

U.S. Army Center for Health Promotion
and Preventive Medicine

**Wildlife Toxicity Assessment for
Aldrin**

**FINAL REPORT
DECEMBER 2005**

**Prepared by
Health Effects Research Program
Environmental Health Risk Assessment Program**

**USACHPPM Document No: 39-EJ1138-01J
Approved for public release; distribution unlimited.**



Wildlife Toxicity Assessment for Aldrin

**FINAL REPORT
DECEMBER 2005**

**Prepared by
Health Effects Research Program
Environmental Risk Assessment Program**

**USACHPPM Document No: 39-EJ1138-01J
Approved for Public Release; Distribution Unlimited**

Acknowledgements

Key Technical Authors:	Christopher J. Salice, Ph.D.	USACHPPM; Directorate of Toxicology, Health Effects Research Program
	George Holdsworth, Ph.D.	T N & Associates Oak Ridge, TN
Contributors:	Michael J. Quinn, Jr., Ph.D.	Oak Ridge Institute of Science and Education, Oak Ridge, TN
Outside Reviewers:	Janet A. Burris	Syracuse Research Corp.
	Mark J. Jaber	Wildlife International
	Paul D. Jones, Ph.D.	Michigan State University
Support:	Jody Wireman, Ph.D.	Air Force Institute for Operational Health Brooks AFB, San Antonio, TX

Point of Contact

For further information or assistance contact:

Mark S. Johnson, Ph.D., D.A.B.T.
U.S. Army Center for Health Promotion and Preventive Medicine
Toxicology Directorate: Health Effects Research Program
ATTN: MCHB-TS-THE, Bldg. E2100
Aberdeen Proving Ground, MD 21010-5403
(410) 436-3980 / DSN 584-3980
mark.s.johnson@us.army.mil

When referencing this document use the following citation

USACHPPM. 2005. Wildlife Toxicity Assessment for Aldrin. U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM) Project Number 39-EJ1138-01J, Aberdeen Proving Ground, Maryland, December 2005.

Table of Contents

1.	INTRODUCTION	5
2.	TOXICITY PROFILE	5
2.1	Literature Review.....	5
2.2	Environmental Fate and Transport.....	6
2.3	Summary of Mammalian Toxicity	7
2.3.1	Mammalian Toxicity - Oral	7
2.3.1.1	Mammalian Oral Toxicity - Acute	7
2.3.1.2	Mammalian Oral Toxicity – Subacute	8
2.3.1.3	Mammalian Oral Toxicity – Subchronic.....	8
2.3.1.4	Mammalian Oral Toxicity – Chronic	9
2.3.1.5	Mammalian Oral Toxicity – Other	11
2.3.3	Mammalian Inhalation Toxicity	15
2.3.4	Mammalian Dermal Toxicity.....	15
2.4	Summary of Avian Toxicology.....	15
2.5	Amphibian Toxicology	16
2.6	Reptilian Toxicology	16
3.	RECOMMENDED TOXICITY REFERENCE VALUES.....	17
3.1	Toxicity Reference Values for Mammals	17
3.1.1	TRVs for Ingestion Exposures for the Class Mammalia	17
3.1.2	TRVs for Inhalation Exposures for the Class Mammalia	17
3.3	Toxicity Reference Values for Amphibians.....	18
3.4	Toxicity Reference Values for Reptiles	19
4.	IMPORTANT RESEARCH NEEDS	19
5.	REFERENCES	20

Wildlife Toxicity Assessment for Aldrin

CAS No. 309-00-2

December 2005

1. INTRODUCTION

The cyclodiene pesticide, aldrin, was widely used as a broad-spectrum pesticide between 1948 and 1974, in particular against soil insects that attack field and forage crops, vegetables and fruits (HSDB 2001). Like other organochlorine pesticides, use of aldrin was subsequently restricted due to concerns about potential threats to human health and its capacity to bioaccumulate in ecological food chains. While aldrin is no longer registered for use in the United States, its metabolic product, dieldrin, is frequently detected at environmental sites, indicative of its resistance to bio- or chemical degradation. Aldrin (1,2,3,4,10,10-hexachloro-1,4, 4a,5,8,8a-hexahydro-1,4:5,8-exo-dimethanonaphthalene), is structurally related and readily converted to dieldrin (1,2,3,4,10,10-hexachloro-6,7-epoxy-1,4,4a,5,6,7,8,8a-octahydro-endo,exo-1,4:5,8-dimethanonaphthalene), which can occur via biotic or abiotic epoxidation. Thus, epoxidation of aldrin has been shown to occur in the tissues of animals, in air by photooxidation, and in soil as a result of microbial action. However, while dieldrin is more stable in the environment, it is at least as toxic to insects and other animals as aldrin.

This Wildlife Toxicity Assessment summarizes the current knowledge of the toxicological impacts of aldrin on wildlife. Evaluating the toxicity of aldrin contributes to the derivation of toxicity reference values (TRVs) that could serve as screening-level benchmarks for wildlife in the vicinity of contaminated sites. The protocol for the development of this assessment is documented in the U.S. Army Center for Health Promotion and Preventive Medicine Technical Guide 254, *Standard Practice for Wildlife Toxicity Reference Values* (USACHPPM 2000).

2. TOXICITY PROFILE

2.1 Literature Review

Relevant biomedical, toxicological, and ecological databases were electronically searched June 18, 2001, using Dialog® to identify primary reports of studies and reviews on the toxicology of aldrin. Separate searches were carried out linking the compound to either laboratory mammals, birds, reptiles and amphibians (combined), or wild mammals. In general, a two-tiered approach was used in which all citations were first evaluated as titles and “key words in context.” All available abstracts of those articles

selected in the first tier as possibly relevant to TRV development were then evaluated for relevancy and retention for second tier evaluation. Out of 312 initial hits for aldrin, 56 articles were marked for retrieval. Details of the search strategies and the results of each are documented in Appendix A. Secondary references and sources of information on aldrin included the National Library of Medicine's Hazardous Substances Databank (HSDB 2001), the U.S. EPA's Integrated Risk Information System (IRIS) (U.S. EPA 2001), the Agency's Health Effects Assessment Summary Tables (HEAST) (U.S. EPA 1997), and a section on aldrin in *Priority Toxic Pollutants: Health Impacts and Allowable Limits* (Anon, 1980).

2.2 Environmental Fate and Transport

Although aldrin is readily degraded in the environment as a result of biotic and abiotic processes, its primary metabolic product, dieldrin, resists further transformation and is persistent in the environment. Even though the use of aldrin as a pesticide has been abolished, a primary breakdown product, dieldrin, can be persistent and can bioaccumulate, these compounds probably continue to represent a toxicological threat to wildlife.

