entire bodies. Signs of poisoning occurred after 6 hours.

TABLE V-3

Endrin Short-Term Oral Dietary LC_{50} Values

Species	Sex/Age	Duration	Number of Animals	LC_{50}[a] (ppm endrin in the diet)	Reference
Short-tailed shrew	F/180 days	14 days	5	174	Blus, 1978
	M/105-150 days	14 days	5	87	Blus, 1978
	F/105-150 days	14 days	5	152	Blus, 1978
	M/30-75 days	14 days	5	87	Blus, 1978
	F/30-75 days	14 days	5	152	Blus, 1978
Rat, Wistar	M, F/immature	5 days	50[b]	60.1 (43-83)[c]	McCann et al., 1981
Rat, Wistar	M, F/immature	5 days	50[b]	62.3 (45-85)[c]	McCann et al., 1981

[a] LC_{50} = Dietary dosage (dw) required to kill 50% of test animals in a specified period of time

[b] 5 male and 5 female/group/concentration; five concentrations

[c] 95% = Confidence limit

Endrin poisoning was reported in 15 of a herd of 70 Sa'anen adult female goats after they had been grazing in an uncultivated area of weeds later found to contain endrin-contaminated boxes (Rapaport et al., 1979). Signs included fits of trembling affecting the whole body, convulsions, profuse salivation and collapse with an inability to rise. In most cases signs subsided within a few minutes but resumed within an hour or so. Treatment with atropine, propionyl promazine, fluid (saline and Ringers), corticosteroid (prednisone) and carbachol was not effective. Within 16 hours, 8/15 goats died, with 2 more dying in the next 24 hours. Postmortem examination revealed profuse blood-stained froth in the trachea, diffuse hemorrhagic enteritis, some petechiae on the epicardium, adhesions between the parietal and pulmonary pleurae and Cysticercus tenuicollis cysts in the abdomen, with fluid and pale intestinal contents. Quantities of endrin consistent with those found in poisoning cases were found in the content of the rumen.

Central Nervous System and Behavioral Effects. Sprague-Dawley rats administered single, oral endrin doses ranging from 20-80 mg/kg bw were susceptible to convulsions, which were sometimes followed by catatonic behavior (Speck and Maaske, 1958). In addition, electroencephalograph (EEG) patterns following endrin exposure exhibited irregular slowing and spikes, and frequent convulsive discharges.

EEG patterns in squirrel monkeys were examined following intramuscular endrin exposures of 0.2 mg/kg bw/day or higher for 7 days, and the results were summarized in an abstract (Revzin, 1968). Increased amplitudes and spikings in EEG recordings were observed after 7 days of exposure at 0.2 mg/kg/day, and were reportedly more marked at high total dosages.

Following cessation of dosing, EEG patterns remained abnormal for at least 1 month.

Locomotor activities were measured in nonpregnant female CD-1 mice and CD rats 2-4 hours after a single endrin exposure by gastric intubation (Kavlock et al., 1981). Mice and rats were exposed to 0, 0.5, 1.5 or 4.5, and 0, 0.5, 1.0 or 2.0 mg/kg bw, respectively. Locomotor activities were significantly reduced at the two highest dose levels in both species, and at 0.5 mg/kg bw in rats, but not mice.

Cardiovascular Effects. In the early 1960s, little was known of cardiovascular changes following acute exposure to lethal amounts of endrin. Experiments with male and female dogs to investigate these phenomena were conducted on 30 dogs weighing from 10-19 kg (Emerson et al., 1964) Anesthesia was induced with sodium pentobarbital (30 mg/kg) and, in some cases, succinylcholine was given to prevent convulsions. Endrin (10 mg/kg bw in 95% ethanol) was administered by i.v. infusion. Control animals received an equivalent amount of ethanol. Convulsions started within 5-10 minutes after the beginning of endrin infusion in dogs not given succinylcholine. Observations included bradycardia, an initial drop in arterial blood pressure, increased body temperature, hemoconcentration, decreased venous blood pH, and increased leukocyte counts. Hemolysis was seen in every post-endrin hematocrit. Cerebral venous pressure and cerebrospinal fluid pressure elevations were also prominent features of endrin poisoning. When succinylcholine was given, the results were similar except that arterial pressure increased initially but later fell to hypotensive levels. Blood pH also

decreased more and hemoconcentration was more pronounced. In controls, succinylcholine-induced bradycardia was replaced by tachycardia in some animals. The heart rate would then oscillate between bradycardia and tachycardia. These authors concluded that most of the observed effects appeared to be caused by endrin acting directly on the CNS, although some might have resulted secondarily from altered cerebral hemodynamics.

Endrin-induced convulsions terminating in death are accompanied by marked changed in blood pressure and heart rate. Using 50 mongrel dogs, Reins et al. (1966) determined the relationship between venous return (cardiac output), total peripheral vascular resistance and hypertension after a lethal dose of endrin. All animals were treated with succinylcholine to prevent convulsions. Endrin (10 mg/kg bw in ethyl alcohol) induced a rise in systemic arterial blood pressure, which depended primarily on increased cardiac output caused by an elevated venous return. Increased levels of epinephrine and norepinephrine in blood plasma, rather than CNS stimulation, may be the explanation for the marked alterations in systemic hemodynamics. Total peripheral resistance did not change significantly in either endrin-infused dogs or control animals infused with the solvent, ethyl alcohol. In a similar study with dogs, Hinshaw et al. (1966) also reported large increases in blood catecholamine concentrations, and increased cardiac output. In contrast to the Reins et al. (1966) findings, these investigators reported that total peripheral resistance fell significantly and that cardiovascular alterations were not significantly correlated with blood catecholamines after endrin intoxication. One major difference

between the two studies was that Reins et al. (1966) used succinylcholine to prevent convulsions; anesthesia was achieved with sodium pentobarbital (30 mg/kg bw) in both studies.

Renal Effects. Renal function and hemodynamics were examined in mongrel dogs following acute and chronic exposure to endrin (Reins et al., 1964). In the acute studies, eight dogs were exposed to lethal endrin doses (10 mg/kg) by intravenous infusion via the femoral vein, and an additional four dogs received the same endrin dose by injection into the intestinal lumen. Following a 2-4 hour examination period, histological examinations were conducted. Endrin exposure elicited increased renal vascular resistance, decreased renal blood flow and glomerular filtration rate (GFR) within 1-2 hours of exposure, although marked individual variation was noted. Since these renal alterations could be reversed by treatment with phentolamine, they were considered to result secondarily to endrin-induced systemic hypertension and effects on circulating humoral agents, rather than from a direct toxic effect of endrin on the kidney. An influence of exposure route on these renal effects was not stated. However, convulsions, hypertension and bradycandia, which developed in the intravenously infused dogs, did not occur in those receiving endrin via the intestinal lumen. Histologically, the dogs exhibited protein precipitation in Bowman's space and the renal tubules, and 1/12 dogs developed renal tubular necrosis. Congestion, degeneration and/or swelling were reported in the spleen, liver and lungs, whereas the heart, pancreas and intestine appeared normal.

Hepatic Effects. Oral administration of endrin (15 mg/kg/day) for 3 successive days elicited significant ($p<0.05$) elevations of liver total lipids, liver triglycerides and serum cholesterol in male Sprague-Dawley

rats. SGOT but not SGPT activities were also slightly elevated following endrin exposure (Borady et al., 1983).

Significant elevations in hepatic oxidative demethylation of dimethylnitrosamine were elicited in male Swiss albino mice exposed by oral gavage to endrin (2 mg/kg/day) for 3 consecutive days (Mostafa et al., 1983). The effects of oral endrin exposure on liver microsomal P-450 content, ethylmorphine demethylase and aniline hydroxylase activities in pine voles and ICR white mice have also been reported (Hartgrove et al., 1977). A single dose of 0.5 or 2.0 mg/kg bw was administered to pine voles, whereas mice received a single dose of 4.0 or 10.0 mg/kg bw. The period of time between dosing and sacrifice was not reported. Aniline hydroxylase activities were elevated in both pine voles and mice following endrin exposure. Endrin elicited a decrease in ethylmorphine demethylase activity in pine voles, but an increase in this activity in the mice. An elevation in total cytochrome P-450 content was elicited in mice, but not pine voles.

Female guinea pigs were chosen for a study of the effects of endrin on hepatic and renal microsomal electron transport because of their sensitivity to the toxic effects of the pesticide (Pawar and Kachole, 1978). Six animals (600-650 g) were injected i.p. with endrin (3 mg/kg bw/day in safola oil) for 3 successive days; six control animals were injected with an equivalent amount of oil. Microsomes were prepared from liver and kidney tissue 24 hours after the third injection. The liver weights of endrin-treated animals were increased and microsomal protein content was decreased. Kidney weight was elevated, but renal microsomal protein was not affected. Decreased hepatic microsomal NADPH-linked aminopyrine

N-demethylation was attributed to decreased levels of cytochrome P-450. Endrin treatment increased in vitro NADH-mediated aminopyrine N-demethylation in renal microsomes. A significant increase in lipid peroxidation in hepatic microsomes was evident when NADPH or ascorbate was the electron donor.

Four chlorinated hydrocarbons including endrin were tested for their possible interference with heme synthesis in Japanese quail, a species chosen because of high sensitivity to chlorinated organics as determined by urinary porphyrin concentrations (Nagelsmit et al., 1979). There was no indication that endrin was porphyrinogenic (1-3 or 5 mg/kg bw/day for 3 days given orally in a capsule), which suggested that urinary porphyrin would not reflect endrin exposure in exposed humans.

Effects of acute endrin exposure are summarized in Table V-4.

Subchronic Effects of Endrin

Maternal body-weight and liver-to-body weight ratios were measured in two studies concerning perinatal endrin toxicity in hamsters, rats and mice. Endrin was administered orally to golden Syrian hamsters on days 4-15 of pregnancy, in single daily doses of 0, 0.75, 1.5, 2.5 or 3.5 mg/kg/day (Chernoff et al., 1979). Doses $\geq$1.5 mg/kg/day produced maternal lethality, which was preceded by significant weight loss. Neither lethality nor effects on maternal weight were elicited at 0.75 mg/kg/day.

Endrin was administered orally in single daily doses to CD rats on days 7-20 of gestation, and to CD-1 mice on days 7-17 of gestation (Kavlock et al., 1981). Doses of 0, 0.075, 0.150, 0.300 or 0.450 mg/kg/day were

TABLE V-4

Effects of Acute Endrin Exposure

Species/ Strain	Sex/ Number	Route	Dose/ Exposure	Comments	Reference
Dogs/mongrel	male, female	i.v. infusion	10 mg/kg	Convulsions, bradycardia, arterial blood pressure fall, elevated body temperature, hemolysis and other hemolological changes	Emerson et al., 1964
Dogs/mongrel	gender not stated/50 dogs	i.v. infusion	10 mg/kg, in presence of succinylcholine	Arterial blood pressure increase, decreased heart rate	Reins et al., 1966
Dogs/mongrel	gender not stated/5-7 experiments: number of dogs not clearly stated	i.v. infusion	3 mg/kg	Increased cardiac output and increased blood catecholamines, fall in total peripheal vascular resistance	Minshaw et al., 1966
Rat Sprague-Dawley	male	oral	15 mg/kg/day for 3 successive days	Elevated total liver lipids, liver triglycerides, serum cholesterol and slighlly elevated SGOT	Borady et al., 1983
Mice/Swiss albino	male	oral	2 mg/kg/day for 3 successive days	Increased oxidative demethylation of dimethylnitrosamine	Mostafa et al., 1983
Mice/ICR white	gender not stated/ 4-11 mice per treatment group	oral	4.0 and 10 mg/kg/ bw, single dose; time until sacri-	Increased hepatic cytochrome P-450 content, aniline hydroxylase and ethylmorphine demethylase activities	Hartgrove et al., 1977
Voles/pine	gender not stated/ 14-18 per treat-ment group	oral	0.5 or 2.0 mg/kg bw single dose; time until sacri-fice not reported	Increased hepatic aniline hydroxylase activity, decreased ethylmorphine demethylase activity	Hartgrove et al., 1977
Guinea pigs/ strain not stated	female/6 group	i.p.	3 mg/kg/day for 3 successive days	Decreased hepatic cytochrome P-450 and aminopyrine N-demethylation, increased liver weight	Pawar and Kachole, 1978
Mice/CD-1	female	oral intubation	0, 0.5, 1.5 or 4.5 mg/kg bw, single dose	Reduced locomotor activity at 1.5 and 4.5 mg/kg bw	Kavlock et al., 1981
Rats/CD	female	oral intubation	0, 0.5, 1.0 or 2.0 or 4.0 mg/kg bw, single dose	Reduced locomotor activity at all exposure levels	Kavlock et al., 1981
Monkeys/Squirrel	3, gender not stated	intramuscular	0.2 mg/kg/day for 7 days	Increased amplitudes and spiking in EEG recordings	Revzin, 1968

administered to rats; doses of 0, 0.5, 1.0, 1.5 or 2.0 mg/kg/day were given to mice. Results from the range finding study are reported in Table V-4. Mice and rats were killed on days 18 and 21 of gestation, respectively. Fetal mortality, weight, degree of skeletal and visceral maturation, and incidence of skeletal and visceral anomalies showed no dose-related effects. Maternal weight gain was significantly reduced in rats exposed to 0.300 mg/kg/day ($p<0.01$) and markedly reduced at 0.450 mg/kg/day, but did not differ from controls at 0.75 or 0.150 mg/kg/day. Neither maternal deaths nor elevations in liver-to-body weight ratios occurred in exposed rats. Elevated liver-to-body weight ratios were reported in the mice at all exposure levels, and maternal lethality occurred at doses $\geq$1.5 mg/kg/day.

Hepatobiliary function and hepatotoxicity have been assessed in rats dietarily exposed to endrin (Young and Mehendale, 1986). Treatment groups of six male and six female Sprague-Dawley rats were given a powdered chow diet containing 0, 5 or 10 ppm endrin for 15 days. The total endrin doses for the 15 days of exposure (and the corresponding dose expressed as mg/kg/day) were 7.4$\pm$1.1 mg/kg (0.5 mg/kg/day) and 14.2$\pm$0.9 mg/kg (0.9 mg/kg/day) for males; the female endrin doses were 7.4$\pm$0.4 mg/kg (0.5 mg/kg/day) and 12.8$\pm$1.8 mg/kg (0.9 mg/kg/day) for 5 and 10 ppm, respectively. On day 16, heptatotoxicity in all animals was assessed by serum enzymology, and hepatobiliary function was assessed by measuring biliary flow rates and excretion rates of phenolphthalein glucuronide (PG).

Serum enzyme levels were not significantly elevated in the endrin exposure groups. In males exposed to 5 ppm endrin, PG excretion and bile flow rates were reduced to 66 and 68% of control levels, respectively. At

10 ppm, PG excretion was reduced to 75% of control, but no significant change in bile flow rate was observed. In females exposed to 5 ppm endrin, the rate of PG excretion was 10% higher than control, whereas the rate of bile flow was not significantly different than control. At 10 ppm, rates of PG excretion and bile flow were elevated to 30% and 25% above control levels, respectively. It was concluded that endrin had a sex-dependent effect on hepatobiliary function.

In the only reported subacute study involving dermal exposure (Treon et al., 1955), three female rabbits/group were exposed to 100-mesh, dry endrin powder 75 or 150 mg (equivalent to 67-91 mg/kg bw/day at the high-dose and 20-42 mg/kg bw/day at the low-dose) under a rubber sleeve 2 hours daily, 5 days/week. In the high-dose group the rabbits died after 19, 19 and 25 applications. At the low-dose 1 of 3 died after the 40th application.

Subchronic and chronic endrin toxicity were evaluated in Carworth rats, beagle dogs and an unspecified species of rabbit (Treon et al., 1955). Four of five female rabbits that were orally administered 1 mg/kg/day endrin 5 days/week died during the 10-week exposure period. Mortality occurred in 3/3 male rats after oral administration of endrin at 5 mg/kg/day. Mortality occurred in 2/5 females but no deaths occurred in males at the 2 mg/kg/day dose level. All treated animals developed hypersensitivity to stimuli and weight loss but generally male rats were less affected than female rats. Weight gains in groups of 20 male and 20 female rats (initial age 28 days) given diets containing 0, 1, 5, 25, 50 or 100 ppm endrin for 20 and 40 weeks were also reported. In 5 ppm males, weight gain was significantly reduced at 20 but not 40 weeks of exposure. At 25 ppm, significant weight gain

reduction was observed at both 20 and 40 weeks. In contrast, female weight gain was significantly elevated at ≥5 ppm following both 20 and 40 weeks of exposure.

Beagle dogs were administered diets containing 4-50 ppm endrin for periods ranging from ~1-10 months. Mortality occurred at exposure ≥5 ppm. After ~6 months of exposure to 4 ppm, the liver-to-body weight ratio was elevated, and liver-, kidney- and brain-to-body weight ratios were elevated in dogs exposed to 8 ppm. Dogs that died during endrin exposure exhibited degenerative lesions in brain, heart, liver and kidneys, in addition to pulmonary hyperemia and edema. The renal damage was particularly severe (Treon et al., 1955).

Sprague-Dawley rats were fed diets containing various concentrations of endrin for up to 16 weeks (Nelson et al., 1956). The endrin concentrations were 0, 1, 5, 25, 50 and 100 ppm, and were administered to groups of 10 rats (5 of each gender). Mortality occurred within 4 weeks in males and females fed concentrations ≥5 and 25 ppm, respectively. For the 100 ppm group, this mortality was 100%. After 16 weeks, some mortality had occurred in all male exposure groups, but only in female groups exposed to ≥25 ppm.