As discussed in ATSDR (1993), when used as a pesticide, aldrin was readily detected in the air. For example, a mean concentration of 0.4 ng/m³ was reported in 13 percent of 2,479 samples taken from 16 states during the period of 1972–1974. This compares to a mean concentration of 1.6 ng/m³ dieldrin (94 percent incidence), a difference probably attributable to the ease with which aldrin undergoes conversion to dieldrin. After formation from aldrin by photochemical epoxidation in the presence of hydroxyl radicals, dieldrin becomes dispersed in the atmosphere and may undergo subsequent wet or dry deposition.

The physico-chemical characteristics of aldrin and dieldrin explain the observed persistence of the chemicals in soil. The behavior of dieldrin in soil is emphasized since epoxidation of residual aldrin occurs readily as a result of microbial interaction. The non-polar nature of dieldrin and its low solubility in water enhance binding to soil particles, leaving little potential for leaching to groundwater. However, during and subsequent to the 1970's, aldrin/dieldrin was detected in groundwater at contaminated environmental sites. In addition, even though the vapor pressure of the compound is low, dieldrin also can be released from the soil to the atmosphere by volatilization.

Tables 1 summarizes physico-chemical data relating to the environmental fate and transport of aldrin.

Table 1. Summary of Physical-Chemical Properties of Aldrin

CAS No.	309-00-2
Molecular weight	364.93
Color	White (pure), tan (technical grade)
Physical state	Crystalline solid
Melting point	104°C
Boiling point	145°C
Odor	Mild
Solubility in water	0.2 mg/L at 25 °C: miscible in most organic solvents
Partition coefficients:	
Log K _{ow}	3.01
Log K _{oc}	4.69
Vapor pressure at 25 °C	1.4 × 10 ⁻⁴ mm Hg
Henry's Law constant at 25 °C	3.2 × 10 ⁻⁴ atm.m ³ /mole
Conversion factors	1 ppm = 14.96 mg/m ³ 1 mg/m ³ = 0.067 ppm

Source: ATSDR (1993)

2.3 Summary of Mammalian Toxicity

2.3.1 Mammalian Toxicity - Oral

2.3.1.1 Mammalian Oral Toxicity - Acute

Single oral median lethal dose (LD₅₀) values for aldrin have been published by a number of investigators. For example, Gaines (1969) surveyed the acute lethality of 98 pesticides and 2 metabolites of DDT in Sherman rats, deriving values for aldrin (grade and vehicle unstated) of 39 and 60 mg/kg for males and females, respectively. These data show substantial agreement with LD₅₀ values from a number of studies summarized by Hodge et al. (1967). Values ranging from 10–120 mg/kg were listed for 9 laboratory and domestic animals and cattle.

In a more recent study, laboratory animals were acutely exposed to aldrin while endpoints other than lethality were monitored. Ali and Shakoori (1990) provided aldrin in the diet for 48 hours to 8 female Sprague-Dawley rats, half of which were sacrificed after 24 hours, the rest after 48 hours. The authors report the ingested dose to be approximately 20 mg aldrin/kg (body weight)/day. Blood samples were collected to measure clinical chemistry and hematological parameters, and excised livers were processed for histopathological and biochemical studies. Compared to controls, marked fluctuations occurred in hematological parameters of aldrin-exposed rats. For example, statistically significant increases were observed in white blood cell count, mean corpuscular volume, and mean corpuscular hemoglobin, and decreases occurred in hemoglobin concentration, red blood cell count, packed cell volume, and mean

corpuscular hemoglobin concentration. The 48-hour values closely resemble the intermediate data. Changes in the activity of some serum enzymes and in concentrations of other clinical chemistry parameters also were evident after 24 hours, with further increases or decreases beyond the 24-hour levels after 48 hours. In a single example out of several, this resulted in an overall doubling of the serum activity of isocitrate dehydrogenase after 48 hours (570.26 ± 44.04 SiU/ml in exposed rats vs. 243.18 ± 14.8 in controls, the 24-hour activities being intermediate). Far fewer fluctuations were observed in liver biochemistry parameters than in serum when aldrin-exposed rats were compared to controls. In addition, the true nature of any apparent changes in liver biochemistry is uncertain since the results were expressed per gram of liver rather than per specific amounts of supernatant protein. However, some hepatic changes caused by aldrin treatment are suggested by the parallel histological findings of hepatomegaly, necrosis, vacuolation, and fatty degeneration. In another phase of the research, the same authors used female Sprague-Dawley rats dosed at 8 mg/kg-day to extend the in-life phase of the experiment to 15 days. Ali and Shakoori (1990) report a similar pattern of changes in hematological, clinical chemistry, liver biochemistry and histopathology compared to those described in the 48-hour study.

2.3.1.2 Mammalian Oral Toxicity – Subacute

No data were found describing the toxicological effects in laboratory animals exposed to aldrin under subacute conditions. However, a study by Hutson (1976) explored the putative metabolites of the compound by gavaging male CFE rats and male CF1 and LACG mice with radiolabeled dieldrin after a period in which subjects received either 20 ppm (rats) or 10 ppm (mice) dieldrin in the diet for 28 days. Animals were maintained in metabolic cages for an additional 8 days before sacrifice. Among the key findings to emerge from this study was that most of the counts were recovered from the feces, with far fewer in the urine or deposited in tissues. In all cases, the metabolites of dieldrin appeared to be the same, and included 12-hydroxydieldrin and its glucuronide, 4,5-trans-dihydroaldrindiol, an unspecified pentachloroketone metabolite, and an "aldrin-derived dicarboxylic acid." Since most or all administered aldrin is rapidly converted to dieldrin, these compounds might also be expected to represent major products of aldrin metabolism.

2.3.1.3 Mammalian Oral Toxicity – Subchronic

An article by Pallade et al. (1968) describes a toxicological experiment in rats (strain and sex unstated) in which some of the dosing strategies were subchronic to chronic in duration. For example, groups of 10–20 rats were gavaged with aldrin as follows: 3 mg/kg-day for the first six months, then 4.5 mg/kg-day for eight months for a total of 14 months. Sequential sacrifices allowed for an evaluation 3 and 3 and 4.5 mg/kg-day treatments. Stage two involved five treatments (0, 3, 4.5, 5, 6, and 9 mg/kg-day) exposed for 20, 73 and 97, 75, 81 and 105, 24, and 20 days, respectively. While the predominant effects were of hepatic origin, the authors noted that a dose-dependent increase in mortality was obtained when only the

two lowest dose groups had rats that survived the entire duration of exposure. Unfortunately, insufficient data were presented in the report to identify a no-observed-adverse-effect level (NOAEL) for increases in relative liver weight; however, it was implicit that levels below 5 mg/kg-day did not. However, increases in liver relative liver weights were associated with decreases in glycogen in exposures \geq 5 mg/kg-day and serum cholesterol is increased in the 9 mg/kg-day groups, relative to controls. Steatosis (fatty liver) was also seen in histological preparations of the liver from 6 and 9 mg/kg-day animals. Mortality rates are presented as follows: 0% (0/20) at 3mg/kg-d, 10% (4/10) at 4.5 mg/kg-d, 40% (8/20) at 5 mg/kg-d, 50% (10/20) at 6 mg/kg-d, and 85% (17/20) at 9 mg/kg-d.

The appearance of dieldrin as a metabolite of aldrin was the focus of a study where aldrin was administered to beagle dogs at 0.6 mg/kg in gelatin capsules, 5 days/week for 10 months (Deichmann et al. 1969). While the primary focus of the study was the formation of dieldrin in important metabolic, transport, and storage sites such as liver, blood, and adipose tissue, the authors reported a number of neurological consequences of treatment like excitability and tremors. This suggests that a time-weighted average dose of 0.43 mg/kg-day might be a lowest-observed-adverse-effect (LOAEL) for the neurological effects of aldrin in this animal model.

2.3.1.4 Mammalian Oral Toxicity – Chronic

The record for aldrin in the IRIS database (U.S. EPA 2001) cites a number of chronic experimental studies focused on the liver as the principal target organ and on the capacity for inducing hepatic neoplasms in mice. Although not relevant to the development of a toxicity reference value, hepatic neoplasm induction appears to be characteristic of organochlorine pesticides in general for susceptible species such as mice, where the spontaneous tumor rate in aging animals is appreciable. Hepatocellular tumors as a result of aldrin administration have not been observed in less susceptible species such as rats, although the liver remains the primary target organ. For example, a 2-year study of aldrin in Osborne-Mendel rats was chosen as the principal study for noncarcinogenic effects in the development of a reference dose. Twelve rats/sex/group received dietary levels of 0, 0.5, 2, 10, 50 or 150 ppm aldrin. Survival was significantly affected at 100 and 150 ppm aldrin and liver lesions were observed at all dietary levels, suggesting a LOAEL of 0.5 ppm (Fitzhugh et al. 1964). For IRIS, an associated dose of 0.025 mg/kg-day was derived by using a rat-specific default food factor of 0.05. While liver effects appeared to be the most sensitive index of aldrin toxicity in rats, the authors also described the incidence of hemorrhagic urinary bladders and nephritis in male rats exposed to the compound at dietary concentrations of 50 ppm and above. This observation is consistent with a NOAEL of 0.5 mg/kg-day (equivalent to dietary levels of 10 ppm aldrin) and a LOAEL of 2.5 mg/kg-day.

Fitzhugh et al. (1964) also administered aldrin (0.2, 1.0, 2.0, and 5.0 mg aldrin/kg-day) or dieldrin (0.2, 1.0, 2.0, 5.0, and 10 mg dieldrin/kg-day) to dogs for up to 25 months via the diet. A variety of

histopathological changes in the liver, kidney and bone marrow were observed. While the number of animals involved in these studies was too small to draw any statistically supported conclusions, the authors assigned a dose level of 0.2 mg/kg-day as a NOAEL and a dose of 0.5 mg/kg-day as the associated LOAEL.

The review by Hodge et al. (1967) summarizes NOAELs and LOAELs from earlier studies that were based on changes in relative liver weight in rats and dogs as a result of dietary supplementation with aldrin. Assuming a dietary default food factor of 0.05 for rats, these doses ranged from 0.125–1.25 mg/kg-day for a NOAEL, and 0.025–7.5 mg/kg-day for a LOAEL. The individual values are provided in Figure 1. The equivalent NOAEL and LOAEL in dogs would be 0.025 and 0.075 mg/kg-day, respectively, if a default food factor of 0.025 is used.

The experimental studies of Pallade et al. (1968) contained a chronic exposure component in which rats (sex and strain unstated) were gavaged with 3 mg aldrin/kg-day for 6 months, then with 4.5 mg aldrin/kg-day for 8 months. Serial sacrifices of 10 exposed and 10 control animals were made to monitor gross and histopathological changes in the liver. Statistically significant increases in relative liver weight were evident after the first sacrifice point at 31 days. Subsequently, the TWA dose level of 3.85 mg/kg-day represents a LOAEL for the hepatotoxic effects described in this experiment.

The potential of aldrin to induce tumors was the primary focus of an experiment in which 50 Osborne-Mendel rats/sex/group were fed 0, 10, 15 or 25 ppm for the first ten weeks followed by 0, 20, 30 or 50 ppm of the pesticide for the remainder of the study, which ran for a total of approximately 20 months (Deichmann et al. 1970). Animals were monitored regularly for clinical signs then subjected to a gross necropsy. Excised pieces of the liver, kidney and lungs were processed for histopathological examination. A number of compound-related changes were observed, for example, reduced survival was seen among high-dose females. Changes in the gross appearance of some organs at necropsy and in liver histopathology were evident, but no apparent aldrin-induced increases in tumor incidence. Among the important noncarcinogenic effects of the compound were the increases in relative liver weight in male rats exposed to 30 and 50 ppm aldrin. Provided a default food factor of 0.05 is appropriate to the Osborne-Mendel rats employed in this study, these data suggest 1.0 mg/kg-day as a NOAEL and 1.5 mg/kg-day as a LOAEL.

The occurrence of hepatic vein thrombosis was investigated in C3H mice that had been given organochlorine pesticides as part of earlier Food and Drug Administration (FDA) toxicological investigations (Reuber 1977). Archived tissue blocks and/or sections from the Davis and Fitzhugh (1962) study provided the experimental evidence for Reuber (1977) to (1) evaluate the incidence of hepatic thrombosis, and (2) update the hepatic tumor incidence according to the 1975 experimental pathology standards. An 8 percent incidence of hepatic vein thrombosis as a result of aldrin exposure was on the

borderline of statistical significance, and potentially implied a compound-related effect in this animal model.

The National Cancer Institute (NCI) sponsored a 2-year toxicological study of aldrin and dieldrin in Osborne-Mendel rats and B6C3F1 mice (NCI, 1978). Fifty (10 for control) rats/sex/dose were fed 30 or 60 ppm aldrin for either 74 weeks (males) or 84 weeks (females), all survivors were observed for a period of 37–38 weeks post-exposure and prior to termination. Also, 50 (10 for control) mice were exposed for 80 weeks to differing dietary concentrations of aldrin amounting to TWA concentrations of 4 and 8 ppm in males and 3 and 6 ppm in females. Survivors were removed from the exposure conditions for a 10–13 week post-exposure observation period prior to termination. Incidence of tumors and of noncarcinogenic lesions were compared to those in a small number of controls (10–20) and a larger number of untreated animals from similar bioassays of other chemicals.

In addition to the increased incidence of hepatocellular carcinomas in male mice, in rats a number of aldrin-related carcinogenic effects were described, such as combined thyroid follicular cell adenomas and carcinomas in low-dose rats of both sexes, and cortical cell adenomas in low-dose females. However, the lack of a clear-cut dose-response effect suggests that these "effects" may not have been compound related. As described by the authors, a number of noncancerous inflammatory, degenerative or proliferative lesions were seen with broadly similar frequency in both aldrin-treated and control animals. Such findings do not allow compound-related NOAELs and LOAELs to be defined for these effects.