Dose-related weight loss was reported in animals exposed for up to 8 weeks. Serum alkaline phosphatase was consistently elevated from weeks 10-16 among survivors fed 25 or 50 ppm; this elevation occurred but was not persistent at the lower exposure levels. Hypersensitivity to various stimuli was reported at all exposure levels, but was most pronounced and followed by convulsions at the higher (25-100 ppm) exposures only. These

animals also exhibited dysenteric symptoms, intermittent blindness and slight nasal bleeding. The nasal bleeding also occurred in the 1 and 5 ppm exposure groups. The latency to hypersensitivity, nasal bleeding, dysenteric symptoms and blindness was not reported.

Endrin (3.5 mg/kg bw/day) was administered to groups of male Sprague-Dawley rats by oral gavage 5 days/week for periods ranging from 1 week to 7 months (Speck and Maaske, 1958). After 1 week of exposure, 4/30 animals died. Surviving animals exhibited an elevated respiration rate, excitability or irritability, and were predisposed to convulsions following auditory stimulation. Irregular EEG recordings were also observed following 1 week of exposure.

EEG changes were minimal in the chronic groups. However, after 3 months of exposure, livers appeared spotty with zones of basophilic cells around the central and portal veins. Furthermore, plasma specific gravity was significantly reduced following 3 months of endrin exposure; this effect was reversible upon discontinuation of endrin exposure.

Cattle and sheep were not affected by 5 ppm in the feed ingested over a 112-day period (Radeleff, 1956). Chickens (7 days old) were not made excitable by a ration containing 1.5 and 3 ppm endrin for 42 days. This was not so for concentrations of 6-12 ppm endrin; decreased weight gains were also shown at these concentrations (Sherman and Rosenberg, 1954).

Feeding studies were conducted to estimate the maximum tolerated doses of endrin in Osborne-Mendel rats and B6C3F1 mice for a National Cancer

Institute study of carcinogenicity (NCI, 1979). Endrin was first dissolved in acetone and then added to the feed. Corn oil was added to all feed (2% of final weight of feed) as a dust suppressant. Five males and five females were given food with or without endrin for 6 weeks, followed by observation for 2 weeks.

For rats, endrin was added to the feed in 2-fold increasing concentrations, ranging from 2.5-80 ppm (NCI, 1979). There were no deaths at 10 ppm and mean weight gains were not different from controls. At 20 ppm, one animal of each sex died, but weights of survivors were not significantly affected. In the same 1979 NCI subacute study, mice were given feed containing from 2.5-20 ppm endrin. At 10 ppm, 3 males and 4 females died in the group of 10 mice. No mortality occurred in the 5 ppm group; mean weight gains were comparable with that of controls. In these subacute exposures, increased mortality was the only toxic effect reported other than hyperexcitability in male mice receiving >5 mg/kg diet.

Effects of subchronic endrin exposure are summarized in Table V-5.

Chronic Effects

In a series of experiments, Treon et al. (1955) explored the effects of endrin ingestion in a number of species including rats, rabbits and dogs. Included in this study was the only report found of an inhalation exposure of animals to "vapors" of endrin (Table V-6). No convulsions were reported among this group of animals. Pathological findings were similar to those observed following other routes of administration.

TABLE V-5

Effects of Subchronic Endrin Exposure

Species/Strain	Sex/Number	Route	Dose/Exposure Regimen	Comments	Reference
Rabbit/not stated	F/5	oral	1 mg/kg/day, 5 days/weeks for 10 weeks	4/5 rabbits died	Treon et al., 1955
Rat/Carworth	M/6 and F/5	oral	2 mg/kg/day	2/5 female rats died; no deaths in males	Treon et al., 1955
Rat/Carworth	M/20 and F/20	oral	diets contained 0, 1, 5, 25, 50 or 100 ppm endrin for 20-40 weeks	Reduced weight gain in rats exposed at >5 ppm.	Treon et al., 1955
Dogs/beagle	15 total animals	oral	diets contained 4-50 ppm endrin for 1-10 months	Mortality in some animals ≥5 ppm. Elevated liver-to-body weight ratio at 4 ppm, elevated liver-, kidney- and brain-to-body weight ratios at 8 ppm.	Treon et al., 1955
Rabbits	3F/group	dermal	20-42 or 67-91 mg/kg/day 2 hours/day, 5 days/week for up to 8 weeks	Mortality in both exposure groups after 19-40 applications.	Treon et al., 1955
Rats/Sprague-Dawley	M/5 and F/5	oral	dietary exposure at 0, 1, 5, 25, 50 or 100 ppm for up to 16 weeks	Mortality in some male rats in all exposure levels and in females exposed to ≥25 ppm. Nasal bleeding in 1 or 5 ppm exposure groups. Weight loss, elevated serum alkaline phosphatase, dysenteric symptoms and intermittent blindness.	Nelson et al., 1956
Rats/Sprague-Dawley	M	oral gavage	3.5 mg/kg/day, 5 days/week for 1 week to 7 months	4/30 died after 1 week of exposure, abnormal EEG patterns in survivors. After 3 months exposure, spotty livers with zones of basophilic cells, reduced plasma specific gravity.	Speck and Maaske, 1958
Rats/Osborne Mendel	M/5 and F/5 per group	oral	diets contained 0, 2.5, 5, 10, 20, 40 or 80 ppm for 6 weeks, followed by 2 weeks of observation	No deaths or weight gain effects at ≤10 ppm. Mortality occurred at 20 ppm, weights of survivors were unaffected.	NCI, 1979

TABLE V-5 (cont.)

Effects of Subchronic Endrin Exposure

Species/Strain	Sex/Number	Route	Dose/Exposure Regimen	Comments	Reference
Mice/B6C3F1	M/5 and F/5 per group	oral	diet contained 0, 2.5, 5, 10 or 20 ppm endrin for 6 weeks, followed by 2 weeks of observation	No deaths or weight gain effects at ≤5 ppm. Mortality in 10 ppm group.	NCI, 1979
Hamsters/golden Syrian	20-38f per exposure group	oral	single daily doses of 0, 0.75, 1.5, 2.5 or 3.5 mg/kg bw were administered to pregnant hamsters on days 4-15 of gestation	Weight loss and mortality occurred at ≥1.5 mg/kg/day.	Chernoff et al., 1979
Rats/CD	15-30f per exposure group	oral	single daily doses of 0, 0.075, 0.150, 0.300 or 0.450 mg/kg bw were administered to pregnant rats on days 7-20 of gestation	Depressed maternal weight gain at 0.300 and 0.450 mg/kg bw.	Kavlock et al., 1981
Mice/CD-1	20-39f per exposure group	oral	single daily doses of 0, 0.5, 1.0, 1.5 or 2.0 mg/kg bw were administered to pregnant mice on days 7-17 of gestation	Lethality and/or depressed maternal weight gain at doses ≥1.0 mg/kg bw/day. Elevated liver-to-body weight ratio at all exposure levels.	Kavlock et al., 1981
Rats/Sprague-Dawley	M/6 and F/6 per group	oral	diets contained 0, 5 or 10 ppm endrin for 15 days. Approximate corresponding mg/kg/day doses were 0, 0.5 and 0.9, respectively	Altered hepatobiliary function which was sex-dependent.	Young and Mehendale, 1986

TABLE V-6

Mortality of Animals Exposed to 0.36 ppm (5.62 mg/m³) Endrin "Vapor"[a,b]

Species	No. of Exposure (days)	No. Dead/ No. Exposed	Daily Inhalation Volume (m^3/day)	µg Endrin[c] (7-hour day)
Cat	130	0/1	0.15	0.25
Guinea pig	130	0/2	0.074	0.12
Hamsters	101-130	0/2	0.037	0.061
Rats	130	0/3	0.26	0.43
Rabbits	118	2/4	1.6	2.6
Mice	107	1/3	0.05	0.082

[a]Source: Treon et al., 1955

[b]Exposed by inhalation 7 hours/day, 5 days/week for 185 days

[c]The original paper does not provide any weight data for these species in these experiments.

Treon et al. (1955) fed groups of 20 male and 20 female Carworth rats diets containing 0, 1, 5, 25, 50 or 100 ppm endrin for 2 years. Rats receiving 50 or 100 ppm exhibited hypersensitivity to external stimuli, occasional convulsions and liver degeneration. In addition, after 80 weeks of treatment, increased mortality in rats was noted at 25, 50 and 100 ppm in males and at 50 and 100 ppm in females. Effects on body weight were reported at 20 and 40 weeks. Females at 5 and 25 ppm appeared to have a greater rate of body weight gain than controls, while body weights in males appeared to be slightly depressed at these levels. At $\geq$50 ppm, rats of both sexes appeared to have a slightly increased rate of body weight gain, but since mortality was high in these groups, the survivors may have been the larger rats. Males at 5 and 25 ppm had increased relative liver weights compared with controls, while rats at 1 ppm were not different from controls.

Treon et al. (1955) also conducted a study with beagle dogs in which groups of 1-4 were fed diets containing 0-50 ppm endrin for up to 18 months. All dogs fed 10-50 ppm (0.49-4.00 mg/kg/day) died, and >50% of those fed 5-8 ppm (0.20-0.65 mg/kg/day) died. Actual endrin intakes were reported by the authors. All dogs receiving $\leq$4 ppm (0.15-0.21 mg/kg/day) survived, but growth was affected in the 4 ppm groups. The 3 ppm (0.12-0.25 mg/kg/day) group had significantly higher relative kidney and heart weights than controls. Dogs fed 1 ppm endrin were similar to controls in all parameters, including gross pathology and histopathology. According to the authors, the dogs (two males and two females) on the 1 ppm diet actually consumed 0.045-0.120 mg/kg/day.

In a 2-year dog study, beagle dogs (7/sex/group) received diets containing 0, 0.1, 0.5, 1.0, 2.0 or 4.0 ppm endrin for >2 years (U.S. EPA,

1987). Interim sacrifices (2 dog/sex/group) were performed at 6 and 12 months. Parameters monitored included growth, food consumption, behavior, serum and urine chemistry, organ weights and histopathology of all major organs. Animals treated at the 2 and 4 ppm dose levels experienced convulsions, slight increase in relative liver weights, and mild histopathological changes in liver cells. Because of the effects observed in the dogs consuming diets containing 2 ppm endrin (0.05 mg/kg/day), this level was considered the LOAEL. No adverse effects were observed in dogs receiving diets containing $\leq$1 ppm endrin. Therefore, 1 ppm (0.025 mg/kg/day) was considered the NOAEL.

Renal function and hemodynamics were examined in mongrel dogs following acute and chronic exposure to endrin (Reins et al., 1964). In the chronic study, five female dogs were given endrin (1 mg/kg) by intramuscular injection 5 days/week until death or sacrifice. Results concerning renal function were reported as inconclusive due to marked individual variation, and histological evaluation of the renal tubules, as well as the brain, pancreas, heart and intestines, showed no definitive pathological changes. However, chronic endrin exposure elicited conjestion and occasional hemorrhage in the lungs, and adrenal lipid depletion and congestion.

Deichmann et al. (1970) conducted a chronic study for the primary purpose of providing information on the possible carcinogenicity of endrin, aldrin and dieldrin. Carcinogenic outcomes of chronic studies are reported in the Carcinogenicity section. Endrin dissolved in corn oil was added to ground Purina rat chow and administered to Osborne-Mendel rats (50 males and 50 females) at 1, 3 or 6 ppm for 10 weeks and at 2, 6 or 12 ppm until death

or 31 months. There was no significant effect on mean body weight or weight gain in endrin-treated rats. Two hundred rats (100/sex) were fed an uncontaminated diet. No mention was made whether corn oil was added to the control diet. Signs of toxicity observed during the course of the experiment were limited to episodes of tremors and clonic convulsions with "outcries." These signs were dose related; however, the statement was made in general for all three insecticides. The mean survival rate for 12 ppm endrin-treated male rats was 17.6±6.9 months, and for 2 ppm treated rats, 18.1±4.9 months; mean survival for control rats was 19.7±4.8 months (statistical analysis not reported). The mean survival of female rats was about the same or slightly longer. Liver-to-body weight ratios were not significantly different from those observed in control animals. Histologic changes in the livers of rats fed endrin (2, 6 or 12 ppm) were similar to those receiving the control diet with the exception of a moderate increase in the incidence of centrilobular cloudy swelling; there was also an increase in cloudy swelling of the renal tubular epithelium.

Male and female Osborne-Mendel rats (24/group) were fed diets containing 0, 0.1, 1, 5, 10 or 25 ppm endrin for 2 years (Reuber, 1978). Although this study was intended to be a carcinogenicity bioassay, data on the total incidence and severity (none, mild, moderate or severe) of chronic interstitial nephritis that developed in both control and exposed groups were also reported. There appeared to be a trend toward increased incidence and severity of nephritis with increasing endrin exposure, particularly in the males exposed to ≥1 ppm. The author concluded that endrin exposure induced dose-related increases in the incidence and severity of chronic

nephritis in the males. However, statistical evaluation of these data was not reported, and such an evaluation appeared necessary in order to justify this conclusion.

The NCI (1979) conducted a chronic study with Osborne-Mendel rats and B6C3F1 mice to determine the possible carcinogenicity of endrin. Endrin was added to feed as described in subacute effects. Fifty animals of each sex constituted a treatment group of rats or mice. Ten animals of each sex were matched controls and data from 40 or 50 untreated animals from similar bioassays were pooled for statistical evaluation.

Groups of rats (100 each) were administered one of two doses of endrin for 80 weeks (NCI, 1979), and then observed until survivors were sacrificed at 110-114 weeks. Male rats received 2.5 or 5 ppm endrin in the diet. There was neither a significant effect on mean body weight nor a significant dose-related trend in mortality. Clinical signs usually associated with aging were observed earlier in dosed rats than in controls: alopecia, diarrhea, epistaxis, tachypnea, pale mucous membranes, hematuria, rough hair coats and dermatitis. Thyroid hyperplasia and pituitary cysts were observed in exposed animals, but not in matched controls. However, the spontaneous occurrence of these lesions in aged Osborne-Mendel rats was described as not uncommon. Testicular atrophy was reported in 8/42 and 14/45 low- and high-dose rats, respectively; none was reported in matched controls.

Mice were administered endrin in the diet for 80 weeks and observed until sacrifice at 90-91 weeks. Initial doses of 2.5 or 5 ppm were not well tolerated by male mice and were reduced to 1.2 and 2.5 ppm (NCI, 1979). The

TWA was calculated to be 1.6 and 3.2 ppm. Female mice were kept at the 2.5 or 5 ppm level. Mean body weights were similar to corresponding controls and there was no dose-related trend in mortality in female mice. Survival was decreased in high-dose male mice; a large number of the low-dose males died following the accidental overdose at 66 weeks and survival could not be determined. Before the overdose, clinical signs included alopecia, diarrhea, epistaxis, rough hair coats, tachypnea, hematuria and discolored urine. After about 4 months, all of the high-dose male group appeared hyperexcitable, and doses for males were lowered as indicated above. Lowering the dose did not change the hyperexcitable behavior in the majority of the group. In the last half of the first year, clinical signs were apparent in both sexes: abdominal distension, alopecia and rough hair coats. Because of an error at week 66, excessive amounts of endrin were given to the 1.2 ppm dosed male mice which caused animals to be hyperexcitable until termination. Researchers determined that a rather fine line exists between endrin levels causing CNS toxicity and those virtually nontoxic.

Kreitzer (1980) determined whether behavioral effects would be produced by endrin at levels below those that produced overt signs of intoxication. Adult male bobwhite quail, Colinus virginianus, were fed endrin dissolved in propylene glycol and blended into feed at levels of 0.1 and 1.0 ppm. An equal amount of propylene glycol was added to the feed of controls. There were four controls and four birds at each treatment level for all tests that measured performance on nonspatial discrimination reversal tasks. Birds were dosed (beginning at the age of 3 days) for 138, 185 and 240 days before Tests 1, 2 and 3, respectively. The fourth test began after 267 days of

dosing followed by 25 days of untreated feed, and the fifth test after 278 days of dosing followed by 50 days of untreated feed. Endrin-treated birds made from 36-139% more errors than did controls ($p<0.025$). The difference between acquisition error scores of controls and treated birds increased exponentially over the first four tests. The 0.1 ppm diet dosed birds made significantly more errors than the 1.0 ppm birds after reversal of black and white patterns used for discrimination to receive a reward. There was no explanation for this effect. Endrin effects were reversed after 50 days of untreated feed. The principal effects of endrin was to impair the birds' ability to solve a novel problem. Mean brain residues in endrin-treated birds were 0.075 mg endrin/kg ww for the 0.1 ppm dose and 0.35 mg endrin/kg ww for the 1.0 ppm dose.

Jager (1970) published an extensive review of the epidemiology and toxicology of long-term exposure to aldrin, dieldrin, endrin and telodrin. In a discussion of endrin toxicity in animals, Jager concluded that even though endrin is a stereoisomer of dieldrin, it differs from dieldrin in the following respects: higher acute toxicity, more rapid metabolism, and less persistence in vertebrates. The endrin LD_{50} varied with the vehicle and experimental species used, endrin being 4-5 times more acutely toxic than dieldrin. The dietary NOEL for endrin in chronic feeding studies in the rat and the dog was 1 ppm endrin in the diet.

The effects of chronic endrin exposure are summarized in Table V-7.

Teratogenicity and Reproductive Effects

Mammals. Two studies of endrin toxicity in rodents were conducted in the 1960s at doses that were toxic to the mother. Endrin was added to the

TABLE V-7

Summary of Oral Chronic Effects After Endrin Exposure

Species/Strain	Sex/Number	Dose/Exposure Regimen	Comments	Reference
Rats/Carworth	M&F/5-20 per group	diets contained 0, 1, 5, 25, 50 or 100 ppm endrin for 2 years	Mortality at ≥25 ppm. Elevated liver-to-body weight in males exposed to ≥5 ppm, lesser but nonsignificant elevations at 1 ppm in males, and 1-5 ppm in females.	Treon et al., 1955
Dogs/beagle	M/50 and F/50	diets contained 0-50 ppm for 18-19 months	Enlarged kidneys and hearts at 3 ppm but not 1 ppm.	Treon et al., 1955
Rats/Osborne-Mendel	M/50 and F/50	diets contained 2, 6 or 12 ppm endrin until death or for 31 months	Early mortality in exposed groups relative to controls. No effects on body weight gain or liver-to-body weight ratios. Moderately increased incidence of cloudy swelling in centrilobular liver zones and in renal tubular epithelium. Also, moderate increases in incidence of lung congestion and focal hemorrhages.	Deichmann et al., 1970
Rats/Osborne-Mendel	M/24 and F/24 per group	diets contained 0, 0.1, 1, 5, 10 or 25 ppm endrin for 2 years	Chronic interstitial nephritis, tending toward increased incidence and severity with increasing dose.	Reuber, 1978
Rats/Osborne-Mendel	M/50 and F/50 per group	diets contained TWA endrin levels of 2.5 or 5 ppm for males, and 3 or 6 ppm for females for 110-114 weeks	Clinical signs associated with aging appeared earlier in dosed rats than in controls. Testicular atrophy was reported in exposed males, but not in matched controls.	NCI, 1979
Mice/B6C3F1	M/50 and F/50 per group	diets contained TWA endrin doses of 1.6 and 3.2 ppm for males or 2.5 and 5 ppm for females, for 90-91 weeks	Decreased survival in high-dose males. Hyperexcitability in high-dose males. Clinical signs including alopecia, abdominal distension and rough hair coats were reported in dosed groups prior to controls.	NCI, 1979
Rats/Long-Evans	M/7 and F/7 per group	diets containing 0, 0.1, 0.5, 1.0, 2.0 or 4.0 ppm for >2 years	Convulsions, slight increase in relative liver weight and mild histopathological changes in liver cells at 2 and 4 ppm. No adverse effects at 1 ppm.	U.S. EPA, 1987b

feed of Sprague-Dawley rats (Green, 1969) and of CFW Swiss mice (Good and Ware, 1969) at 5 ppm and fed to the animals before and during gestation (Table V-8). Green (1969) reported increased early resorption of embryos and Good and Ware (1969) reported increased maternal mortality and significantly smaller litter size, also indicating increased resorption.

At about the same time, Morris (1968) studied the effects of endrin feeding on field-captured deer mice (Peromyscus maniculatus osgoodi) for parental survival, fertility, litter size and survival of young to weaning (see Table V-8). Reproductive performance was recorded for 6 months before a 7-month feeding program was initiated (0, 1, 2, 4 and 7 ppm endrin in the diet). Postnatal mortality of the young appeared to be the major effect of endrin on the offspring of deer mice; however, soft and skeletal tissues were not examined for the incidence of malformations. Survival of parents was significantly decreased at endrin levels $\geq$2 ppm.

A single oral dose of endrin, 5 mg/kg bw (1/2 LD_{50}), administered by intubation to pregnant Syrian golden hamsters, caused a marked and statistically significant increase in fetal deaths in animals treated on day 7 or 8 of gestation (Ottolenghi et al., 1974). In these studies (Table V-9), two control groups were used, one group receiving the corn oil vehicle and a second group receiving no treatment. Comparisons of litters from pesticide treated hamsters were made with the corn oil-treated group for evaluation of the incidence of embryocidal and teratological effects by using the Mann-Whitney U-test. Dunnett's multiple comparisons test was used to evaluate differences in fetal weight. A statistically significant increase in the incidence of fused rib and cleft palate ($p<0.01$) occurred in litters from

TABLE V-8

Teratogenicity and Reproductive Studies Performed with Endrin in the 1960s

Species	Sex	Dose (ppm)	Feeding Procedure	Effects	Reference
Sprague-Dawley rats	females	5	60 days before and during gestation	Increase in resorptions	Green, 1969
CFW Swiss mice	males and females	5	4 months before and during gestation	Parental mortality (1/3) Significantly smaller litter size	Good and Ware, 1969
Deer mice (Peromyscus maniculatus osgoodi)	14 parental pairs/dose	2 4 7	At intervals over 7-month period	Parental mortality Significant decrease in survival of offspring at 21 days	Morris, 1968

dams treated on day 7, 8 or 9 and sacrificed on day 14 of gestation. A significant increase in open eye and webbed foot occurred only in litters from dams treated on day 8. Fetal weight was reduced in all treated litters. The association of webbed foot and open eye with low fetal weight suggests that these effects may be an expression of growth retardation (Ottolenghi et al., 1974).

Ottolenghi et al. (1974) also examined the effects of orally administered endrin in corn oil (day 7, 8 or 9 of gestation) on the fetuses of CD-1 mice (see Table V-9). The frequency and gravity of defects produced by a single dose of 2.5 mg/kg bw (1/2 LD_{50}) administered to mice on day 9 of gestation were less pronounced than those seen in hamsters at 5 mg/kg. Abnormalities included an increased incidence of eye opening ($p<0.5$) and a low occurrence of cleft palate. No significant effects were found with regard to fetal survival or fetal weight.

A single dose of endrin in corn oil administered to Syrian golden hamsters by oral gavage on day 8 of gestation produced meningoencephaloceles at doses above 1.5 mg/kg bw and fused ribs at doses above 5.0 mg/kg (see Table V-9). Open eyes, cleft palate and webbed foot were not observed. No significant effects were noted in either maternal mortality and weight gain or fetal mortality and weight gain. In a multiple dose study, the administration of endrin on days 5-14 of gestation produced maternal lethality at doses $\geq$1.5 mg/kg bw/day. Fetal toxicity (including increased mortality, reduced fetal weight and reduced skeletal ossification) resulted at doses above 0.75 mg/kg/day (see Table V-9). Endrin crossed the placenta and was identified in the fetus. 12-Ketoendrin was found in both mother and fetus but not quantified (Chernoff et al., 1979).

TABLE V-9

Reproductive Effects of Endrin for Studies Performed Since 1970

Species	Route of Administration	Dose (mg/kg/day)	Vehicle	Day of Gestation	No. of Litters	Effects	Reference
Golden syrian hamsters	oral gavage	5	corn oil	7 8 9	7 21 8	fetal death (32% of implantations), growth retardation, congenital abnormalities in 20% of feluses treated on day 8: open eye, 22%; webbed foot, 16%; cleft palate, 5%; cleft lip, 1%; fused ribs, 8%	Ottolenghi et al., 1974
Golden syrian hamsters (LVG strain)	oral gavage	>0.75	corn oil	5-14	19	Marked maternal toxicity; hypoactivity, tremors, reduced weight gain, lethality; fetal toxicity; increased mortality, reduced fetal weight, reduced skeletal ossification	Chernoff et al., 1979
Golden syrian hamsters (LVG strain)	oral gavage	≥1.5	corn oil	5-14	21	Significant maternal lethality and weight reductions. meningoencephaloceles in feluses of two litters	Chernoff et al., 1979
Golden syrian hamsters	oral gavage	≥5.0	corn oil	8	50 34 24	Fused ribs and meningoencephaloceles; no overt embryolethal or maternotoxic effects	Chernoff et al., 1979
Golden syrian hamsters	oral gavage	1.5	corn oil	5-14	13	Persistent elevation of locomotor activity in offspring; nonlocomotor behavior of offspring unaffected; 57% of dams died during dosing period.	Gray et al., 1981
CD rats	gastric intubation	0.075	corn oil	7-20	14	No effect on maternal weight gain or fetus	Kavlock et al., 1981
CD rats	gastric intubation	0.15	corn oil	7-20	27	No effect on maternal weight gain or fetus	Kavlock et al., 1981
CD rats	gastric intubation	0.3	corn oil	7-20	29	Significant decrease in maternal weight. No effect on fetus.	Kavlock et al., 1981
CD rats	gastric intubation	0.450	corn oil	7-20	12	87% decrease in maternal weight gain, no apparent effect on the fetus	Kavlock et al., 1981

TABLE V-9 (cont.)

Species	Route of Administration	Dose (mg/kg/day)	Vehicle	Day of Gestation	No. of Litters	Effects	Reference
CD rats	oral gavage	0.075 0.15 0.30	corn oil	7 through day 15	13 13 5	Pups 30% more active in the mazes than controls or 0.075 mg/kg endrin dose groups; at 90 days of age, no endrin-induced differences were apparent; did not affect pup survival or growth.	Gray et al., 1981
CD-1 mice	oral gavage	2.5	corn oil	9	10	Congenital abnormalities: open eye; cleft palate	Ottolenghi et al., 1974
CD-1 mice	gastric intubation	0.5	corn oil	7-17	31	Maternal liver enlargement	Kavlock et al., 1981
CD-1 mice	gastric intubation	1.0	corn oil	7-17	32	Reduced maternal weight gain; decrease in fetal weight and skeletal and visceral maturation	Kavlock et al., 1981
CD-1 mice	gastric intubation	1.5	corn oil	7-17	12	Maternal lethality; no teratogenic effect or embryo lethality; decreased locomotor activity, reduced weight gain in pups; activity levels depressed after first and third doses but no significant difference after tenth dose.	Kavlock et al., 1981
CD-1 mice	gastric intubation	2.0 single dose	corn oil	7-17	2	No dose-related evidence of open eyes and cleft palate	Kavlock et al., 1981
CD-1 mice	gastric intubation	2	corn oil	8-12	17	Reduced maternal weight, reduced fetal weight	Chernoff and Kavlock, 1982
CD-1 mice	gastric intubation	7 9	corn oil	8	14 16	Reduced maternal weight gain, fetal weight, percent of supernumary ribs, sternal and caudal ossifications. Exencephaly and fused ribs were observed in a few offspring.	Kavlock et al., 1985
CD-1 mice	gastric intubation	2	NS	14-18	NS	Reduced locomotor activity in figure eight mazes.	Gray et al., 1986
ICR/SIM mice	gastric intubation	2.2	corn oil	8-12	24	Reduced neonatal weight	Seidenberg et al., 1986

NS = Not stated

In the hamster, exposure to endrin in corn oil at 1.5 mg/kg bw/day on days 5-14 of gestation produced a significant elevation in locomotor activity of offspring that was still present at 125 days of age (see Table V-9). Nonlocomotor behavior of the offspring (including rearing in the open field, running wheel activity and mounting) were not altered by treatment. Dams were markedly hypoactive using the same testing conditions in which the pups were hyperactive. More than half of the group receiving 1.5 mg/kg/day died. Rats exposed on days 7 through 15 of gestation to endrin at 0.15 or 0.30 mg/kg/day were 30% more active than controls before weaning but not as adults. These doses did not kill the dams or affect pup survival or growth. In this study, a dose of 0.075 mg/kg/day appeared to have no effect on behavior. Behavioral effects may be of special concern in view of the persistence of endrin in the environment and its capability for magnification in the food chain (Gray et al., 1981).

Kavlock et al. (1981) found that endrin was not teratogenic or embryolethal in the CD rat or CD-1 mouse when administered by gastric intubation at maternally-toxic dose levels throughout the period of organogenesis (see Table V-9). However, evidence of fetal toxicity (depressed fetal weight and caudal vertebrae number; elevated supraoccipital score) was reported among offspring of mice exposed to 1.0 or 1.5 mg endrin/kg/day. Adult female rats tolerated 2-3 times less endrin than did adult mice or hamsters, but the rat is the only one of the three species in which endrin did not induce fetotoxicity. The difference in fetal sensitivity was attributed to lower levels of 12-ketoendrin present in the rat fetus than observed in the hamster fetus. More recently, fetal outcomes were examined following oral exposure of CD-1 mice to a low (7 mg/kg) or moderate (9 mg/kg) maternally toxic dose of endrin on day 8 of gestation (Kavlock et al., 1985).

Statistically significant ($p<0.05$) reductions in fetal weight and number of sternal and caudal ossifications were reported at 7 mg/kg, but not 9 mg/kg endrin. Significant reductions in the percent of supernumary ribs ($p<0.05$) were reported for both doses. Exencephaly and fused ribs were observed in 2/157 and 3/184 fetuses examined. These data were interpreted as indicative of a low but significantly elevated incidence of terata following endrin exposure.

Chernoff and Kavlock (1982) assayed 28 compounds of known teratogenic potential by an in vivo teratology screening procedure (see Table V-9). Endrin was administered by oral gavage (2 mg/kg bw) to 25 gravid CD-1 mice on days 8-12 of gestation. Dams were allowed to give birth, and litter size and weight on postpartum days 1 and 3 were compared with concurrent controls. Results indicated significantly reduced maternal weight and reduced fetal weight on postpartum day 1. In a similar screening study, reduced neonatal weight, but not viability, was reported following exposure of ICR/SIM mice to endrin (2.2 mg/kg/day) by oral intubation on days 8-12 of gestation (Seidenberg et al., 1986).

Behavioral development of CD-1 mouse offspring prenatally exposed to endrin has also been evaluated by measuring figure eight maze reactive locomotor activity (Gray et al., 1986). Endrin (2 mg/kg bw) was administered by oral gavage to pregnant females on days 14-18 of gestation, and locomotor activities were measured in offspring 22, 58 and 200 days after birth. Locomotor activity was less than the control at days 58 and 200; this effect was statistically significant ($p<0.05$) at day 58 only.

Birds. A disastrous die-off of brown pelicans, which reduced the population from 400 to 250 birds, occurred in Louisiana in May and June 1975. Several months earlier, a die-off of ~100 white pelicans occurred near the same area. Shell thickness of pelican eggs from 1971 through 1976 averaged 6.7-13.5% less than the mean thickness for eggs collected before 1947. Statistical analysis of data on residues in eggs indicated that there were significant differences in DDT and DDE mean concentrations for several years but no pronounced trend. PCB residues remained essentially the same. Dieldrin residues increased significantly during the study; endrin residues increased significantly through 1975, and then dropped sharply in 1976. Endrin has been considered the major factor in the die-offs because endrin residues were detected in brains of several pelicans and because the die-off in 1975 coincided with the peak in endrin residues in pelican eggs. The effect of endrin on reproductive success is unknown, but the egg with the highest residues (1.47 mg/kg ww) contained an embryo that died while pipping (Blus et al., 1979).

On the basis of further studies, the critical level of endrin in brown pelican eggs was roughly estimated at $\geq$0.5 µg/g. More exact determination was not possible because of the small population. Of the avian species studied, the brown pelican was the most sensitive to organochlorine contaminants, particularly DDE and endrin (Blus, 1982). In mallard ducks dietarily exposed to 0.5 or 3.0 ppm endrin, egg production, fertility and hatchability were not affected, but embryo survival was reduced in the 3.0 ppm treatment group (Roylance et al., 1985). A similar study reported no adverse reproductive outcomes for mallards dietarily exposed to 1 ppm endrin, but equivocal evidence of poor reproduction at 3 ppm exposure (Spann

et al., 1986). However, application of endrin directly to mallard eggs at doses greater or less than the LC_{50} elicited reduced growth and malformations in surviving embryos (Hoffman and Albers, 1984).

Mutagenicity

Endrin was one of 228 pesticides tested for mutagenicity in a Salmonella typhimurium reverse mutation assay using strains TA1536, TA1537, TA1538, TA98 and TA100 (Ames et al., 1975). Endrin was not mutagenic for any of the above bacterial strains, nor for Escherichia coli WP2 hcr. These in vitro assays were done both with and without addition of rat hepatic homogenates (S9) to supply mammalian metabolic enzymes (Moriya et al., 1983). The National Toxicology Program (U.S. DHHS, 1982) also reported endrin to be nonmutagenic for Salmonella, although no details of testing procedures were given. A third study utilized a modification of the standard reverse mutation assay wherein the Salmonella strains were streaked on agar plates poured so as to obtain a concentration gradient of the test compound. Endrin was not mutagenic for any of the above strains nor for the following: his G46, his C3076, or his D3052 (Probst et al., 1981). Similarly, endrin was not mutagenic in the absence of S-9 in S. typhimuirum strains TA98, TA100, TA1535 or TA1537. Further, mutagenicity was not observed in TA98 or TA100 in the presence of S-9, nor in TA98 plus S-9 and TCPO, an epoxide hydratase inhibitor (Glatt et al., 1983).

Endrin exposure of primary rat or hamster hepatocytes did not result in increased unscheduled DNA synthesis (Probst et al., 1981; Williams, 1980). This nonreplicative DNA synthesis is regarded as an indicator of repair of DNA damage. Endrin (as well as DDT, mirex, kepone, hexachlorocyclopentadiene, heptachlor and chlordane) produced no increases over control numbers

of mutants at the hypoxanthine-guanine phosphoribosyl transferase (HGPRT) locus when tested in adult rat liver epithelial cells (Williams, 1980; Telang et al., 1981). Genotoxicity was not elicited by a variety of organochlorine pesticides including endrin tested in vitro in a hepatocyte primary culture DNA repair assay using hepatocytes from male Fischer F344 rats (300-375 g), CD-1 mice (25-35 g) and Syrian hamsters (85-130 g) (Maslansky and Williams, 1981). The potent procarcinogen, dimethylbenzanthracene, was the positive control and DMSO was the solvent control. The lack of endrin-induced genotoxicity agrees with the negative mutagenicity in sensitive microbial assays.

Adult Drosophila were exposed to endrin by abdominal injection, and the Muller-5 test for recessive lethal mutation on the X-chromosome was done. The authors noted no positive responses for endrin or any other chlorinated pesticide tested (Benes, 1969).

In an abstract, Grant (1973) reported that among a number of organochlorine pesticides, endrin, aldrin, chlordane, dieldrin, DDT, heptachlor and lindane, all caused chromosome breakage. The organisms and dosage routes were not described. Dikshith and Datta (1973) reported the effects of endrin on rat chromosomes. Male albino rats (200-250 g), treated intratesticularly with 0.25 mg endrin (in saline) per testis and sacrificed 10 days after dosing, exhibited chromosomal aberrations in germinal tissue. Abnormalities included breaks, fragments, ring formation, stickiness and chromatin bridges.