A review article by Deichmann et al (1979) describes an experiment in which 50 female Sprague-Dawley and Osborne-Mendel rats/group were chronically exposed to 0, 20 or 50 ppm aldrin in the diet (overall duration unspecified). There was a marked dose-dependent reduction in survival, especially in high-dose rats, suggesting systemic toxicity of aldrin. No other compound-related effects were mentioned in the report. However, tumors of the mammary gland and uterus, the primary focus of the study, were observed in controls as well as in treated animals, and there were no compound-related increases in tumors of the liver.

2.3.1.5 Mammalian Oral Toxicity – Other

Ottolenghi et al. (1974) examined reproductive and developmental effects of aldrin in pregnant Syrian golden hamsters and CD1 mice that had received doses of aldrin in corn oil of either 50 mg/kg-day on gestation days (GD) 7, 8 and 9 (hamsters) or 25 mg/kg-day on GD 9 only (mice) via gavage. All hamsters were sacrificed on GD 14 and mice on GD 18, and the uteri were examined for live versus dead fetuses, visceral and skeletal abnormalities, etc. Both hamsters and mice showed an increased number of dead fetuses and a similar pattern of anomalies such as open eye, cleft palate and webbed feet. These data suggest the doses of aldrin used may be LOAELs for reproductive/developmental effects.

In a later experiment, Gellert and Wilson (1979) dosed pregnant Sprague-Dawley rats with 3 mg/kg aldrin in sesame oil on GDs 14–20 and monitored the F₁ females for changes in ovary, uterine or adrenal weights, while F₁ males were compared to untreated controls in mating trials. No aldrin-related effects were observed.

2.3.1.6 Studies Relevant for Mammalian TRV Development for Ingestion Exposures

Many of these toxicological studies suggest that the liver or the central nervous system is the target organ from aldrin exposure. In an attempt to forge the link between the observed toxicological consequences of the chemicals in different target species and the known effects of the compounds at the cellular and sub-cellular levels, Stephenson et al. (1999) examined the toxicology and metabolism of aldrin/dieldrin. The authors expressed the opinion that many of the toxicological/carcinogenicity studies of aldrin and dieldrin do not conform to current experimental design and documentation. In many of the studies, experimental design was altered part-way through, and often, exact measurements of exposure are not possible, requiring the use of default food factors in many cases. Notwithstanding the inadequacies of many of the experiments that provide data on which this Stephenson et al (1999) survey is built, however, there is adequate evidence that aldrin/dieldrin is one of a number of organochlorine compounds that (1) promote spontaneous liver tumor formation in aged mice, and (2) induce a number of non-carcinogenic hepatotoxic effects in other experimental animals.

Although the liver appears to be the primary target of aldrin toxicity, these effects are limited to cancer mechanisms or metabolism. Other important aspects include reports that aldrin has been linked to deleteriously affect survival of adults (Fitzhugh et al. 1964) and development of offspring (Ottolenghi et al. 1974). Adults survival of dogs in the Fitzhugh and Deichmann studies are not robust, since few animals were used and of these few deaths were attributable to treatment by the authors.

Ecological and health-related relevance of some hepatic observations may be equivocal if linked to cell proliferation and not adverse non-cancer cellular effects. However, where liver mass data are corroborated with necrosis, fatty degeneration and other adverse hepatic effects and where increase exposures lead to decreased survival and developmental abnormalities they clearly have relevance. This logic provides the basis for inclusion of studies in Table 2.

Neurological effects, either marked (e.g. convulsion) or less obvious (wasting) can be important adverse health effects (Fitzhugh et al. 1964, Deichmann et al 1969). The Ottolenghi et al (1973) study on the developmental effects of aldrin directly addresses an ecologically relevant parameter, but only one dose level was used precluding a dose-response relationship. These data suggest that adverse effects to pups occur at levels higher than that which are reported to cause neurological effects in other species (Fitzhugh et al. 1964, Deichmann et al 1969). Ideally, data from a chronic study is most relevant in deriving a TRV. Therefore, the two-year study on the effects of aldrin in rats (Fitzhugh et al 1964) was

chosen as most pertinent to TRV development. Rats exposed to aldrin, in this study, showed increased mortality with increased doses of aldrin.

Table 2. Summary of Relevant Mammalian Data for TRV Derivation

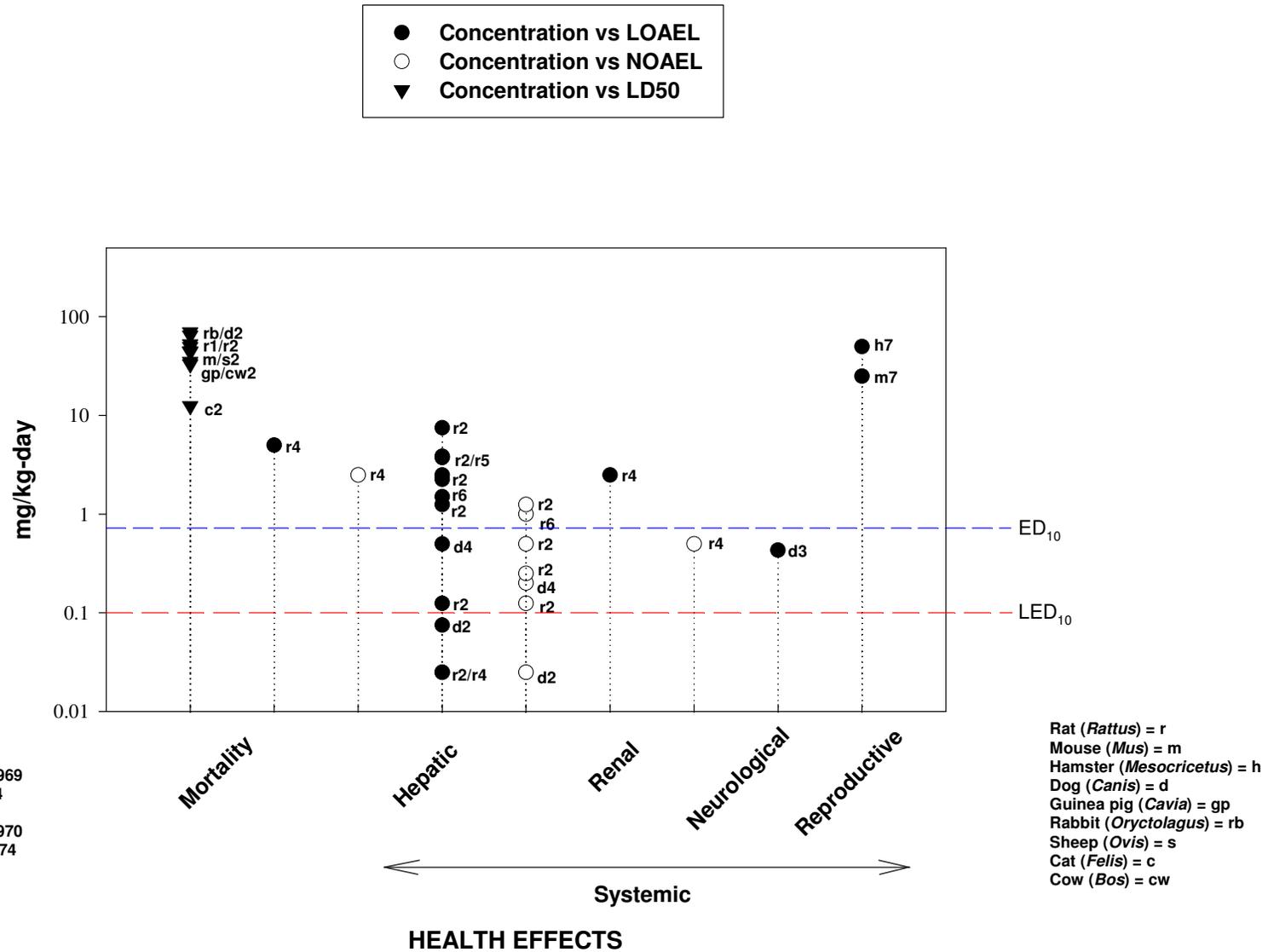
Study	Test Organism	Test Duration	Test Results		
			NOAEL (mg/kg/d)	LOAEL (mg/kg/d)	Effects Observed at the LOAEL
Deichmann et al. 1969	Dogs (Beagles)	10-m	NA	0.43	Neurological signs, excitation, tremors, etc
Fitzhugh et al. 1964	Rats (Osborne-Mendel)	2-y	NA 2.5	0.025 5.0	Histopathological lesions in the liver Adult mortality
	Dogs (Mongrel)	25-m	0.2	0.5	Histopathological lesions of the liver, kidney and bone marrow. Mortality/convulsions at 2 mg/kg/d and higher.
Hodge et al. 1967	Rats	Various	0.125–1.25	0.025–7.5	Increases in relative liver weight
	Dogs	ND	0.025	0.075	Increases in relative liver weight
Pallade et al. 1968	Rats	14-m	3	4.5	Mortality; increases in relative liver weight (steatosis)
Deichmann et al. 1970	Rats (Osborne-Mendel)	Lifetime	1.0	1.5	Increases in relative liver weight
Ottolenghi et al. 1974	Golden hamster	GD-7	NA	50	Increased mortality and abnormalities in litters.

GD = gestation day

NA = not applicable

Figure 1

ALDRIN: HEALTH EFFECTS TO MAMMALS



- 1 = Gaines 1969
- 2 = Hodge et al. 1967
- 3 = Deichmann et al. 1969
- 4 = Fitzhugh et al. 1964
- 5 = Pallade et al. 1968
- 6 = Deichmann et al. 1970
- 7 = Ottolenghi et al. 1974

2.3.3 Mammalian Inhalation Toxicity

No data are available on the inhalation toxicity of aldrin.

2.3.4 Mammalian Dermal Toxicity

No data are available on the dermal toxicity of aldrin.

2.4 Summary of Avian Toxicology

Numerous studies have been conducted to survey the presence of pesticides, polychlorinated biphenyls (PCBs), polycyclic aromatic hydrocarbons (PAHs), dioxins and dioxin-like residues in the bodily tissues, brains, or eggs of birds. The bibliographic database also contains some studies that have measured the dose-related impacts in birds of organochlorine pesticides such as aldrin/dieldrin in closely controlled experimental settings. For instance, an important concept to emerging from the research of Stickel and coworkers (see, for example, Stickel et al., 1983) is that it is possible to estimate levels of toxicants or their primary metabolites in the brains of birds indicating of (or correlating with) a state of ill-health or failure-to-thrive for a particular species. A related range of mostly lower concentrations of organochlorine residues representing "no adverse impact" tissue levels may also be discernable. In passerine species, Friend and Franson (2001) have collated mean sub- and supra-threshold brain concentration data for aldrin/dieldrin and other organochlorine pesticides. Respective concentrations of <8 or >18 ppm wet weight for dieldrin were documented, however, these data contrast with experimental observations in pheasants given capsules containing 0.5, 1.0, or 1.5 mg aldrin/week for 7 weeks (Hall et al. 1971). Dieldrin concentrations in the brains of 50% (22 total) high-dose recipients that died within 48 hours of the start of the experiment ranged from 2.13 to 4.25 ppm wet weight; equivalent values among survivors were 0.12–0.20 ppm.

Elevated levels of dieldrin in the brain also have been observed in birds involved in a "die-off" in the field (Flickinger 1979). In 1972 and 1974, a number of dead or moribund snow geese were found in an area of Texas close to rice fields that had been flooded with heavy rains soon after aldrin-treated seed had been planted. Brains of snow geese found moribund had an average concentration of dieldrin of 8.2 ppm, while brains of a sub-set of dead birds averaged 14.1 ppm dieldrin. Flickinger cites an earlier monograph by Stickel et al. (1969) to support a lower limit for the lethal level of dieldrin in brains of experimental and wild birds of 4–5 ppm, which agrees with the data of Hall et al. (1971).

Kan (1978) reviewed the ability of a number of organochlorine pesticides including aldrin/dieldrin to accumulate in birds by comparing the measured amounts of target substances in body fat or egg to the amount of these same substances in feed. When the parameters were expressed as a ratio, aldrin/dieldrin were shown to be among the compounds with high accumulation potential. That levels of aldrin/dieldrin

may be harmful to developing embryos has been demonstrated by Kuzan and Prahlad (1975) who injected fertile chicken eggs with either 0, 10, 20, 30, 40, or 50 ppm technical grade aldrin in corn oil. While hatchability was comparatively unaffected, in chicks receiving the higher concentrations of aldrin, increased mortality occurred within 3 days of hatching.

2.4.1 Studies Relevant for Avian TRV Development for Ingestion Exposures

Field studies have shown that aldrin can cause severe toxicity to exposed avian populations (Flickinger 1979). However, since exposure information is unavailable this data cannot be used to derive a TRV. The availability of suitable experimental data on the toxicity of aldrin to avian species is limited to two studies. Kuzan and Prahlad (1974) injected chicken eggs with several concentrations of aldrin and showed that while there were no effects on development or post-hatch chick mortality, but this study cannot be used to derive a TRV because the experimental design does not permit a realistic exposure route/level. Hall et al. (1971) conducted an oral toxicity study in which pheasants were given three levels of encapsulated aldrin on a weekly basis for six weeks. Observed effects included diminished growth and survival in pheasants exposed to the higher levels of aldrin. The no-observed-adverse-effect-level (NOAEL) for growth was 0.5 mg aldrin/kg/week and the corresponding low-observed-adverse-effect-level (LOAEL) was 1.0 mg aldrin/kg/week. Since TRVs are based on daily exposures, the weekly exposures incorporated by this study slightly compromise using the data for an avian TRV. However, given the low availability of suitable data and the toxicokinetics of aldrin (rapid conversion to dieldrin with deposition in fat), the weekly exposure levels were divided by 7 to estimate daily exposures. Dividing the NOAEL and LOAEL values by 7 yields the daily estimates of, respectively, 0.07 mg/kg/day and 0.14 mg/kg/day.