Endrin, 10^{-4}, 10^{-5} and 10^{-6} M, did not significantly affect sister-chromatid exchange frequencies in both activated and nonactivated

human lymphoid cells of the LAZ-007 cell line over 48 hours (Sobti et al., 1983). However, sister-chromatid exchange frequencies were significantly elevated in 15 central mud minnows per exposure following exposure of 5.4×10^{-12} to 5.4×10^{-9} M endrin in aquaria water for 2 weeks (Vigfusson et al., 1983).

Carcinogenicity

Endrin has been examined for carcinogenicity in mice (B6C3F1, C57B1/6J, C3D2F1/J and C3HF strains), rats (Osborne-Mendel, Sprague-Dawley), and dogs (beagle and mixed breeds). Reuber (1979) has strongly claimed carcinogenicity for rats, and less strongly for other animal species; however evidence accumulated to date remains somewhat conflicting since results have been negative for most studies. In studying mice and dogs, clear conclusions have been much more difficult to reach, owing to toxicity problems and the inadequate numbers in most investigations. The following studies are summarized in Table V-10.

The first study of endrin carcinogenicity was conducted by Treon et al. (1955). Endrin was administered to 28-day-old rats, 20 males and 20 females/group, in doses of 0, 1, 5, 25, 50 or 100 ppm endrin in the feed for 106 weeks. The 100 ppm dose approximated 10 mg/kg bw/day. Doses $\geq$25 ppm for females and $\geq$50 ppm for males resulted in significant mortality by 106 weeks so that few animals remained at these higher doses for pathological examination. Signs of overt toxicity (hypersensitivity to external stimuli, or occurrence of convulsions) were not evoked at doses $\leq$25 ppm. The authors reported that the incidence of neoplasia was no greater among experimental animals than among controls in the tissues studied (liver, kidney, brain,

TABLE V-10

Negative Studies of the Carcinogenic Potential of Endrin

Animal	Strain	No. in Group	Sex	Route	Carrier	Doses (ppm feed)	Study Duration (weeks)	Malignancy Information	Reference
Rat	Carworth	20 20	M F	oral (feed)	95% ethanol	0, 1, 5, 25, 50, 100	106	No excess	Treon et al., 1955
	Osborne-Mendel	50[a] 50[a]	M F	oral (feed)	corn oil	0, 1, 3, 6 (10 weeks) then 0, 2, 6, 12 ppm	116	Not considered carcinogenic	Deichmann et al., 1970
	Osborne-Mendel	50[b] 50[b]	M F	oral (feed, corn oil)	acetone	0, 2.5, 5.0 0, 3.0, 6.0	114 (80 weeks exposure)	Not carcinogenic	NCI, 1979
Mice	C57B1/6J	100 100	M F	oral (feed)	95% ethanol	0, 0.3, 3.0	78	No excess	Witherup et al., 1970
	C3B2F1/J	100 100	M F	oral (feed)	95% ethanol	0, 0.3, 3.0	72	Not carcinogenic	Witherup et al., 1970
	B6C3F1	50[b] 50[b]	M F	oral (feed, corn oil)	acetone	0, 1.6, 3.2 0, 2.5, 5.0	90 (80 weeks exposure)	Not carcinogenic	NCI, 1979

[a]Control number was 100

[b]Control number was 10. Data from 40 pooled controls from other studies added for statistical analyses.

NR - Not reported

heart, adrenal gland, spleen, skin, lung, and other unidentified tissues). No primary data were presented. Subsequent independent assessment of histological specimens led to the report (Reuber, 1979) that one animal ingesting 25 ppm had a carcinoma of the pituitary and one ingesting 50 ppm a bronchogenic carcinoma. No malignancies were originally reported in untreated rats although these (and endrin-treated animals) were later reported to have developed benign tumors of the breast and reticulum sarcomas.

In addition to the above, three independent studies were conducted with the same species (rats, Osborne-Mendel) under similar conditions. Deichmann et al. (1970) found that animals ingesting endrin dissolved in corn oil and admixed with ground Purina chow developed malignant tumors; however, similar incidences occurred in control animals. In this study, Osborne-Mendel weanling rats, 50 male and 50 female per treatment and 100 male and 100 female per control group were administered 1, 3 or 6 ppm endrin in the feed for 10 weeks and then twice those concentrations until sacrifice, the time of which varied considerably (5-29 months). Male animals treated with final doses of 2, 6 or 12 ppm showed 15, 9 and 24% incidences, respectively, of malignant tumors, compared with 18% in controls. In females the corresponding incidence of malignancies was 21, 11 and 22%, with 24% in control animals. The predominant tumor type in both sexes in all groups was malignant lymphoma. In this study excess cancer incidence in animals ingesting endrin was not reported in the liver, endocrine organs or reproductive tissues, as was observed in the previous studies. The authors concluded that endrin fed for a lifetime to albino rats was neither tumorigenic nor carcinogenic.

In a second Osborne-Mendel rat study reported by Reuber (1978), 22-day-old male and female rats, 24/group, were fed 0, 0.1, 1.0, 5, 10 and 25 ppm

endrin admixed in corn oil with the diet (1%) for 104 weeks. Owing to high and early mortality in the highest concentration group, additional groups of animals ingesting this concentration were subsequently established. Some of the tissues studied on sacrifice were lung, spleen, kidney, heart, liver, pancreas, stomach, small intestine, colon, kidney, adrenals, thyroid, ovary, leg muscle, leg bone, bone marrow, bladder and prostate. In male rats, endrin induced hyperplastic nodules in the liver. For both nodules and "malignant lesions" (defined as the sum of carcinomas and sarcomas), endrin appeared most active at a dose of 0.1 ppm. The tabulated data were often confusing. The incidence of malignant hepatic neoplasia in males and females was relatively low (Tables V-11 and V-12). No malignant tumors in the liver were observed in control animals of either sex. In addition to developing liver lesions, endrin-treated rats of both sexes developed neoplasms at a number of other sites. In males these included reticulum cell sarcomas of the lungs and lymph nodes and some rare malignant tumors, as well as carcinomas of the thyroid and renal cortex. The observations showed no preferred cancer site (greater than two instances) although frequencies never exceeded 13% for a specific site at a given dose. In females, carcinomas and leiomyosarcomas of the mammary gland, stromal cell sarcomas of the uterine endometrium, reticulum cell sarcoma of the lung and hepatic Kupffer cell sarcoma were observed (see Table V-12). The preferred cancer sites in this study were the mammary gland, the thyroid and the uterus, in that order. On the basis of the above findings, the author concluded that endrin was a carcinogen. The data appear more conclusive for female rats than for male rats. Doses below 5 mg/kg appeared to elicit few overt signs of toxicity in the animals. Inherent difficulties are encountered when interpreting Reuber's (1978) report. Statistics were based on

TABLE V-11

Incidence of Malignant Tumors in Male Rats Ingesting Endrin[a]

Endrin Concentration (ppm feed)	No. Animals Examined	Liver		Lung	Mammary Gland		Other		Total Malignant Tumors
		Carcinoma	Sarcoma	Sarcoma	Carcinoma	Sarcoma	Carcinoma	Sarcoma	
0	15	0	0	0	0	0	0	0	0
0.1	16	2	0	1	0	1	4[b]	3[c]	11
1	18	0	0	0	0	1	1[d]	1[e]	3
5	18	0	0	0	1	0	0	0	1
10	20	1	1	0	0	1	0	1[f]	4
25	19	1	0	1	0	0	1[g]	2[h]	5

[a]Source: Reuber, 1978

[b]Two thyroid, adenocarcinoma (site unknown) and adrenal cortex

[c]Two in lymph nodes and one in the stomach

[d]Stomach

[e]Kidney

[f]Hemangioendothelial

[g]Thyroid

[h]Lymph node and osteogenic

TABLE V-12

Incidence of Malignant Tumors in Female Rats Ingesting Endrin[a]

Endrin Concentration (ppm feed)	No. Animals Examined	Liver		Lung Sarcoma	Mammary Gland		Other		Total Malignant Tumors
		Carcinoma	Sarcoma		Carcinoma	Sarcoma	Carcinoma	Sarcoma	
0	23	0	0	0	6	1	2[b]	0	9
0.1	23	0	1	0	10	2	0	1[c]	14
1	23	0	0	1	14	0	2[d]	1[c]	18
5	20	1	0	1	13	0	0	0	15
10	18	0	1	0	8	1	1[e]	0	11
25	19	1	0	0	1	2	5[f]	1[c]	10

[a]Source: Reuber, 1978

[b]Papillary adenocarcinoma, site unknown

[c]Uterus

[d]Thyroid and colon

[e]Adrenal cortex

[f]Four in thyroid and one in the adrenal cortex

the number of animals with malignant tumors. From the data, the reader cannot justify the numbers reported in the text; also one animal may develop more than one lesion.

In a study by NCI (1979), 35-day-old male Osborne-Mendel rats were fed a diet incorporating endrin initially dissolved in acetone to a level of 2.5 or 5.0 ppm diet. Females (50) were fed a diet containing 0, 3.0 or 6.0 ppm technical grade endrin for 80 weeks and surviving animals were sacrificed at 111-114 weeks. There were 10 control rats of each sex. The tissues utilized for histopathology were the following: skin, lungs and bronchi, trachea, bone and bone marrow, spleen, lymph nodes, heart, salivary gland, liver, pancreas, stomach, intestines, kidneys, bladder, pituitary, adrenal, thyroid, parathyroid, mammary gland, prostate or uterus, testis or ovary and brain. Comparing incidences of malignant tumor formation in individual tissues between control and treated animals, the authors of the study concluded that endrin was not carcinogenic in either sex. Malignant tumors that were observed in two or more male animals per group (4% incidence in treated animals) were hematoma of the kidney (4% at the high dose), adrenal carcinoma (4% at the low dose), islet cell carcinoma of the pancreas (6% at the high dose) and fibrous histocytoma (4% at the high dose). The increased incidence of islet cell carcinomas in the high dose group was statistically significant compared with controls applying the Cochran-Armitage, but not the Fisher exact test. Cancer incidence at other sites was not statistically significant. In female animals, two or more animals had malignancies in the pituitary (4% at the low dose) and adrenal (14% at the low and 6% at the high dose but 11% in controls). None of these increased incidences were statistically significant, but the increases of pituitary

adenomas, and combined increased incidences of adenomas and carcinomas of the adrenal were significant. Data interpretation in this study was complicated by the use of only 10 matched controls per gender.

The opposite conclusions to those made above were reached, however, by a later reviewer of this study (Reuber, 1979) after re-examination of the pathology slides, and based on comparisons of cumulated cancer incidences at different sites, i.e., endocrine and reproductive tissues, or control vs. treated groups. In males and females, increased cancer incidence compared with controls was thereby observed for both doses of endrin for endocrine organs (pituitary and adrenal glands) and the liver. In addition, females showed an increase in incidence of malignant tumors of the ovary, uterus and mammary gland. In males, the numbers of animals with malignant tumors (carcinomas and sarcomas) were 67% and 64% at the low and high dose, respectively, compared with 10% in the control groups. In females, the corresponding values were 74 and 82% compared with 40% in the control groups. In female rats, 74 and 67% of animals ingesting the low and high dose, respectively, had carcinomas of the endocrine organs, compared with 10% of untreated animals. In male rats, the corresponding incidences were 36 and 42% in treated and 10% in control animals. Statistically significant increases in carcinoma incidence in the pituitary (43% low-dose, 30% high-dose, 0% control) and adrenal glands (33, 31 and 0%, respectively) were observed in female rats at both endrin doses (Table V-13), and in the pituitary gland of males at the lower dose (29% compared with 0% in controls) (Table V-14). In female rats, 40 and 28% developed malignant tumors of the reproductive system at the low and high endrin doses, respectively, compared with 10% of control animals (see Table V-13). Hepatocellular carcinoma

TABLE V-13

Number of Osborne-Mendel Female Rats with Carcinomas[a]

Dose (ppm endrin in the diet)	Number Examined	Endocrine	Pituitary	Adrenal	Reproductive System	Liver	Total No. with Carcinomas
0 matched	10	1 (10%)[b]	0	0	1 (10%)	0	1 (10%)
Pooled	49	11 (23%)	6 (12%)	0	3 (6%)	0	5 (10%)
2.78	46	34 (74%)[c]	20 (43%)[d]	15 (33%)[e]	17 (40%)[f]	1 (2%)	29 (63%)[g]
5.56	46	31 (67%)[h]	14 (30%)[i]	14 (31%)[j]	13 (28%)[k]	4 (9%)	35 (76%)[l]
Low + high dose	92	65 (71%)[m]	34 (37%)[n]	29 (32%)[j]	30 (33%)[f]	5 (5%)	64 (70%)

[a]Sources: NCI, 1979; Reuber, 1979

[b]Percentage of animals examined with tumor of tissue specified

[c]$p<10^{-3}$, one-sided test

[d]$p<10^{-8}$, one-sided test

[e]$p<5\times10^{-6}$, one-sided test

[f]$p<3\times10^{-4}$, one-sided test

[g]$p = 2\times10^{-3}$, one-sided test

[h]$p<10^{-8}$, one-sided test

[i]$p = 2.7\times10^{-2}$, one-sided test

[j]$p<1.2\times10^{-3}$, one-sided test

[k]$p = 3.4\times10^{-3}$, one-sided test

[l]$p = 1.8\times10^{-2}$, one-sided test

[m]$p<10^{-7}$, one-sided test

[n]$p = 7\times10^{-4}$, one-sided test

TABLE V-14

Number of Osborne-Mendel Male Rats with Carcinomas[a]

Dose (ppm endrin in the diet)	Number Examined[b]	Endocrine	Pituitary	Adrenal	Liver	Total No. with Carcinomas
0 matched	10	1 (10%)	0	1 (10%)	0	1 (10%)
Pooled	49	5 (10%)	3 (6%)	1 (2%)	0	4 (8%)
2.5	45	17 (36%)	13 (29%)[c]	1 (2%)	1 (2%)	24 (53%)[d]
5.0	45	19 (42%)	7 (16%)	4 (9%)	2 (4%)	22 (49%)[d]
Low + high dose	90	36 (40%)	30 (22%)[e]	5 (6%)	3 (3%)	44 (49%)[d]

[a]Sources: NCI, 1979; Reuber, 1979

[b]Percentage of number examined

[c]p = 0.003, one-sided test

[d]p<0.000,009) one-sided test

[e]p = 0.001, one-sided test

incidences observed in low and high-dose endrin-treated female rats, compared with controls, were 2, 9 and 0%, respectively, but were not statistically significant. The corresponding figures for male rats were 2, 4 and 0%, respectively and also not significant. Female rats therefore appeared to be more susceptible than male rats at the various target sites mentioned above. The incidences of benign tumors in male or female rats were not reported to be significantly different from values in controls or any endrin dose (Tables V-15 and V-16).

Re-evaluation of the tissue sections by Reuber (1979) thus has resulted in dramatically increased tumor incidences in both control and exposed groups. Reuber's criteria for classifying tissues as tumorigenic appear to differ from those of other investigators. Until differences between Reuber's criteria and those of others is resolved it will be difficult to draw conclusions from his findings.

In a study with mice (Witherup et al., 1970), males and females of the C57B1/6J and C3D2F1/J strains ingested Purina mouse chow admixed with endrin dissolved in 95% ethanol to give concentrations of 0, 0.3 or 3.0 ppm in the diet. For both strains, 100 males and 100 females constituted each treatment group and two control groups. Tissues analyzed histopathologically were the following: heart, lungs, liver, spleen, kidneys, GI tract, lymph nodes, urinary bladder, gonads, pancreas, thyroid, thymus, adrenals, brain, pituitary, spinal cord, eyes, bone marrow, nasal passages, skin and peripheral blood smears. In this lifetime study (up to 119 weeks) the overall incidence of neoplasms found in each strain and diet group was not influenced by the content of endrin in the daily diet. The authors concluded

TABLE V-15

Number of Osborne-Mendel Female Rats with Benign Tumors[a]

Dose (ppm endrin in the diet)	Number Examined	Endocrine	Pituitary	Adrenal	Reproductive System	Liver	Total[b]
0 matched	10	4 (40%)	1 (10%)	2 (20%)	0	0	3 (30%)
Pooled	49	14 (30%)	6 (12%)	3 (6%)	4 (8%)	1 (2%)	14 (29%)
2.78	46	6 (13%)	3 (7%)	8 (18%)	9 (20%)	9 (20%)	2 (4%)
5.56	46	10 (22%)	7 (15%)	13 (28%)	3 (7%)	14 (30%)	5 (11%)
Low + high dose	92	16 (17%)	10 (11%)	21 (23%)	12 (13%)	23 (25%)	7 (8%)

[a]Sources: NCI, 1979; Reuber, 1979

[b]Total number of animals bearing benign tumors

TABLE V-16

Number of Osborne-Mendel Male Rats Ingesting Endrin with Benign Tumors[a]

Dose (ppm endrin in the diet)	Number Examined	Endocrine[b]	Pituitary[b]	Adrenal[b]	Liver[c]	Total[d]
0 matched	10	2 (20%)[e]	1 (10%)	2 (20%)	1 (10%)	5 (50%)
Pooled	49	14 (49%)	8 (16%)	3 (6%)	4 (8%)	17 (49%)
2.5	45	19 (49%)	5 (11%)	12 (27%)	13 (29%)	10 (22%)
5	45	16 (36%)	10 (22%)	3 (11%)	6 (13%)	9 (20%)
Low + high dose	90	35 (39%)	15 (17%)	15 (17%)	19 (21%)	19 (21%)

[a]Sources: NCI, 1979; Reuber, 1979

[b]Adenomas

[c]Hyperplastic nodules

[d]Total number of animals bearing benign tumors

[e]Statistical analysis (one-sided t test) revealed no statistical significance for any experimental group compared with controls

that when endrin was added to the daily diet of C57Bl/6J inbred mice and C3D2F1/J hybrid mice in the amounts of 3.0 and 0.3 ppm, the pesticide was not carcinogenic to the animals. Reuber in his independent analysis of the slides of this study came to the opposite conclusion for the 0.3 ppm dose (Reuber, 1979).

In an NCI study (1979), female B6C3F1 mice 35 days of age ingested endrin admixed with the diet for 80 weeks at concentrations of 0, 2.5 or 5.0 ppm and 0, 1.6 and 3.2 ppm for males. All surviving mice were killed at 90 or 91 weeks. Each treated group contained 50 animals and each control group 10 animals. In male mice, two or more animals per treated group had hepatocellular carcinoma (16% at the high dose) compared with one (10%) in the control group. A corresponding number of mice with malignancies was not observed in females. Significant incidences for any site in either sex were not observed. Because of the high mortality in the treated groups, histological examination was limited to only one section of the liver and since the numbers of control animals were only 10, an independent reviewer stated (Reuber, 1979) that no conclusions could be reached from this study.

Four bioassays for carcinogenicity were done in rats and three were on mice. These bioassays were done at different institutions, namely Food and Drug Administration (FDA) during 1955-1957 as reevaluated by Reuber (1978), the National Cancer Institute (NCI, 1979), the University of Cincinnati (Kettering Laboratory) (Witherup et al., 1970), and the University of Miami (Deichmann et al., 1970). All the bioassays on rats and mice were reported as negative by those authors. There were, however, deficiencies in the studies which is explained below, which render the findings inadequate to properly assess the carcinogenic potential in animal test systems.

In the FDA rat (Osborne-Mendel) study the animals at highest dose (25 ppm) did not survive well and additional animals were started in that dose. The remainder of the groups lived for the programmed two year study. It also appeared that every animal came to autopsy and not all sections from grossly observed animals were studied microscopically. In spite of some deficiencies there were a sufficient number of animals in the studies particularly in the aspect of liver and kidney, in all experimental and control groups (Reuber, 1978). This study was originally reported as negative. It was reevaluated by a panel of pathologist whose report was referenced in a CAG document (U.S. EPA, 1978). One pathologist considered the finding positive (Table V-11 and V-12) but did not provide slide by slide tabulation of his findings and did not distinguish between primary and/or metastatic tumors in the liver. A second pathologist whose original finding indicated that the study was negative, provided slide by slide tabulation of diagnosis which was confirmed by the panel review. In the FDA mice (C3HF1) study the survival was very poor in both control and experimental group.

The Kettering study used two strains of mice (C57B1/6J and C3D2F1/J). The C57B1/6J strain exhibited mainly leukemia and liver tumors with low incidence. These tumors appeared equally in the experimental and control groups and the latent period of tumor formation was similar. But in the C3D2F1/J strain, the incidence of liver tumors in the dose group (3 ppm) was slightly higher in the female than in controls and the latent period of tumor formation was decreased than other groups (Witherup et al., 1970).

The NCI bioassay was done in Osborne-Mendel rats and B6C3F1 mice. These studies were reported as negative. A primary reviewer for NCI noted that the negative findings could be a reflection of the high toxicity of endrin, which only permitted the administration of relatively low chronic dosages. Furthermore, the reviewer observed that an accidental overdose among low dose male mice resulted in early death of several animals in this treatment group and the study was marred by a small (10) if matched controls; however, this deficiency was compensated by the use of pooled controls (see Table V-17). There were significant increases in hemangioma in low dose male rats, adrenal adenoma and/or carcinoma in high dose in males, pituitary adenomas in the high dose female, adrenal adenoma and/or carcinoma in low dose female rats as compared to the pooled controls. Although, the islet-cell carcinoma in male rats had a significant trend but no statistical significance at either dose group, the NCI concluded that these tumors could not be clearly considered related to the adminstration of endrin (NCI, 1979). Although NCI concluded that the bioassays of endrin were not carcinogenic, the responses noted above can not be totally ignored.

Endrin was not mutagenic in any bacterial strains but exhibited chromosomal aberration in germinal tissues. Endrin is also structurally related to aldrin, dieldrin, chlordane, chlorendic acid and heptachlor which are known to carcinogenic in animals. The available cancer epidemiologic data involving several studies is inadequate to demonstrate or refute a carcinogenic hazard because of study design limitations and/or mixed exposures. Using the criteria in the U.S. EPA (1986) guidelines for classification of carcinogens, endrin is most appropriately classified in Group D; i.e. a chemical for which there is inadequate evidence to assess the potential carcinogenicity for humans. This classification is based on

TABLE V-17

Analysis of Incidence of Primary Tumors in Osborne-Mendel rats fed Endrin in the diet

Sex	Site	Pooled Control	Matched Control	Low Dose	High Dose
Male	Hemangioma	0/49(0)	0/10(0)	5/46(11)	3/47(6)
	P Values+	NS	NS	P=0.024*	NS
	Adrenal Carcinoma	0/44(0)	0/9(0)	2/46(4)	0/44(0)
	P Values+	NS	NS	NS	NS
	Adrenal-Adenoma or Carcinoma	2/44(5)	2/9(22)	4/46(9)	8/44(18)
	P Values+	P=0.028	NS	NS	P=0.045*
	Pancreatic Islet Cell Carcinoma	0/46(0) P=Values 0.039	0/10	0/45	3/47(6)
Female	Pituitary-Adenoma	4/44(9)	2/7(29)	11/47(23)	13/45(29)
	P Values+	P=0.015	NS	NS	P=0.016*
	Adrenal-Carcinoma	2/46(4)	1/9(11)	7/49(14)	3/47(6)
	P Values+	NS	NS	NS	NS
	Adrenal: Adenoma or Carcinoma	4/46/(9)	3/9(33)	14/49(33)	7/47(15)
	P Values	NS	P=0.041	P=0.004*	NS

Source: NCI, 1979

NS = Non significant
* = Significant with respect to pooled control
+ = Beneath the incidence of tumors in the control groups is the probability level for the Cochran Armitage test when P <0.05, otherwise not significant (NS) is indicated.

the nonpositive but suggestive results in some of the animal studies. The negative conclusions as reported by the study authors of the four bioassays do not support a Group E classification, because of the inadequacies of the studies. A Group D weight-of-evidence is thought to be the best classification until additional studies can be done to clarify the situation.

Later studies suggested that endrin or its rapidly-produced metabolites might act as promoters, although some have produced conflicting evidence. Ito et al. (1980) showed that endrin (25 ppm in diet) promotes the development of preneoplastic changes in rat liver after initiation with N-nitrosodiethylamine or N-2-fluorenylacetamide. Maslansky and Williams (1981) showed that endrin (10^{-8} to 10^{-4} M) was not genotoxic in the hepatocyte primary culture (HPC)/DNA repair assay utilizing hepatocytes from male Fischer F344 rats, male CD-1 mice and male Syrian hamsters. DNA repair was observed in response to a positive control in all three systems. Thus, the mechanism of the weak hepatocarcinogenicity of endrin may reflect an epigenetic mechanism, probably involving a promotional rather than a genotoxic effect. Kurata et al. (1982) demonstrated that endrin above 5 mg/ℓ in the HGPRT system using wild-type 6-thioguanine-sensitive V79 Chinese hamster cells and mutant 6-thioguanine-resistant cells inhibited metabolic cooperation (reciprocal exchange of material between cells in contact), as do recognized tumor promoters. A concentration of 20 mg endrin/ℓ caused 80% inhibition whereas 10 mg endrin/ℓ elicited ~25% inhibition. On the other hand, Miller et al. (1981), in an abstract, reported that endrin (0-40 μM) did not change the frequency of transformation of C3H 10T1/2 cells by 3-methylcholanthrene or benzo(a)pyrene (0-10 mg/ℓ) after a 3-hour incubation.

Summary

The acute oral LD_{50} of endrin given to mammals by oral gavage ranged from 2.3 mg/kg to 43.4 mg/kg bw (see Table V-1). The LD_{50} following dermal exposures ranged from 10.9-92 mg/kg bw and was vehicle-dependent. A lone inhalation study indicated that 130 seven-hour exposures to 0.36 ppm endrin "vapor" were not fatal to rats, hamsters and guinea pigs; however, two of four rabbits died after 188 exposures and one of three mice died after 107 exposures (see Table V-5). Young animals appeared to be more sensitive to dietary endrin than older animals (see Table V-3). Metabolites of endrin were more acutely toxic in rats than the parent compound (see Table V-2), with 12-ketoendrin being the most toxic in both male and female rats and having acute oral LD_{50}s of 1.1 and 0.8 mg/kg bw, respectively. The acute oral LD_{50} values for endrin itself were 5.6 and 5.3 mg/kg bw, respectively, in this same study.

Short-term endrin exposures reportedly elicit CNS effects, including convulsions (Emerson et al., 1964), reduced locomotor activity (Kavlock et al., 1981), and altered EEG recordings (Revzin, 1968). Reported hepatic effects include elevated liver weight, lipids and trigycerides, and changes in cytochrome P-450 content and P-450-mediated enzyme activities (Hartgrove et al., 1977; Pawar and Kachole, 1978; Borady et al., 1983; Mostafa et al., 1983). Endrin also elicits changes in cardiac output, blood pressure, hemolysis and other hematological parameters (Emerson et al., 1964; Hinshaw et al., 1966; Reins et al., 1966).

Longer exposure to endrin elicits mortality, depressed weight gain or weight loss, and elevated organ-to-body weight ratios (Treon et al., 1955; Nelson et al., 1956; Chernoff et al., 1979; Kavlock et al., 1981). Abnormal

EEG patterns, elevated serum alkaline phosphatase, reduced plasma specific gravity and intermittent blindness have also been reported, as well as altered hepatobiliary function, following endrin exposure ranging from 2 weeks to several months (Nelson et al., 1956; Speck and Maaske, 1958; Young and Mehendale, 1986).

Chronic endrin exposure causes mortality or early appearance of clinical signs associated with aging (Treon et al., 1955; Deichmann et al., 1970; NCI, 1979). Organ-specific effects reported include elevated organ-to-body weight ratios, lung congestion and hemmorhage, swelling of renal tubules, and chronic interstitial nephritis (Treon et al., 1955; Diechmann et al., 1970; Reuber, 1978). Prenatal exposure to endrin elicited terata, mortality and/or reduced neonatal weight or weight gain in offspring of hamsters and mice. These outcomes were not consistently observed in rats. However, evidence of altered behavioral development, measured by maze locomotor activity, was observed in offspring of rats, mice and hamsters following prenatal endrin exposure.

Endrin was not mutagenic in microbial systems with or without metabolic activation, and endrin exposure did not significantly affect sister-chromatid exchange frequencies in a human lymphoid cell line. However, a significant elevation of sister-chromatid exchange frequency was observed in minnows following endrin exposure.

Conclusions concerning endrin carcinogenicity have not been entirely consistent. Endrin was determined to lack carcinogenicity in Osborne-Mendel rats and B6C3F1 mice under the conditions of an NCI (1979) bioassay. This conclusion is consistent with those of three previously reported studies

concerning endrin carcinogenicity in rats and mice. In contrast, Reuber (1979) has concluded that an increased tumor incidence is elicited by chronic endrin exposure, based on his independent evaluation of the NCI (1979) bioassay tissue sections, and on a separate study (Reuber, 1978).

VI. HEALTH EFFECTS IN HUMANS

Acute Toxicity

In September 1978, the U.S. Department of Health and Human Services issued an occupational health guideline for endrin (U.S. DHHS, 1978). Symptoms of overexposure were described as follows:

> Exposure to endrin may cause sudden convulsions which may occur from 30 minutes to 10 hours after exposure. Headache, dizziness, sleepiness, weakness and loss of appetite may be present for 2-4 weeks following this exposure. A number of deaths have occurred from swallowing endrin. In less severe cases of endrin poisoning, the complaints include headache, dizziness, abdominal discomfort, nausea, vomiting, insomnia, agitation and mental confusion.
>
> Electroencephalograms may show dysrhythmic changes which frequently precede convulsions; withdrawal from exposure usually results in a normal, electroencephalogram within 1-6 months. In most cases, recovery is rapid, but headache, dizziness, lethargy, weakness and anorexia may persist for 2-4 weeks.

Accidental and Intentional Poisonings. Several incidents of endrin poisoning from contaminated flour have been reported in the literature. In Wales, bread made from flour contaminated with endrin during shipment in a railway car resulted in 59 poisoning cases with no deaths in 1956. The bread contained up to 150 mg endrin/kg bread and the smallest acute dosage to elicit serious effects was calculated to be 0.2 mg/kg bw (Davies and Lewis, 1956).

In 1967, explosive outbreaks of acute endrin poisoning occurred in Doha, Qatar and Hofuf in Saudia Arabia as a result of the ingestion of food prepared with endrin-contaminated flour (Weeks, 1967; Curley et al., 1970). Twenty-six persons died and 874 were hospitalized. Many others were probably poisoned to a lesser degree but did not seek medical aid. The concentration of endrin in bread eaten by patients ranged from 48-1807 mg/kg

bread. Flour used to made the bread contained 2153-3367 mg endrin/kg flour. Coble et al. (1967) reported acute endrin poisoning with sudden convulsions in three Egyptians, following ingestion of bread made with contaminated flour. In these cases, recovery was spontaneous. A serum endrin concentration of 0.053 ppm was reported for one of these patients 5 hours after its apparent consumption in contaminated bread, and 30 minutes after a convulsion was observed.

In the Punjab province of Pakistan between July 14 and September 26, 1984 there were 194 cases of probable endrin poisoning (Anonymous, 1984; Rowley et al., 1987). Of the 194 cases, 19 (70%) deaths occurred among persons between 1 and 9 years of age. Males and females were equally affected. Symptoms included sudden collapse, "bilateral jerking of the upper extremities followed by general tonic, clonic contractions and frothing and vomiting". Older patients reported headaches and/or nausea and minor muscular spasms about one-half hour before collapsing. Repeated attacks were associated with hypoxia, pulmonary congestion and death. Serum levels from 12 of 18 patients with convulsions had measurable levels of endrin. Values from the 12 patients ranged from 0.3-254 ppb with a mean of 30.10 ppb. No endrin was detected in the urine of these 12 patients (Rowley et al., 1987). A case-control study did not implicate causative food or environmental factors. However, a common food product, sugar, may have been contaminated. One composite sugar sample taken from the homes of three patients had endrin levels of 0.04 ppm (Rowley et al., 1987). The presence of endrin in 57% of patients with seizures tested in Pakistan suggests that endrin was the cause of this outbreak (Anonymous, 1984; Rowley et al., 1987).

Cases of fatal endrin poisoning have been reported from intentional ingestion and accidental ingestion. Tewari and Sharma (1978) reported 11 fatal poisonings; the time periods from administration of the pesticide (route not known in seven cases) to death ranged from 1-6 hours. Endrin ingestion with milk or alcohol appeared to increase toxicity as death occurred within an hour or two. Increased toxicity was attributed by the authors to more rapid absorption through the GI tract.

A pediatric hospital in Mexico reported endrin intoxication in 33 patients ranging in age from 1-16 years (Montoya Cabrera et al., 1982). Accidental ingestion accounted for 22 cases, 7 were suicides and 4 were attributed to criminal intent. The accidental poisonings resulted from the uncontrolled use of endrin in the home as a rodenticide.

A 19-year-old male who attempted suicide by ingestion of endrin developed severe pulmonary edema as well as CNS involvement. Pulmonary edema was thought to be due to chemical pneumonitis and aspiration pneumonia. The authors believed that the use of PEEP (positive end-expiratory pressure) up to 28 cm H_2O in treatment of the pulmonary edema contributed to the patient's complete recovery (Jedeikin et al., 1979).

Effects of Occupational Exposures. No illnesses were noted in seasonal workers dusting potatoes with 1% endrin dust at a calculated dermal exposure of 2.0 mg/kg bw/day in combination with a calculated respiratory exposure of 0.044 mg/kg bw/day (Wolfe et al., 1963). Also, no illnesses were noted when endrin was applied at 544-634 kg/acre as an emulsifiable

concentrate for mice control at a calculated dermal dose of 0.28 mg/kg/day in combination with a calculated respiratory exposure of 0.0011 mg/kg bw/day (Wolfe et al., 1963).

Immunology. Thirteen pesticides including endrin were tested for their in vitro effects on human lymphocyte mitogenic responses to phytohemaglutinin and neutrophil chemotaxis (Lee et al., 1979; Park and Lee, 1980). This study was undertaken in an effort to clarify the immunosuppressive effects of many pesticides. Endrin inhibited the lymphocyte response in whole blood 11.5% and 14.2% in mononuclear cells. Neutrophil chemotaxis was inhibited 27% (77±4 vs. 105±10 cells per high power field in control cultures). In each case, inhibition was not reported to be statistically significant. All pesticides tested inhibited lymphocyte responses to some degree, and the authors suggested that the immunosuppressive effect of pesticides could be a direct effect of those chemicals on leukocytes.

Epidemiological Studies. Jager (1970) reported an epidemiological study conducted on 826 male workers at the insecticide plant of Shell Nederland Chemie located at Pernis, Netherlands. A unit for the production of endrin was begun in February 1957. During the first 2 years of plant operation seven cases of endrin intoxication had occurred and were accompanied by convulsive seizures. All were due to acute overexposure either following an accident or to obvious neglect of precautions. Normal recovery was rapid, usually within 1-3 days.

Concentrations of endrin in the blood of 45 operators from the endrin plant were determined at least once a year from 1964-1968. The threshold

level of endrin in the blood below which no sign or symptoms of intoxication were seen was 0.050-0.100 µg/mL. The half-life of endrin in the blood, and thus in the body, was estimated to be ~24 hours. Medical files and routine medical examinations revealed no abnormalities other than those that would be expected in any group of 233 long-term workers (4-13.3 years exposure). Results of determination of alkaline phosphatase, SGOT, SGPT, LDH, total serum proteins, and the spectra of serum proteins did not show any changes that could be correlated with the influence of the degree or duration of exposure to these insecticides on these parameters. In all cases of intoxication characterized by typical EEG changes, EEG patterns returned to normal. In the study of the parameters of enzyme induction, the data showed that occupational exposure in endrin manufacturing may cause enzyme induction in hydroxylating enzyme systems although this response appeared not to affect the health of the workers. It was not known whether endrin or its manufacturing precursors were the causative agents (Jager, 1970).