2.5 Amphibian Toxicology

Joseph and Rao (1990) reported aldrin LC₅₀s in *Rana hexadactyla* of 2.6 ppm (24 hours) and 2.4 ppm (48 hours) from waterborne exposures. The researchers also reported oral LD₅₀s of 2.2 mg/kg after 24 hours and 2.5 mg/kg after 48 hours.

2.6 Reptilian Toxicology

Aldrin/dieldrin was one of a number of organochlorine pesticides surveyed in non-viable Morelet's crocodile eggs collected from two lagoons in northern Belize (Wu et al. 2000). Although other residues such as DDE and methoxychlor were found, none tested positive for the aldrin. In one egg, the total concentration of organochlorines was 0.7 ppm. Lagoon sediments and nest material also tested positive for a range of organochlorine pesticides.

3. RECOMMENDED TOXICITY REFERENCE VALUES

3.1 Toxicity Reference Values for Mammals

3.1.1 TRVs for Ingestion Exposures for the Class Mammalia

Decreased survival was chosen as the endpoint on which the aldrin TRV is based because survival has clear and direct implications for wildlife populations. Rat mortality in the Fitzhugh et al (1964) study showed a clear dose-response. Other mortality reported in dogs were weak given few animals and other extraneous circumstances (Fitzhugh et al. 1964, Deichmann et al 1969). Other endpoints were ambiguous regarding adverse effects (e.g. hepatic changes). Using a default food factor for rats of 0.05, a NOAEL for this study was 2.5 mg/kg/d with original aldrin levels converted from ppm. The Fitzhugh et al (1964) study was suitably designed and executed and since this study evaluated the aldrin chronic toxicity, the data meets the minimum requirements of the Standard Practice, Section 2.2 (USACHPPM 2000) and therefore no uncertainty factors are required in the derivation of the TRV. The TRV for aldrin was derived using the Benchmark Dose approach and the results are presented in Table 4. Although three orders of mammals are represented by the studies, due to required estimation of dose in mg/kg/d units and due to the poor experimental design of many of the studies, a medium confidence rating is applied to these TRVs. Comparison of these values with that of reported adverse effects in other studies and species strongly suggest that they are relevant and protective of mammalian species.

Table 4. Selected Ingestion TRVs for the Class Mammalia

TRV	Dose	Confidence
LED ₁₀	0.1 mg/kg/d	Medium
ED ₁₀	0.7 mg/kg-d	Medium

3.1.2 TRVs for Inhalation Exposures for the Class Mammalia

Not available at this time.

3.2 Toxicity Reference Values for Birds

The endpoint chosen as the basis of the aldrin TRV for avian species was decreased growth seen in pheasants fed encapsulated aldrin (Hall et al. 1971). A lower growth rate can have ecologically relevant effects on birds because fledglings with greater mass have a higher probability of recruiting into the breeding population (Both et al 1999). Since only one study was located which characterized aldrin oral toxicity in birds, and that the study was of subchronic duration, the TRV was derived using the approximation approach. An uncertainty factor of 10 was used to obtain the NOAEL-based TRV from the subchronic NOAEL (0.07 mg/kg/day) and an uncertainty factor of 4 was used to derive the LOAEL-based TRV from the subchronic LOAEL (0.14 mg/kg/day). A low confidence rating was assigned to this avian TRV because only one study was located and, the experimental design included weekly, not daily, administration of aldrin.

Table 5. Selected Ingestion TRVs for the Class Aves

TRV	Dose	Confidence
NOAEL-Based	0.007mg/kg/d	Low
LOAEL-Based	0.035 mg/kg-d	Low

3.3 Toxicity Reference Values for Amphibians

There is very limited data on the effects of aldrin on amphibian species. Joseph and Rao (1990) reported oral LD₅₀s for aldrin in *Rana hexadactyla* of 2.2 mg/kg after 24 hours and 2.5 mg/kg after 48 hours. Since this data does not meet the minimum requirements outlined in the Standard Practice, Section 2.2 (USACHPPM 2000), uncertainty factors must be used to derive the TRV from the available acute toxicity data. The TRV is based on the 24 hour LD50 with an uncertainty factor of 100 for the NOAEL-based TRV and 20 for the LOAEL-based TRV. The amphibian TRV is given a low confidence rating due to the poor availability of data and the lack of representative species.

Table 6. Selected Ingestion TRVs for the Class Amphibia

TRV	Dose	Confidence
NOAEL-Based	0.02 mg/kg/d	Low

LOAEL-Based

0.1 mg/kg-d

Low

3.4 Toxicity Reference Values for Reptiles

Not available at this time.

4. IMPORTANT RESEARCH NEEDS

The limited availability of data on the toxicity of aldrin to wildlife species precludes the development of a high-confidence TRV. Hence, more studies on the toxicity of aldrin to wildlife species are needed. Particularly warranted are long-term (subchronic) toxicity studies focusing on non rodent species and exploring neurological endpoints. These studies should build on what has been done and refine consistent dose-response relationships. Reproductive studies investigating effects on F1 and F2 generations are also needed. Although there are a number of studies on the effects of aldrin on mammalian species, many of these are old and of poor quality. Further experimentation, with close attention to experimental design, would greatly increase confidence in aldrin TRVs. Controlled laboratory data are also needed for reptiles and bird investigating reproduction.