A follow-up mortality study on 233 of these workers having at least 4 years of exposure by 1970 has recently been reported (Ribbens, 1985). Of these 233 workers who were occupationally exposed to aldrin, dieldrin, endrin and/or Telodrin, 232 were accounted for. The mean and range of exposure durations were 11 and 4-27 years, respectively. These periods, as well as the exposure levels, were considered sufficient for meaningful mortality evaluation. The total mortality of this population was 25, significantly lower than the expected mortality of 38 based on death statistics of Dutch men. Nine of 25 deaths were caused by neoplasms, versus 12 expected cancer deaths; 3/9 neoplasms were lung tumors. The remaining six cases were comprised of six different neoplasms, none of which were liver tumors.

These results were concluded to reveal no evidence for specific carcinogenicity of endrin, aldrin or dieldrin in this exposed population.

Hoogendam et al. (1962, 1965) conducted a parallel study at the same plant. Of the 122 men exposed to all pesticides at the plant, 25 workers had EEG abnormalities (Hoogendam et al., 1962). A worker was accidentally covered with a 50% isodrin solution in xylene. He experienced dizziness and headache and profusely perspired 2 hours later. This worker suffered a typical epileptiform convulsion 6 hours after the exposure, regained consciousness within 10 minutes and rapidly recovered. There is some evidence to suggest that isodrin was partially converted to endrin in the liver of this patient (Brooks, 1969). The EEGs of patients with endrin intoxication showed paroxysms of predominantly bilateral synchronous theta-waves. In the other report (Hoogendam et al., 1965) three endrin workers suffered convulsive intoxications, two being examined for recovery of abnormal EEGs. One was exposed for 1.5 years and the other for 3 years. One recovered in 1 month, and the other in <6 months. The authors suggested that the prevailing exposure in the manufacture of aldrin, dieldrin and endrin did not disturb liver function since the levels of SGOT and SGPT returned to normal in the four workers who initially showed increases.

Ottevanger and Van Sittert (1979) continued the enzyme induction studies of Jager (1970) on 29 endrin workers at the endrin manufacturing plant in Pernis. The D-glucaric acid concentration in urine was considered to be a useful test for enzyme induction. After 7 days of exposure, levels of the metabolite, anti-12-hydroxyendrin, increased (up to 0.360 mg/g creatinine) accompanied by a sharp rise in D-glucaric acid levels. After the long weekend, the anti-12-hydroxyendrin levels decreased, but D-glucaric acid levels

remained above normal. The normal values obtained after a 6-week shutdown and maintenance period indicated that enzyme induction in endrin workers is reversible. A urinary anti-12-hydroxyendrin level of 0.130 mg/g creatinine was considered the threshold level below which enzyme induction does not occur, although exceptions were noted.

Vrij-Standhardt et al. (1979) examined urinary excretion of D-glucaric acid and total porphyrin in endrin workers. The excretion of D-glucaric acid after working was significantly increased compared with excretion after a long weekend and with a control group. The results indicated that D-glucaric acid was a useful test for exposure to endrin, but porphyrin excretion was not.

An epidemiological study was made of 216 patients with contact dermatitis in rural regions of Japan from 1968-1970 (Matsushita et al., 1980). All participants except three were farmers. Exposure occurred mainly from spraying operations. Chlorinated hydrocarbons (BHC and endrin) were thought to be responsible for 9.7% of the cases. Inadequate protection of the spray personnel, poor health conditions and carelessness were largely responsible for the dermatitis.

Wang and Grufferman (1981) performed a case control study of the association between fatal aplastic anemia and occupations entailing pesticide exposure. They found no correlation between use of chlorinated hydrocarbon pesticides, including endrin, and aplastic anemia mortality in the United States from 1950 through 1975.

Ditraglia et al. (1981) conducted a retrospective cohort study to examine the mortality of workers employed in the manufacture of chlordane, heptachlor, DDT and aldrin/dieldrin/endrin. The four plants selected for study are described in Table VI-1. Workers selected for the study had been employed at least 6 months; the personnel in contact with endrin were located at plants 2 and 3, and numbered 305 and 1155, respectively.

The only major category where observed deaths were greater than expected was "nonmalignant respiratory system disease" at Plant 3 (22 observed vs. 10.4 expected: SMR=212) and for "other respiratory diseases" (11 observed vs. 5.2 expected: SMR=213, $p \leq 0.05$). No statistically significant excesses or deficits in mortality for any specific cancer site were noted. In Plant 3 there was a slight excess of cancer of the esophagus (2 observed vs. 0.85 expected), cancer of the rectum (3 observed vs. 1.24 expected), cancer of the liver (2 observed. vs. 0.57 expected), and cancer of the lymphatic and hematopoietic system (6 observed vs. 4.09 expected). There was a deficit for respiratory cancer (7 observed vs. 12.64 expected) at Plant 3. Additional analyses are necessary to determine if an excess in nonmalignant respiratory disease observed at Plant 3 was associated with specific occupational exposure. Since malignant respiratory disease was not reported at Plant 2, which also manufactured endrin, endrin alone probably did not induce the lethal respiratory disease reported at Plant 3 unless exposures were much higher than those at Plant 2. However, Ditraglia et al. (1981) did not report exposure data.

TABLE VI-1

Description of Plants Included in the Study of Manufacturers of Organochlorine (OC) Pesticides*

	Plant 1	Plant 2	Plant 3	Plant 4
Starting date for OC pesticide production	1946	1951	1946	1947
OC pesticides produced	Chlordane	Heptachlor, endrin	Aldrin, dieldrin, endrin	Dichloro-diphenyl-tri-chloroethane (DDT)
Other pesticides produced	None	None	Organo-bromines; organo-phosphates	None
Other chemicals at plant	Chlorine, dicyclo-pentadiene	Chlorine, chlorendic anhydride, hexachloro-cyclopenta-diene, vinyl chloride	Numerous precursors	Tri-chloro-acetaldehyde, sulfuric acid, monochloro-benzene
Location	Illinois	Tennessee	Colorado	California

*Source: Ditraglia et al., 1981

Summary

Exposure to endrin is reported to cause CNS effects, convulsions and death. In less severe poisoning, recovery is usually rapid and there are no permanent effects.

A number of cases of acute poisoning resulting from accidental or intentional ingestion of endrin have been reported. The approximate oral dose producing convulsions is between 0.2 and 0.25 mg/kg bw.

No potential hazard existed during typical dermal or respiratory exposures encountered by seasonal agricultural workers exposed to endrin through dusting and spraying operations.

No fatalities or permanent abnormalities were recorded in a 1970 epidemiological study of 233 workers engaged in the manufacture of chlorinated hydrocarbon insecticides including endrin for more than 4 years. Convulsions and CNS effects were observed in some workers. Exposure did not elicit an elevation in total mortality of these workers through 1985. Occupational exposure in endrin manufacturing may cause enzyme induction in hydroxylating enzyme systems, but this response appeared to be reversible and to have no effect on the health of workers. Anti-12-hydroxyendrin levels excreted in the urine of endrin-exposed workers were correlated with excretion of D-glucaric acid.

No correlation was found between mortality from aplastic anemia and the use of chlorinated pesticides including endrin in the United States from 1950 through 1975, although no exposure data were provided to allow assessment of the importance of endrin in this study.

A mortality study of workers engaged in the manufacture of organochlorine pesticides did not identify a specific cancer risk but further studies were recommended.

VII. MECHANISMS OF TOXICITY

Acute Toxicity

The order of acute oral toxicity to endrin in various adult male species is monkey > rabbit > pheasant = quail > chicken = cattle = dog > hamster > guinea pig = rat. Young animals and female animals are more susceptible than adult males, at least in rats (Treon and Cleveland, 1955). Endrin and its metabolites are quickly eliminated except at grossly high doses, and the total half life varies between 1 and 4 days (see Chapter IV). Doses of >0.2 mg endrin/kg bw can cause convulsions (Jager, 1970); lethality to humans may occur at doses >6 g/person (Reddy et al., 1966).

The unsubstituted methylene group in endrin is rapidly attacked to produce mostly anti- and some syn-12-hydroxyendrin, the former being eliminated as the sulfate in the urine of rabbits, female rats and hens, as the aglycone in the feces of male rats, as the glucuronide in the urine and the feces of humans, and as the free metabolite in the urine of the cow (see Chapter IV). The syn-alcohol is quickly transformed to 12-ketoendrin, which is the most acutely toxic to rats of all endrin derivatives including endrin itself (Bedford et al., 1975a). In fact, associations between lethality and the presence of 12-ketoendrin residues in the brain have been made for rats (Hutson et al., 1975), rat fetuses (Kavlock et al., 1981) and hamster fetuses (Chernoff et al., 1979) but not for birds (Stickel et al., 1979a,b); 12-ketoendrin has been postulated as the ultimate toxicant, at least in rats (Bedford et al., 1975a), hamster fetuses (Chernoff et al., 1979) and rat fetuses (Kavlock et al., 1981).

The CNS is the major target system for acutely administered endrin. Emerson et al. (1964) suggested that endrin-induced hyperexcitability and convulsions were caused by a direct action of endrin on the motor cortex and/or spinal cord. It was further suggested that endrin acted directly on the medulla since the bradycardia that followed endrin exposure preceded pressure increases in the cerebrospinal fluid and sagital venous sinus, which were also elicited by endrin exposure. Walsh and Fink (1972) suggested that the mechanism of acute endrin toxicity involved induction of a biochemical lesion in the CNS, followed by a time-dependent process culminating in toxic manifestations. It was postulated that interference with plasma membrane or mitochondrial ATPase may be involved in the mechanism. However, Mehrotra et al. (1982) reported that although some ATPase activities of rat brain and beef heart were inhibited by cyclodiene pesticides (including endrin) in vitro, these inhibitions could not be easily related to the toxicity of the compounds. For example, endrin was more toxic to rats than aldrin, but ATPase activities were inhibited to a greater extent by aldrin relative to endrin.

A series of more recent studies suggests that mechanism of CNS disturbance and toxicity for endrin are related to interference with gamma-aminobutyric acid (GABA)-mediated functions. The toxic and convulsant potencies in mice of a series of 14 polychlorocycloalkane (PCAA) insecticides, including endrin, were determined and related to their in vivo potencies for inhibiting the mouse brain t-butylbicyclophosphorothionate (TBPS) binding site, which is associated with GABA-regulated chloride transport (Cole and Casida, 1986). Following LD_{50} estimations, male Swiss-Webster mice were administered LD_{50}, $LD_{50}/2$ or $LD_{50}/4$ doses of each compound by intraperitoneal injection. Mice were sacrificed 30 minutes later, brains were

removed and binding of [^{35}S]TBPS to brain membranes was determined. For endrin specifically, the LD_{50} was 8 mg/kg bw, and the percent inhibitions for LD_{50}, $LD_{50}/2$ and $LD_{50}/4$ doses were 77±7, 39±6 and 0%, respectively. These data were consistent with two previous reports suggesting binding of cyclodiene insecticides (including endrin) to the GABA receptor (Lawrence and Casida, 1984; Tanaka et al., 1984; Abalis et al., 1985). It was concluded that the toxicity or convulsant activities of PCAA insecticides were correlated with *in vivo* disruption of the mouse brain TBPS binding site.

Abalis et al. (1986) also reported that a GABA-inducted $^{36}Cl^-$ influx into rat brain microsacs is reduced by *in vitro* exposure to cyclodiene insecticides. Microsacs exposed to endrin (1 µM) exhibited an 82% reduction in $^{36}Cl^-$ influx relative to control. These data were interpreted as supportive of previous suggestions that cyclodiene insecticides (including endrin) inhibit functions mediated by the GABA receptor.

Peripheral vascular effects of acute endrin exposure were examined in partially isolated forelimbs of 10 mongrel dogs (Emerson and Hinshaw, 1965). Following the surgical forelimb separation and, in 5/10 dogs, denervation of the forelimb, endrin (10 mg/kg) was intravenously infused. After about 10 minutes of infusion, innervated limb vascular resistance increased ~80%; this increased resistance was accompanied by a decrease in limb blood flow. Similar results were observed in the denervated forelimbs after about 10 minutes of infusion. However, in contrast to the innervated limbs, vascular resistance subsequently increased steeply to high levels, and limb blood flow virtually ceased. It was concluded that sympathetic innervation was not necessary for vascular resistance increases following endrin exposure,

and it was suggested that the vascular effects of endrin may be due to circulating catecholamines.

Endrin toxicity may also be mediated through effects on membrance permeability, since hemolysis has been observed for postendrin hematocrits in dogs (Emerson et al., 1964), and "hemorrhagic enteritis" has been noted in rats and birds (Stickel et al., 1979b).

Subchronic studies in human workers are consistent with a reversible induction of liver microsomal activity, as denoted by urinary levels of D-glucaric acid, which is dependent on the level of cytochrome P-450 (Ottevanger and Van Sittert, 1979). D-glucaric acid was not detected in urine when anti-12-hydroxyendrin urine levels were <0.13 mg/g of creatinine.

In rats (Treon et al., 1955), the only long-term degenerative changes in the organs from fatally-poisoned animals studied occurred in the liver and kidneys. The mechanisms responsible for such changes are not known.

Endrin was reported to lack carcinogenicity in several studies (Treon et al., 1955; Deichmann et al., 1970; Witherup et al., 1970; NCI, 1979), but Reuber (1978, 1979) has concluded that endrin is a carcinogen. It is noteworthy that endrin lacks genotoxicity in bacterial assays (Ames et al., 1975; Moriya et al., 1983), and like other organochlorine pesticides, in rat, mouse and hamster hepatocytes (Maslansky and Williams, 1981). In view of these results, Maslansky and Williams (1981) proposed that the carcinogenicity of organochlorine pesticides reflects an epigenetic rather than a genotoxic mechanism. This proposal is consistent with the observations of

Kurata et al. (1982), which indicated that organochlorine pesticides (including endrin) inhibited metabolic cooperation in Chinese hamster cells. It was suggested that the pesticides that inhibited metabolic cooperation might be tumor promotors. Further, Ito et al. (1980) reported that dietary endrin exposure (25 ppm for 6 weeks) elicited an increase in the area of hyperplastic liver nodules in hepatectomized Fischer F344 rats previously treated with diethylnitrosamine, although the number of nodules was not affected by endrin. A classification system was also proposed; endrin would be classified by this system as a weak promotor.

It is emphasized that the discussion in the above paragraph should not be construed as positive evidence for endrin tumorigencity, but rather, as evidence of a possible epigenetic action of endrin. Conclusions concerning endrin carcinogenicity are presented in the following chapter.

Interactions

Ludke (1976) demonstrated that prior treatment with a closely-related insecticide can increase bird mortality. Fourteen-week-old male and female white quail (Colinus virginianus) were divided into four groups; four birds constituted the control group. All groups were fed turkey maintenance mash with 1% (w/w) propylene glycol mixed in the diet. Pesticides were dissolved in propylene glycol and mixed into the diet. Twenty-eight birds received 10 ppm technical chlordane in the diet for 10 weeks and 20 of these were then fed 10 ppm 98% pure endrin in the diet for 6-10 days. A fourth group (N=20) was fed 10 ppm endrin in the diet. No mortality occurred in the control group nor in the group fed chlordane alone. For endrin-fed birds, mortality occurred on days 1 (1 bird), 6 (7), 9 (5) and 10 (2). For the chlordane-endrin-treated groups, mortality occurred on days 3 and 6-10 (14 birds) of

endrin exposure, and survivors were sacrificed on days 9 and 10 of endrin exposure. All surviving birds treated with endrin alone or chlordane-endrin lost weight and showed depleted lipid content in the carcasses (Table VII-1). Control and chlordane-treated birds showed no significant decreases. Birds that survived exposure to chlordane-endrin or endrin alone had lower brain residues of endrin than the dead birds. Birds dying of endrin poisoning alone had brain residues ranging from 0.34-1.84 mg endrin/kg ww (survivors = 0.28-0.62 mg endrin/kg ww). In chlordane-endrin-treated birds, the dead birds contained 0.17-1.25 mg endrin/kg brain, whereas the survivors had 0.14-0.56 mg/kg brain. The latter two groups differed at $p<0.10$. Dead or moribund birds treated with the two pesticides contained significantly lower ($p<0.025$) endrin brain residues than the corresponding birds treated with endrin alone. Thus, birds may be more vulnerable to a toxicant if the bird already carries a body burden of one or more closely related chemicals. In this study, mortality from endrin alone was associated with as little as 0.34 mg endrin/kg brain.

Meena et al. (1978) investigated endrin-induced toxicity in normal rats and rats irradiated with gamma radiation by dividing 128 male albino rats (150-200 g) into four equal groups. The control group received groundnut oil i.p.; group 2 received a single i.p. injection of 10 mg endrin/kg bw in groundnut oil; group 3 served as irradiated controls (900 rads); group 4 received 10 mg endrin/kg bw 0.5 hours after irradiation. In both normal and irradiated rats, endrin caused a significant increase in SGOT, SGPT and ATPase; acid and alkaline phosphatase, succinic dehydrogenase and glucose-6-phosphatase decreased significantly during varying periods of 2-48 hours after treatment. In irradiated rats given endrin, the changes appeared earlier and were more pronounced than in normal rats given endrin alone,

TABLE VII-1

Weight Loss and Lipid Content (Mean % ± S.E.) of Quail Carcasses After Technical Chlordane, 98%-Pure Endrin, and Chlordane-Endrin Treatments*

Treatment		Condition	No.	% Lipid	% Weight Loss
Chlordane	Endrin				
None	none	S	4	4.69±0.77	0
10 ppm diet: 10 weeks	none	S	4	3.45±0.56	0
None	10 ppm diet: 6-10 days	D	13	0.43±0.14	32.2±2.4
		M	1	0.73	68.6
		S	3	2.73±0.97	14.7±1.1
10 ppm diet: 10+ weeks	10 ppm diet: 6-10 days	D	12	0.39±0.06	31.4±3.0
		M	3	0.27±0.04	37.2±11.7
		S	3	2.78±1.29	19.1±3.5

*Source: Ludke, 1976

S = Sacrificed, no apparent signs of toxicity; D = dead; M = moribund or sick (reduced activity and lowered appetite)

except in the case of ATPase where endrin appeared to neutralize the effect of radiation on the mitochondrial membrane. The study indicated that endrin leads to injury of liver and kidney tissues, and that this may occur sooner after gamma irradiation of rats.

Following 2 weeks of dietary exposure to 0, 5 or 100 ppm endrin, rats were administered a single dose of CCl_4 (0.1 mL/kg) by intraperitoneal injection, and hepatotoxicity was assessed the following day by determination of serum enzyme activities (Young and Mehendale, 1986). No significant elevations in enzyme activities were observed following exposure to endrin alone. Following exposure to CCl_4 alone, modest but significant elevations in serum of male rats was reported for SGPT, SGOT and isocitrate dehydrogerase (ICD) activities. In females, CCl_4 exposure elicited significant but modest elevations in SGOT and ICD activities and a more substantial elevation in ornithine-carbanyl transferase (OCT) activity. However, exposure to CCl_4 plus endrin elicited marked elevation in SGPT and ICD activities in females relative to the untreated controls. Further, these activities were statistically significantly higher than those of animals exposed to CCl_4 alone. It was concluded that dietary endrin pretreatment potentiated CCl_4 hepatotoxicity.

Summary

Acute exposure to endrin causes death, which is preceded by convulsions and other CNS disturbances. Acute toxicity is associated with the presence of 12-ketoendrin, and this metabolite has been postulated to be the ultimate toxicant. Evidence suggests that endrin (and other polychlorocycloalkene insecticides) may induce convulsions and death by interfering with GABA-regulated functions in the CNS, particularly chloride transport. Increased

vascular resistance that follows endrin exposure may be mediated through effects of circulating catecholamines. Studies of human workers exposed subchronically to endrin suggest induction of liver microsomal enzymes. Mechanisms of chronic endrin toxicity are not known.

As with other organochlorine pesticides, endrin lacks genotoxicity in bacterial systems and in rodent hepatocytes, but can inhibit metabolic cooperation in Chinese hamster cells. These observations are consistent with, but do not necessarily indicate, a capability of endrin to influence tumor development by epigenetic mechanisms.

Evidence for interactions augmenting endrin toxicity exists for birds carrying a body burden of closely related chemicals, and for rats pretreated with gamma irradiation. Pretreatment with endrin potentiated CCl_4-induced hepatic injury in rats.

VIII. QUANTIFICATION OF TOXICOLOGICAL EFFECTS

Introduction

The quantification of toxicological effects of a chemical consists of separate assessments of noncarcinogenic and carcinogenic health effects. Chemicals that do not produce carcinogenic effects are believed to have a threshold dose below which no adverse, noncarcinogenic health effects occur, while carcinogens are assumed to act without a threshold.

In the quantification of noncarcinogenic effects, a Reference Dose (RfD), [formerly termed the Acceptable Daily Intake (ADI)] is calculated. The RfD is an estimate (with uncertainty spanning perhaps an order magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious health effects during a lifetime. The RfD is derived from a no-observed-adverse-effect level (NOAEL), or lowest-observed-adverse-effect level (LOAEL), identified from a subchronic or chronic study, and divided by an uncertainty factor(s) times a modifying factor. The RfD is calculated as follows:

$$\text{RfD} = \frac{\text{(NOAEL or LOAEL)}}{\text{[Uncertainty Factor(s) x Modifying Factor]}} = \_\_\_\_ \text{ mg/kg bw/day}$$

Selection of the uncertainty factor to be employed in the calculation of the RfD is based upon professional judgment, while considering the entire data base of toxicological effects for the chemical. In order to ensure that uncertainty factors are selected and applied in a consistent manner,

the U.S. EPA (1988a) employs a modification to the guidelines proposed by the National Academy of Sciences (NAS, 1977, 1980) as follows:

Standard Uncertainty Factors (UFs)

- Use a 10-fold factor when extrapolating from valid experimental results from studies using prolonged exposure to average healthy humans. This factor is intended to account for the variation in sensitivity among the members of the human population. [10H]

- Use an additional 10-fold factor when extrapolating from valid results of long-term studies on experimental animals when results of studies of human exposure are not available or are inadequate. This factor is intended to account for the uncertainty in extrapolating animal data to the case of humans. [10A]

- Use an additional 10-fold factor when extrapolating from less than chronic results on experimental animals when there is no useful long-term human data. This factor is intended to account for the uncertainty in extrapolating from less than chronic NOAELs to chronic NOAELs. [10S]

- Use an additional 10-fold factor when deriving an RfD from a LOAEL instead of a NOAEL. This factor is intended to account for the uncertainty in extrapolating from LOAELs to NOAELs. [10L]

Modifying Factor (MF)

- Use professional judgment to determine another uncertainty factor (MF) that is greater than zero and less than or equal to 10. The magnitude of the MF depends upon the professional assessment of scientific uncertainties of the study and data base not explicitly treated above, e.g., the completeness of the overall data base and the number of species tested. The default value for the MF is 1.

The uncertainty factor used for a specific risk assessment is based principally upon scientific judgment rather than scientific fact and accounts for possible intra- and interspecies differences. Additional considerations not incorporated in the NAS/ODW guidelines for selection of an uncertainty factor include the use of a less than lifetime study for deriving an RfD, the significance of the adverse health effects and the counterbalancing of beneficial effects.

From the RfD, a Drinking Water Equivalent Level (DWEL) can be calculated. The DWEL represents a medium specific (i.e., drinking water) lifetime exposure at which adverse, noncarcinogenic health effects are not anticipated to occur. The DWEL assumes 100% exposure from drinking water. The DWEL provides the noncarcinogenic health effects basis for establishing a drinking water standard. For ingestion data, the DWEL is derived as follows:

$$\text{DWEL} = \frac{\text{(RfD) x (Body weight in kg)}}{\text{Drinking Water Volume in ℓ/day}} = \_\_\_\_ \text{ mg/ℓ}$$

where:

Body weight = assumed to be 70 kg for an adult
Drinking water volume = assumed to be 2 ℓ/day for an adult

In addition to the RfD and the DWEL, Health Advisories (HAs) for exposures of shorter duration (1-day, 10-day and longer-term) are determined. The HA values are used as informal guidance to municipalities and other organizations when emergency spills or contamination situations occur. The HAs are calculated using an equation similar to the RfD and DWEL; however, the NOAELs or LOAELs are identified from acute or subchronic studies. The HAs are derived as follows:

$$\text{HA} = \frac{\text{(NOAEL or LOAEL) x (bw)}}{\text{(UF) x (\_\_\_ ℓ/day)}} = \_\_\_\_ \text{ mg/ℓ}$$

Using the above equation, the following drinking water HAs are developed for noncarcinogenic effects:

1. 1-day HA for a 10 kg child ingesting 1 ℓ water per day.
2. 10-day HA for a 10 kg child ingesting 1 ℓ water per day.
3. Longer-term HA for a 10 kg child ingesting 1 ℓ water per day.
4. Longer-term HA for a 70 kg adult ingesting 2 ℓ water per day.

The 1-day HA calculated for a 10 kg child assumes a single acute exposure to the chemical and is generally derived from a study of <7 days duration. The 10-day HA assumes a limited exposure period of 1-2 weeks and is generally derived from a study of <30 days duration. The longer-term HA is derived for both the 10 kg child and a 70 kg adult and assumes an exposure period of ~7 years (or 10% of an individual's lifetime). The longer-term HA is generally derived from a study of subchronic duration (exposure for 10% of animal's lifetime).

The U.S. EPA categorizes the carcinogenic potential of a chemical, based on the overall weight-of-evidence, according to the following scheme:

> Group A: Human Carcinogen. Sufficient evidence exists from epidemiology studies to support a causal association between exposure to the chemical and human cancer.
>
> Group B: Probable Human Carcinogen. Sufficient evidence of carcinogenicity in animals with limited (Group B1) or inadequate (Group B2) evidence in humans.
>
> Group C: Possible Human Carcinogen. Limited evidence of carcinogenicity in animals in the absence of human data.
>
> Group D: Not Classified as to Human Carcinogenicity. Inadequate human and animal evidence of carcinogenicity or for which no data are available.
>
> Group E: Evidence of Noncarcinogenicity for Humans. No evidence of carcinogenicity in at least two adequate animal tests in different species or in both adequate epidemiologic and animal studies.

If toxicological evidence leads to the classification of the contaminant as a known, probable or possible human carcinogen, mathematical models are used to calculate the estimated excess cancer risk associated with the ingestion of the contaminant in drinking water. The data used in these

estimates usually come from lifetime exposure studies using animals. In order to predict the risk for humans from animal data, animal doses must be converted to equivalent human doses. This conversion includes correction for noncontinuous exposure, less than lifetime studies and for differences in size. The factor that compensates for the size difference is the cube root of the ratio of the animal and human body weights. It is assumed that the average adult human body weight is 70 kg and that the average water consumption of an adult human is 2 ℓ of water per day.

For contaminants with a carcinogenic potential, chemical levels are correlated with a carcinogenic risk estimate by employing a cancer potency (unit risk) value together with the assumption for lifetime exposure from ingestion of water. The cancer unit risk is usually derived from a linearized multistage model with a 95% upper confidence limit providing a low dose estimate; that is, the true risk to humans, while not identifiable, is not likely to exceed the upper limit estimate and, in fact, may be lower. Excess cancer risk estimates may also be calculated using other models such as the one-hit, Weibull, logit and probit. There is little basis in the current understanding of the biological mechanisms involved in cancer to suggest that any one of these models is able to predict risk more accurately than any other. Because each model is based upon differing assumptions, the estimates derived for each model can differ by several orders of magnitude.

The scientific data base used to calculate and support the setting of cancer risk rate levels has an inherent uncertainty that is due to the systematic and random errors in scientific measurement. In most cases, only studies using experimental animals have been performed. Thus, there is

uncertainty when the data are extrapolated to humans. When developing cancer risk rate levels, several other areas of uncertainty exist, such as the incomplete knowledge concerning the health effects of contaminants in drinking water, the impact of the experimental animal's age, sex and species, the nature of the target organ system(s) examined and the actual rate of exposure of the internal targets in experimental animals or humans. Dose-response data usually are available only for high levels of exposure and not for the lower levels of exposure closer to where a standard may be set. When there is exposure to more than one contaminant, additional uncertainty results from a lack of information about possible synergistic or antagonistic effects.

Noncarcinogenic Effects

Although the acute LD_{50} for endrin has been determined for a number of species, the available data for defining short-term health advisories (HAs) is more limited. In an abstract, Revzin (1968) reported an increase in the amplitude of the EEG and a tendency toward spiking after seven daily doses of 0.2 mg/kg bw endrin in rats. No effects were noted, however, after 1 or 2 days exposure to the same dose level. Speck and Maaske (1958) reported EEG changes and occasional convulsions after 1 week using daily oral doses of 3.5 mg/kg bw in rats. It was not reported whether effects occurred at lower doses (0.8 and 1.7 mg/kg bw), which were also employed.

Information on acute and subchronic effects of endrin exposure is available from perinatal toxicity studies. Chernoff et al. (1979) reported marked maternal toxicity in Syrian golden hamsters at doses $\geq$1.5 mg/kg bw/day for 10 days. Kavlock et al. (1981) reported decreased locomotor

activities in adult female CD-1 mice after single oral exposures to 1.5 or 4.5 mg/kg endrin, but not to 0.5 mg/kg endrin. In CD rats, single oral endrin doses of 0.5, 1.0 or 2.0 mg/kg bw elicited a dose-related decrease in locomotor activity. Pregnant CD-1 mice exposed to endrin doses of 0.5, 1.0, 1.5 or 2.0 mg/kg bw/day by oral gavage on days 7-17 of gestation exhibited reduced weight gain at the three highest exposure levels and elevated liver-to-body weight ratios at all exposure levels. Pregnant CD rats exposed to endrin doses of 0.075, 0.150, 0.300 or 0.450 mg/kg/day by oral gavage on days 7-20 of gestation exhibited decreased weight gain at the two highest doses only; liver-to-body weight ratios were unaffected in all exposure groups. Thus, 0.150 mg/kg/day may be considered as a NOAEL for a 14-day oral endrin exposure.

Nelson et al. (1956) exposed Sprague-Dawley rats to 1, 5, 25, 50 and 100 ppm endrin in the diet for up to 16 weeks. Body weights and serum alkaline phosphatase, an index of liver damage, were measured weekly. Following 4 weeks of exposure, 40% mortality had occurred at exposure levels $\geq$5 ppm in males, and hypersensitivity to various stimuli and nasal bleeding had occurred at the 1 and 5 ppm exposure levels. Body weight losses and elevated serum alkaline phosphatase occurred at all exposure levels. By 10 weeks of exposure, mortality had occurred at all exposure levels in males and to females at levels $\geq$25 ppm. Mortality within the groups remained the same at week 16.

NCI (1979) in a cancer range-finding study found decreases in body weight gain in rats administered 20 ppm, but not 10 ppm in the diet for 6 weeks. In the same study decreased body weight gains were also reported in mice administered 10 ppm, but not 5 ppm in the diet.

Treon et al. (1955) conducted subchronic and chronic exposure studies on both rats and dogs. Groups of 20 male and 20 female Carworth rats were given diets containing 0, 1, 5, 25, 50 or 100 ppm endrin for up to 2 years. Mortality was high at the 50 and 100 ppm exposure levels. Weight gain was decreased in the males exposed to 5 and 25 ppm, but not 1 ppm, for 20 weeks. Liver-to-body weight ratios were increased in male rats in the 5 and 25 ppm groups, but not the 1 ppm group, after 2 years of exposure. Liver-to-body weight ratios in the female rats exposed to 1 or 5 ppm endrin for 2 years did not differ significantly from controls.

Treon et al. (1955) also conducted a study with beagle dogs in which groups of 1-4 were fed diets containing 0-50 ppm endrin for up to 18 months. All dogs fed 10-50 ppm (0.49-4.00 mg/kg/day) died, and >50% of those fed 5-8 ppm (0.20-0.65 mg/kg/day) died. Actual endrin intakes were reported by the authors. All dogs receiving ≤4 ppm (0.18 mg/kg/day) survived, but growth was affected in the 4 ppm groups. The 3 ppm (0.19 mg/kg/day) group had significantly higher relative kidney and heart weights than controls. Dogs fed 1 ppm endrin were similar to controls in all parameters, including gross pathology and histopathology. According to the authors, the dogs (two males and two females) on the 1 ppm diet actually consumed 0.083 mg/kg/day.

While other chronic studies have been conducted with the primary intent of evaluating carcinogenic response, some toxicity data have also been reported. Deichmann et al. (1970) administered endrin to rats at concentrations of 2, 6 and 12 ppm in the diet for up to 37 months. A moderate increase in cloudy swelling of the liver and renal tubular epithelium along

with a moderate increase in the incidence of lung congestion and focal hemorrhage was reported. Since the authors stated that the effects were not dose-related, it is assumed they occurred at the 2 ppm level as well as the higher doses.

In an NCI (1979) study both mice and rats were chronically exposed to endrin. The mice were administered a time-weighted-average (TWA) concentration in the diet of 1.6 and 3.2 ppm, while the rats received 3 and 6 ppm. Neither mortality nor body weights were affected by either dose. However, a variety of clinical signs usually associated with aging were observed earlier in the exposed mice and rats. Although a NOAEL was not observed in the Deichmann et al. (1970) or the NCI (1979) studies, the results of these investigations provide strong support for a NOAEL no greater than 0.05 mg/kg bw in rats and 0.13 mg/kg bw in mice (1 ppm in the diet).

In a 2-year dog study, beagle dogs (7/sex/group) received diets containing 0, 0.1, 0.5, 1.0, 2.0 or 4.0 ppm endrin for >2 years (U.S. EPA, 1987). Interim sacrifices (2 dogs/sex/group) were performed at 6 and 12 months. Parameters monitored included growth, food consumption, behavior, serum and urine chemistry, organ weights and histopathology of all major organs. Animals treated at the 2 and 4 ppm dose levels experienced convulsions, slight increase in relative liver weights, and mild histopathological changes in liver cells. Because of the effects observed in the dogs consuming diets containing 2 ppm endrin (0.05 mg/kg/day), this level was considered the LOAEL. No adverse effects were observed in dogs receiving diets containing $\leq$1 ppm endrin. Therefore, 1 ppm (0.025 mg/kg/day) was considered the NOAEL.

Only one chronic nonmammalian study appears to have been conducted to date. Kreitzer (1980) measured behavioral effects of endrin in adult bobwhite quail (Colinus virginianus) using nonspatial discrimination reversal tasks. The birds were fed 0.1 and 1.0 ppm endrin in the diet (0.01 and 0.10 mg/kg bw if it is assumed the birds eat an amount equivalent to 10% of bw/day) for up to 240 days. Significantly increased error rates were detected at both levels of exposure. While the results of this study suggest a NOAEL lower than values determined from other chronic studies, it is uncertain how they relate to those of mammalian exposures. Acute LD_{50} studies on pigeons (Revzin, 1966) suggest that some species of birds may be more sensitive to endrin exposure than mammals.