5. REFERENCES

- Agency for Toxic Substances and Disease Registry (ATSDR). 1993. Toxicological Profile for Aldrin/Dieldrin. TP-92/01. U.S. Department of Health and Human Services, Public Health Service.
- Ali, S.S., and A.R. Shakoori. 1990. Toxicology of aldrin in rats. *Punjab Univ. J. Zool.* 5: 1-56.
- Anon. 1980. In: *Priority Toxic Pollutants: Health Impacts and Allowable Limits*. Ed. Sittig, M. Noyes Data Corporation, Park Ridge, NJ.
- Both, C., M.E. Visser and N. Verboven. 1999. Density-dependent recruitment rates in great tits: the importance of being heavier. *Poc. R. Soc. Lond. B.* 266: 465-469.
- Davis, K.T., and O.G. Fitzhugh. 1962. Tumorigenic potential of aldrin and dieldrin for mice. *Toxicol. Appl. Pharmacol.* 4: 187-189.
- Deichmann, W.B., M. Keplinger, I. Dressler, and F. Sala. 1969. Retention of dieldrin and DDT in the tissues of dogs fed aldrin and DDT individually and as a mixture. *Toxicol. Appl. Pharmacol.* 14: 205-213.
- Deichmann, W.B., W.E. MacDonald, and F.C. Lu. 1979. Effects of chronic aldrin feeding in two strains of female rats and a discussion of the risks of carcinogens in man. In: *Toxicology and Occupational Medicine*. Elsevier/North-Holland, New York, NY. pp.407-413.
- Deichmann, W.B., W.E. MacDonald, E. Blum et al. 1970. Tumorigenicity of aldrin, dieldrin and endrin in the albino rat. *Ind. Med* 39: 426-434.
- Epstein, S.S. 1975. The carcinogenicity of dieldrin. Part 1. *Sci. Total Environ.* 4: 1-52.
- Fitzhugh, O.G., A.A. Nelson, and M.L. Quaife. 1964. Chronic oral toxicity of aldrin and dieldrin in rats and dogs. *Food Cosmet. Toxicol.* 2: 551-562.
- Flickinger, E.L. 1979. Effects of aldrin exposure on snow geese in Texas rice fields. *J. Wildlife Manage.* 43: 94-101.
- Friend, M., and J. C. Franson. 2001. Chlorinated Hydrocarbon Pesticides. In: *Field Manual of Wildlife Diseases: General Field Procedures and Diseases of Birds*. U.S. Geological Survey-National Wildlife Health Center, Madison, WI. pp. 295-302.
- Gaines, T.B. 1969. Acute toxicity of pesticides. *Toxicol. Appl. Pharmacol.* 14: 515-534.
- Gellert, R.J., and C. Wilson. 1979. Reproductive function in rats exposed prenatally to pesticides and polychlorinated biphenyls (PCB). *Environ. Res.* 18: 437-443.
- Hall, J.E., Y.A. Greichus, and K.E. Severson. 1971. Effects of aldrin on young pen-reared pheasants. *J. Wildlife Manage.* 35: 429-434.
- Hazardous Substances Databank (HSDB). 2001. On-line Database. National Library of Medicine. Washington, DC.

-
- Hodge, H.C., A.M. Boyce, W.B. Deichmann, and H.F. Kraybill. 1967. Toxicology and no-effects levels of aldrin and dieldrin. *Toxicol. Appl. Pharmacol.* 10: 613-675.
- Hutson, D.H. 1976. Comparative metabolism of dieldrin in the rat (CFE) and in two strains of mouse (CF1 and LACG). *Food Cosmet. Toxicol.* 14: 577-591.
- Joseph, K.V., and K.J. Rao. 1990. Toxic effects of aldrin on histopathology of intestine in the frog *Rana hexadactyla*. *J. Ecobiol.* 2: 161-165.
- Kan, C.A. 1978. Accumulation of organochlorine pesticides in poultry: A review. *J. Agric. Food Chem.* 26: 1051-1055.
- Kuzan, F.B., and K.V. Prahlad. 1975. The effects of 1,2,3,4,10,10-hexachloro-1,4,4a,5,8,8a-hexahydro endo, exo-5,8-dimethionaphthalene (aldrin) and sodium ethylenebisdithiocarbamate (Nabam) on the chick. *Poultry Sci.* 54: 105-1064.
- National Cancer Institute (NCI). 1978. Bioassays of aldrin and dieldrin for possible carcinogenicity. National Cancer Institute, National Institutes of Health, Bethesda, MD. NCI-CG-TR-21.
- Ottolenghi, A.D., J.K. Haseman, and F. Suggs. 1974. Teratogenic effects of aldrin, dieldrin and endrin in hamsters and mice. *Teratology* 9: 11-16.
- Pallade, S., C. Popovici, G. Rotaru, E. Gabrieliescu, and M. Dorobantu. 1968. Quelques donnees concernant l'action de l'aldrin sur le foie. *Med. Lavoro.* 59: 346-356.
- Reuber, M.D. 1977. Hepatic vein thrombosis in mice ingesting chlorinated hydrocarbons. *Arch. Toxicol.* 38: 163-168.
- Stevenson, D.E., E.F. Walborg, Jr., D.W. North et al. 1999. Monograph: Reassessment of human cancer risk of aldrin/dieldrin. *Toxicol. Lett.* 109: 123-186.
- Stickel, L.F., W.H. Stickel, R.A. Dyrland, and D.L. Hughes. 1983. Oxychlorane, HCS-3260 and nonochlor in birds: Lethal residues and loss rates. *J. Toxicol. Environ. Health.* 12: 611-622.
- Stickel, W.H., L.F. Stickel, and J.W. Spann. 1969. Tissue residues of dieldrin in relation to mortality of birds and mammals. In: *Chemical Fallout: Current Research on Persistent Pesticides*. Eds: Miller, M.W., and G.G. Berg. Charles C. Thomas, Springfield, Il. pp. 174-200. (as cited by Flickinger, 1979).
- U.S. Army Center for Health Promotion and Preventive Medicine (USACHPPM). 2000. *Standard Practice for Wildlife Toxicity Reference Values*, Technical guide 254.
- U.S. Environmental Protection Agency (U.S. EPA). 1997. Health Effects Assessment Summary Tables. FY-1997 Annual and FY-1997 Supplement. Office of Research and Development, Office of Emergency and Remedial Response, Washington, DC.
- U.S. EPA. 2001. Integrated Risk Information System. Online. Office of Health and Environmental Assessment, National Center for Environmental Assessment, Cincinnati, OH.
- Wu, T.H., T.R. Rainwater, S.G. Platt, S.T. McMurry, and T.A. Anderson. 2000. Organochlorine contaminants in Morelet's crocodile (*Crocodylus moreletii*) eggs from Belize. *Chemosphere.* 40: 671-678.

APPENDIX A

LITERATURE REVIEW

The following files were searched in DIALOG:

File 155 MEDLINE; File 156, TOXLINE, File 5 BIOSIS, File 35 Dissertation Abstracts, File 76 Life Sciences Collection, and File 185 Zoological Record.

The search strategy for **Amphibians & Reptiles**:

- ◆ The expression aldrin and its CAS number.
- ◆ AND (amphibi? or frog or frogs or salamander? or newt or newts or toad? or reptil? or crocodil? or alligator? or caiman? snake? or lizard? or turtle? or tortoise? or terrapin?)
- ◆ AND (reproduc? or dietary or systemic or development or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ RD (reduce duplicates)

The search strategy for **Birds**:

- ◆ The expression aldrin and its CAS number.
- ◆ And chicken? or duck or duckling? or ducks or mallard? or quail? or (japanese()quail?) or coturnix or (gallus(domesticus) or platyrhyn? or anas or aves or avian or bird? or (song()bird?) or bobwhite? or (water()bird) or (water()fowl)
- ◆ AND (reproduc? or dietary or systemic or development or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ RD (reduce duplicates)
- ◆ NOT (human? or culture? or (cell()line) or gene or vitro or inject or subcutane? or skin? or cancer? or salmonella or carcin? or tumo?)
- ◆ NOT (patient? or cohort? or worker? or child? or infant? or women or men or occupational)

The search strategy for **Wild Mammals**:

- ◆ The expression aldrin and its CAS number.
- ◆ AND (didelphidae or opossum? or soricidae or shrew? Or talpidae or armadillo? or dasypodidae or ochotonidae or leporidae)or canidae or ursidae or procyonidae or mustelidae or felidae or cat or cats or dog or dogs or bear or bears or weasel? or skunk? or marten or martens or badger? or ferret? or mink? Or aplodontidae or beaver? or sciuridae or geomyidae or heteromyidae or castoridae or equidae or suidae or dicotylidae or cervidae or antilocapridae or bovidae arvicolinae or mycocastoridae or dipodidae or erethizontidae or sigmodon? or (harvest()mice) or (harvest()mouse) or microtus or peromyscus or reithrodontomys or onychomys or vole or voles or lemming?