Quantification of Noncarcinogenic Effects

Derivation of 1-Day HA. Previously the study by Revsin (1968) was selected as the basis for the 1-day HA. In this study, Revsin reported alterations in the EEG of squirrel monkeys after 7 daily doses of 0.2 mg/kg endrin. Results of this study were provided as an abstract. Recently the Science Advisory Board of the U.S. EPA (1988c) in their meeting discourage the use of data from an abstract for the derivation of an HA level. Under the circumstances, the Kavlock et al. (1981) study is considered for the 1-day HA. In a preliminary range finding study, Kavlock et al. (1981) reported decreased locomotor activities in adult female CD-1 mice following single oral endrin doses of 1.5 or 4.5, but not 0.5 mg/kg bw. The 0.5 mg/kg dose can be considered a NOAEL. The 1-day HA for a 10 kg child is derived as follows:

$$\text{1-day HA} = \frac{0.5\ \text{mg/kg} \times 10\ \text{kg}}{1\ \text{L/day} \times 100} = 0.05\ \text{mg/L}$$

where:

0.5 mg/kg = NOAEL, based on locomotor activities in mice (Kavlock et al., 1981)

10 kg = weight of protected individual (child)

1 ℓ/day = assumed water consumption by a child

100 = uncertainty factor, chosen in accordance with NAS/ODW and Agency guidelines for use with a NOAEL from a study in animals

Derivation of 10-Day HA. Formerly the 10-day HA value was calculated based on the results of the Nelson et al. (1956) study on rats. However, reevaluation of the study indicated certain observations that should not be ignored. These observations included body weight losses, hypersensitivity to various stimuli, nasal bleeding and increased alkaline phosphatase activity at the lowest endrin level tested. In view of the noted observations, it is prudent to consider the Kavlock et al. (1981) study for derivation of the 10-day HA. Kavlock et al. (1981) reported depressed maternal weight gain in CD rats exposed to endrin doses of 0.300 or 0.450 but not 0.150 or 0.075 mg/kg/day for 14 consecutive days; 0.150 mg/kg/day can be considered a NOAEL for a 10-day exposure. The 10-day HA for a 10 kg child is derived as follows:

$$\text{10-day HA} = \frac{0.150 \text{ mg/kg/day} \times 10 \text{ kg}}{1 \text{ ℓ/day} \times 100} = 0.02 \text{ mg/ℓ}$$

where:

0.150 mg/kg/day = NOAEL, based on weight gain changes in rats (Kavlock et al., 1981)

10 kg = weight of protected individual (child)

1 ℓ/day = assumed water consumption by a child

100 = uncertainty factor, chosen in accordance with NAS/ODW and Agency guidelines for use with a NOAEL from a study in animals

Derivation of Longer-Term HA. Subchronic exposure data appropriate for deriving longer-term HAs are extremely limited. Nelson et al. (1956) reported body weight losses, hypersensitivity to various stimuli, nasal bleeding and increased alkaline phosphatase activity to levels of endrin ≥1 ppm in Sprague-Dawley rats. The reported LOAEL of 1 ppm endrin in the diet corresponds to a dose of 0.05 mg/kg/day (assuming an average daily dietary consumption of 5% of body weight for Sprague-Dawley rats in a subchronic study; U.S. EPA, 1987). By 10 weeks of exposure, mortality had occurred at all exposure levels in males and to females at levels ≥25 ppm.

Treon et al. (1955) reported elevated kidney and heart-to-body weight ratios in beagle dogs exposed for up to 18 months to diets containing 3 ppm, but not 1 ppm endrin. At both doses, organ-to-body weight ratios for liver, brain and spleen did not differ significantly from controls. Based on measured food intake, the daily dose for the 1 ppm dose group varied from 0.045-0.12 mg/kg bw. However, the daily intake of 1 ppm endrin appears to be suspect since this range overlaps with the 3 ppm range of exposure as given in the published report. It is therefore recommended that the DWEL, which is based on lifetime exposure (see Assessment of Lifetime Exposure and Derivation of a DWEL Section), be used as a conservative basis for the longer-term HA. This value is based on a chronic NOAEL of 0.025 mg/kg/day. The Nelson et al. (1956) study is precluded for use since a high rate of mortality occurred in male rats at ≥0.05 mg/kg/day after 10 weeks.

The DWEL of 0.009 mg/l is based on adult body weight and water consumption and therefore is used directly for the longer-term HA for adults. For the 10 kg child, the RfD upon which the DWEL is based is used in the following derivation.

$$\text{Longer-Term HA}_{(\text{child})} = \frac{\text{RfD} \times 10\ \text{kg}}{1\ \text{L/day}} = \frac{0.0003\ \text{mg/kg/day} \times 10\ \text{kg}}{1\ \text{L/day}}$$

$$= 0.003\ \text{mg/L}$$

where:

RfD	= 0.0003 mg/kg/day
10 kg	= assumed weight of exposed individual (child)
1 L/day	= assumed volume of water consumed/day by a 10 kg child

Assessment of Lifetime Exposure and Derivation of a DWEL. A review of the literature, including an unpublished study from the CBI files concerning endrin and the various RfD values that have been promulgated by the different branches of the Agency, has indicated that the CBI study is the most appropriate basis for an RfD (U.S. EPA, 1988b). In this 2-year dog study, beagle dogs (7/sex/group) received diets containing 0, 0.1, 0.5, 1.0, 2.0 or 4.0 ppm endrin for >2 years. Animals treated at the 2 and 4 ppm dose levels experienced convulsions, slight increase in relative liver weights, and mild histopathological changes in liver cells. No adverse effects were observed at $\leq$1 ppm endrin, therefore 1 ppm (0.025 mg/kg/day) was considered the NOAEL. Using the above study, the derivation of the DWEL is as follows:

Step 1 - RfD Derivation

$$\text{RfD} = \frac{0.025\ \text{mg/kg/day}}{100} = 0.0003\ \text{mg/kg/day}$$

where:

0.025 mg/kg/day	= NOAEL for oral exposure in dogs (U.S. EPA,1987)
100	= uncertainty factor appropriate for use with a NOAEL (from animal data and to protect sensitive members of the human population

Step 2 - DWEL Derivation

$$DWEL = \frac{RfD \times 70\ kg}{2\ \ell/day} = \frac{0.00025\ mg/kg/day \times 70\ kg}{2\ \ell/day} = 0.009\ mg/\ell$$

where:

RfD = 0.00025 mg/kg/day

70 kg = assumed weight of protected individual (adult)

2 ℓ/day = assumed volume of water consumed by a 70 kg adult

The recommended lifetime DWEL for a 70 kg adult is 0.009 mg/ℓ endrin. A summary of the data used to calculate the HAs and the lifetime DWEL is provided in Table VIII-1. The values derived for the HAs and DWEL represent estimates of the concentration of endrin in drinking water that will not cause adverse effects after 1-day, 10-day, longer-term or lifetime exposures.

Carcinogenic Effects

There are no clinical reports available relating endrin exposure to induction of cancer in humans. Ditraglia et al. (1981) conducted a retrospective cohort study to examine the mortality of workers employed in the manufacture of chlordane, heptachlor, DDT and aldrin/dieldrin/endrin. No statistically significant excess for any specific cancer site was noted. However, since no exposure data are reported, the results of this study are inconclusive. While there is no evidence linking endrin to cancer induction in humans, the amount of data available is insufficient to allow definite conclusions to be drawn.

Four bioassays for carcinogenicity were done in rats and three were on mice. These bioassays were done at different institutions, namely Food and Drug Administration (FDA) during 1955-1957 as reevaluated by Reuber (1978),

TABLE VIII-1

Summary of Data Used to Derive HAs or DWEL

Criteria	Dose (mg/kg bw/day)	Duration	Effect	Value of HA or DWEL		Reference
				Child (mg/ℓ)	Adult (mg/ℓ)	
1-Day HA	0.5	1 day	NOAEL: locomotor activities in mice	0.05	NC	Kavlock et al., 1981
10-Day HA	0.15	14 days	NOAEL: decreases in maternal weights in rats	0.02	NC	Kavlock et al., 1981
Longer-term HA	0.025	2 years	NOAEL: histological liver lesions and occasional convulsions	0.003	0.009	U.S. EPA, 1987b
DWEL	0.025	2 years	NOAEL: histological liver lesions and occasional convulsions	NC	0.009	U.S. EPA, 1987b

NC = Not calculated

the National Cancer Institute (NCI, 1979), the University of Cincinnati (Kettering Laboratory) (Witherup et al., 1970), and the University of Miami (Deichmann et al., 1970). All the bioassays on rats and mice were reported as negative by those authors. There were, however, deficiencies in the studies which is explained below, which render the findings inadequate to properly assess the carcinogenic potential in animal test systems.

In the FDA rat (Osborne-Mendel) study the animals at highest dose (25 ppm) did not survive well and additional animals were started in that dose. The remainder of the groups lived for the programmed two year study. It also appeared that every animal came to autopsy and not all sections from grossly observed animals were studied microscopically. In spite of some deficiencies there were a sufficient number of animals in the studies particularly in the aspect of liver and kidney, in all experimental and control groups (Reuber, 1978). This study was originally reported as negative. It was reevaluated by a panel of pathologist whose report was referenced in a CAG document (U.S. EPA, 1978). One pathologist considered the finding positive (Table V-11 and V-12) but did not provide slide by slide tabulation of his findings and did not distinguish between primary and/or metastatic tumors in the liver. A second pathologist whose original finding indicated that the study was negative, provided slide by slide tabulation of diagnosis which was confirmed by the panel review. In the FDA mice (C3HF1) study the survival was very poor in both control and experimental group.

The Kettering study used two strains of mice (C57B1/6J and C3D2F1/J). The C57B1/6J strain exhibited mainly leukemia and liver tumors with low incidence. These tumors appeared equally in the experimental and control

groups and the latent period of tumor formation was similar. But in the C3D2F1/J strain, the incidence of liver tumors in the dose group (3 ppm) was slightly higher in the female than in controls and the latent period of tumor formation was decreased than other groups (Witherup et al., 1970).

The NCI bioassay was done in Osborne-Mendel rats and B6C3F1 mice. These studies were reported as negative. A primary reviewer for NCI noted that the negative findings could be a reflection of the high toxicity of endrin, which only permitted the administration of relatively low chronic dosages. Furthermore, the reviewer observed that an accidental overdose among low dose male mice resulted in early death of several animals in this treatment group and the study was marred by a small (10) if matched controls; however, this deficiency was compensated by the use of pooled controls (see Table V-17). There were significant increases in hemangioma in low dose male rats, adrenal adenoma and/or carcinoma in high dose in males, pituitary adenomas in the high dose female, adrenal adenoma and/or carcinoma in low dose female rats as compared to the pooled controls. Although, the islet-cell carcinoma in male rats had a significant trend but no statistical significance at either dose group, the NCI concluded that these tumors could not be clearly considered related to the adminstration of endrin (NCI, 1979). Although NCI concluded that the bioassays of endrin were not carcinogenic, the responses noted above can not be totally ignored.

Endrin was not mutagenic in any bacterial strains but exhibited chromosomal aberration in germinal tissues. Endrin is also structurally related to aldrin, dieldrin, chlordane, chlorendic acid and heptachlor which are known to carcinogenic in animals. The available cancer epidemiologic

data involving several studies is inadequate to demonstrate or refute a carcinogenic hazard because of study design limitations and/or mixed exposures. Using the criteria in the U.S. EPA (1986) guidelines for classification of carcinogens, endrin is most appropriately classified in Group D; i.e. a chemical for which there is inadequate evidence to assess the potential carcinogenicity for humans. This classification is based on the nonpositive but suggestive results in some of the animal studies. The negative conclusions as reported by the study authors of the four bioassays do not support a Group E classification, because of the inadequacies of the studies. A Group D weight-of-evidence is thought to be the best classification until additional studies can be done to clarify the situation.

Existing Guidelines, Recommendations and Standards

The U.S. EPA (1975) has set an interim standard for endrin in finished water of 0.0002 mg/ℓ. The U.S. EPA (1980a) proposed an ambient water criterion for endrin of 0.001 mg/ℓ. This value was the same as the maximum allowable concentration recommended at that time by the Public Health Service.

The World Health Organization (FAO/WHO, 1973) established as a guideline a maximum intake of 2 µg/kg/day, or 138.2 µg/day, for a 69.1 kg person. The proposed Index Alimentarius Commission's maximum residue limit in wheat is 20 µg/kg (Bailey et al., 1982).

The threshold limit value (8-hour TLV/TWA) recommended by the American Conference of Governmental Industrial Hygienists is 0.10 mg/m³ (0.10

µg/ℓ), with a short time exposure limit (15 minutes) of 0.30 mg/m³ (ACGIH, 1982). The Occupational Safety and Health Administration limits are the same, 0.10 mg/m³ (29 CFR 1910-1000).

The history of recommendations concerning endrin is provided in the Federal Register (1979). The U.S. EPA issued a notice of rebuttable presumption against registration and continued registration (RPAR) of endrin-containing products (e.g., Rid-a-Bird and Sorbikill) on July 27, 1976. It included three supportable risk presumptions -- risk of significant population reductions of nontarget organisms, acute toxicity to wildlife, and teratogenicity. After review, the Agency determined that the offsetting economic, social or environmental benefits were still not great enough. Thus, endrin use was cancelled in the following areas: on cotton in all areas east of interstate highway 35; on small grains to control all pests other than army cutworm, the pale western cutworm and grasshoppers; on apple orchards in the eastern United States to control meadow voles; on sugarcane to control the sugarcane borer; and on ornamentals. Registration for new uses of endrin was denied, as well as its use in unenclosed bird perch treatments. Limited use was allowed under specific conditions for the following: on cotton west of interstate 35; on small grains to control army cutworms and pale western cutworms; on apple orchards in the eastern United States to control the pine vole and in the western United States to control meadow voles; on sugarcane to control the sugarcane beetle; for conifer seed treatment; and use in enclosed bird perch treatments. New uses and registration of endrin under specified conditions were allowed as follows: as a tree paint in Texas; on alfalfa and clover seed crops in Colorado; and on small grains to control grasshoppers (in Montana). These determinations were originally issued on October 20, 1978 by the Agency.

In response to the endrin RPAR, the Agency determined that endrin was unlikely to pose an oncogenic risk to humans, and that the risk presumptions for acute dermal toxicity and fatalities to endangered species had been rebutted.

In the case of fish kills, signs stating "Contaminated: No Fishing" must be posted for 1 year after a fish kill, or for 6 months after lesser contamination unless endrin residues in the edible portion of fish are <0.3 ppm ww.

The bird species deemed potentially at risk were the Arctic and American peregrine falcons, bald eagles and brown pelicans. A NOEL of 1.5 mg/kg bw was accepted for teratogenicity in the hamster. The LOEL in the hamster was 5 mg/kg. However, behavioral studies using quail have indicated that either quail are very sensitive to the effects of endrin or the endpoints measured are more sensitive than those used in the past.

Special Considerations

Endrin given to the dam at dose levels ~10-fold in excess of the chronic NOEL in adult nonpregnant animals has been associated with reduced fetal weight in hamsters and mice. At levels comparable to the chronic NOEL, endrin exposure resulted in increased locomotor activity of offspring of rats and hamsters. Thus, unborn children must be considered a potentially sensitive group.

The general public in the Missouri and Mississippi basins between March 1964 and June 1967 were exposed to endrin in drinking water (Schafer et al.,

1969) and in 1976 in Ottawa, Canada (Williams et al., 1978). These situations occurred in agricultural areas. Acid drinking waters are more likely to contain endrin ketone than endrin itself (ApSimon et al., 1982), also keeping in mind that endrin cannot be analyzed well in acid water, in contrast to endrin ketone (Millar et al., 1981). Thus, people living in areas of high endrin use have more potential for risk than have the general population.

Farming communities and workers near areas of endrin application may be exposed not only to endrin (Wolfe et al., 1963, 1967; U.S. EPA, 1971, 1979; Arthur et al., 1976; Jegier, 1964), but also to the major product of sunlight degradation, the half-cage ketone identified also in environmental samples (Zabik et al., 1971). Exposure to this product may increase their risk.

Workers exposed to endrin in occupational environments have been known to suffer convulsions (Jager, 1970). Such workers are the best study populations for monitoring signs of cancer. Poisoning episodes have also been reported for endrin-contaminated flour (Coble et al., 1967; Weeks, 1967; Curley et al., 1970).

Previous exposure to related compounds can increase susceptibility to the toxic effects of endrin. Pretreatment of quail with chlordane at dosages less than the NOAEL (10 ppm in the diet for 10 weeks) resulted in greater mortality in birds subsequently administered 10 ppm endrin in the diet than in those administered endrin alone (Ludke, 1976). Of the birds that died, the ones treated with endrin alone had lower brain endrin concentrations than in those pretreated with chlordane.

Radiation may increase the response to endrin. Irradiation of rats with gamma particles (900 rads) before injection of 10 mg/kg bw endrin to rats resulted in a greater increase in SGOT, SGPT, and a greater decrease in acid and alkaline phosphatase, succinic dehydrogenase and glucose-6-phosphatase than in rats treated with endrin alone (Meena et al., 1978).

Finally, stress may lower the threshold for the toxic effects of endrin. The survival times of female field mice (Peromyscus maniculatus) were shorter during combined cold and starvation, at doses of endrin as low as 1 ppm in the diet, than in stressed mice that received no endrin (Morris, 1968).

Summary

The NOAEL for acute exposure to endrin is determined to be 0.5 mg/kg bw/day based upon locomotor activities in mice. Based upon this NOAEL, a 1-day HA for a 10 kg child of 0.05 mg/l is proposed.

The NOAEL for 14-day exposure to endrin is determined to be 0.150 mg/kg bw/day based upon body weight changes in rats. Utilizing this NOAEL a 10-day HA is proposed to be 0.02 mg/l for a 10 kg child.

The NOAEL for a 2-year exposure to endrin is determined to be 0.025 mg/kg bw/day based upon histological liver lesions in dogs. Utilizing this NOAEL, longer-term HAs of 0.003 mg/l for children and 0.009 mg/l for adults are proposed.

An RfD of 0.00025 mg/kg/day was derived based upon a NOAEL of 1 ppm endrin in the diets of dogs exposed for 2 years and mild histopathological liver changes in exposed animals. Based on this RfD, a lifetime DWEL of 0.009 mg/L is proposed.

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