- ◆ AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ RD (reduce duplicates)

The search strategy for **Laboratory Mammals**:

- ◆ The expression aldrin and its CAS number.
- ◆ AND (rat or rats or mice or mouse or hamster? or (guinea()pig?) or rabbit? or monkey?)
- ◆ AND (reproduc? or diet or dietary or systemic or development? or histolog? or growth or neurological or behav? or mortal? or lethal? or surviv? or (drinking()water))
- ◆ NOT (human? or culture? or subcutaneous or vitro or gene or inject? or tumo? or inhalation or carcin? or cancer?)/ti,de
- ◆ RD (reduce duplicates)
- ◆ NOT (patient? or cohort? or worker? or child? or infant? or women or men or occupational)

The strategy outlined above yielded 23 hits for aldrin with reptiles/amphibians, 102 articles with birds, 61 with wild mammals and 126 articles with laboratory mammals.

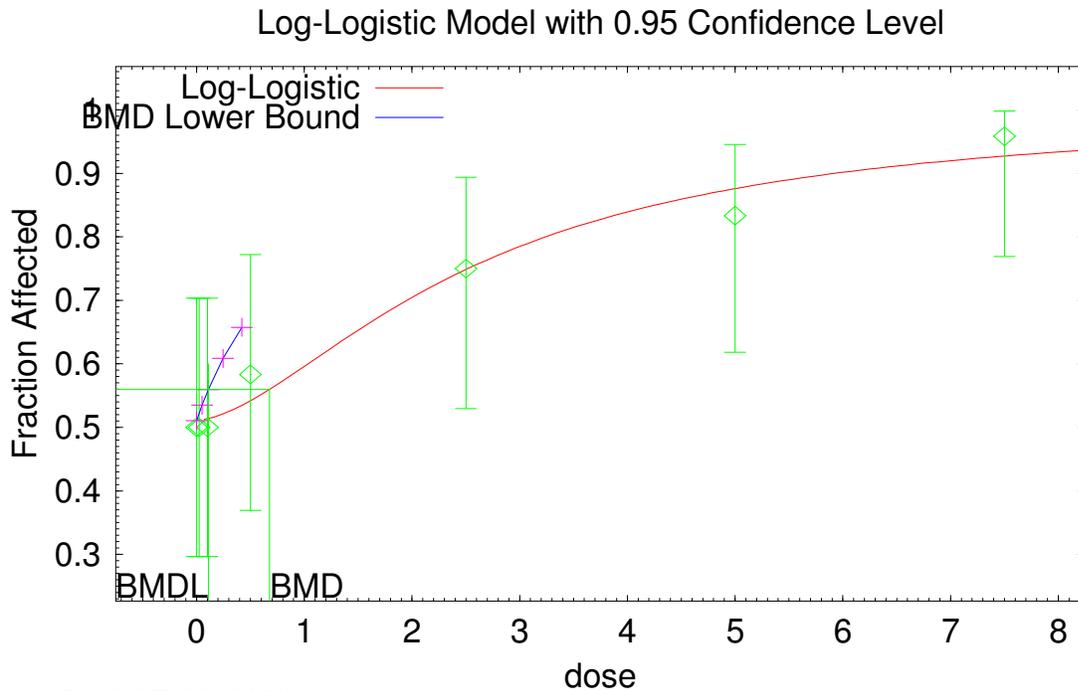
All abstracts from the DIALOG search were reviewed and encoded in ProCite. When the search retrieved an appreciable number of hits, *keywords in context* were reviewed to minimize costs before any abstracts were downloaded (Tier 1). However, when only a limited number of studies were identified by the search, the abstracts were downloaded at the time of the search (Tier 2).

As noted above and in Section 2.1, 312 hits on aldrin were obtained in the initial search, of which 51 were selected (Tier 2) as being relevant to this survey of the impacts of aldrin on wildlife.

APPENDIX B

Benchmark Dose Analysis for Mammals

Mortality data was used to derive the aldrin TRV for mammals and were obtained from Fitzhugh et al (1964). Model fit was acceptable, and a benchmark dose (BMD) and benchmark dose low (BMDL) were obtained from this analysis.



The form of the probability function is:

$$P[\text{response}] = \text{background} + (1 - \text{background}) / [1 + \text{EXP}(-\text{intercept} - \text{slope} * \text{Log}(\text{dose}))]$$

Dependent variable = Column2

Independent variable = COLUMN1

Slope parameter is restricted as slope \geq 1

Total number of observations = 7

Total number of records with missing values = 0

Maximum number of iterations = 250

Relative Function Convergence has been set to: 1e-008

Parameter Convergence has been set to: 1e-008

User has chosen the log transformed model

Default Initial Parameter Values

background = 0.5
 intercept = -0.665441
 slope = 1.07715

Asymptotic Correlation Matrix of Parameter Estimates

	background	intercept	slope
background	1	-0.56	0.48
intercept	-0.56	1	-0.97
slope	0.48	-0.97	1

Parameter Estimates

Variable	Estimate	Std. Err.
background	0.510595	0.0606218
intercept	-1.56308	1.88427
slope	1.63638	1.16633

Analysis of Deviance Table

Model	Log(likelihood)	Deviance	Test DF	P-value
Full model	-94.6737			
Fitted model	-95.1625	0.977634	4	0.9132
Reduced model	-107.614	25.881	6	0.0002343

AIC: 196.325

Goodness of Fit

Dose	Est._Prob.	Expected	Scaled		Residual
			Observed	Size	
0.0000	0.5106	12.254	12	24	-0.1038
0.0250	0.5108	12.260	12	24	-0.1062
0.1000	0.5130	12.311	12	24	-0.127
0.5000	0.5415	12.996	14	24	0.4114
2.5000	0.7475	17.940	18	24	0.02808
5.0000	0.8751	21.001	20	24	-0.6182
7.5000	0.9266	22.237	23	24	0.5968

Chi-square = 0.95 DF = 4 P-value = 0.9178

Benchmark Dose Computation

Specified effect = 0.1

Risk Type = Extra risk

Confidence level = 0.95

BMD = 0.678731

BMDL = 0.109029