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Provisional Peer Reviewed Toxicity Values for

Aldrin
(CASRN 309-00-2)

Superfund Health Risk Technical Support Center
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Acronyms

bw - body weight
cc - cubic centimeters
CD - Caesarean Delivered
CERCLA - Comprehensive Environmental Response, Compensation, and Liability Act of 1980
CNS - central nervous system
cu.m - cubic meter
DWEL - Drinking Water Equivalent Level
FEL - frank-effect level
FIFRA - Federal Insecticide, Fungicide, and Rodenticide Act
g - grams
GI - gastrointestinal
HEC - human equivalent concentration
Hgb - hemoglobin
i.m. - intramuscular
i.p. - intraperitoneal
i.v. - intravenous
IRIS - Integrated Risk Information System
IUR - Inhalation Unit Risk
kg - kilogram
L - liter
LEL - lowest-effect level
LOAEL - lowest-observed-adverse-effect level
LOAEL(ADJ) - LOAEL adjusted to continuous exposure duration
LOAEL(HEC) - LOAEL adjusted for dosimetric differences across species to a human
m - meter
MCL - maximum contaminant level
MCLG - maximum contaminant level goal
MF - modifying factor
mg - milligram
mg/kg - milligrams per kilogram
mg/L - milligrams per liter
MRL - minimal risk level
MTD - maximum tolerated dose
MTL - median threshold limit

NAAQS - National Ambient Air Quality Standards
NOAEL - no-observed-adverse-effect level
NOAEL(ADJ) - NOAEL adjusted to continuous exposure duration
NOAEL(HEC) - NOAEL adjusted for dosimetric differences across species to a human
NOEL - no-observed-effect level
OSF - Oral Slope Factor
p-RfD - provisional Oral Reference Dose
p-RfC - provisional Inhalation Reference Concentration
p-OSF - provisional Oral Slope Factor
p-IUR - provisional Inhalation Unit Risk
PBPK - physiologically based pharmacokinetic
ppb - parts per billion
ppm - parts per million
PPRTV - Provisional Peer Reviewed Toxicity Value
RBC - red blood cell(s)
RCRA - Resource Conservation and Recovery Act
RGDR - Regional deposited dose ratio (for the indicated lung region)
REL - relative exposure level
RGDR - Regional gas dose ratio (for the indicated lung region)
RfD - Oral Reference Dose
RfC - Inhalation Reference Concentration
s.c. - subcutaneous
SCE - sister chromatid exchange
SDWA - Safe Drinking Water Act
sq.cm. - square centimeters
TSCA - Toxic Substances Control Act
UF - uncertainty factor
ug - microgram
umol - micromoles
VOC - volatile organic compound

3-14-2005

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR ALDRIN (CASRN 309-00-2)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions or the EPA Headquarters Superfund Program sometimes request that a frequently used PPRTV be reassessed. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

The HEAST (U.S. EPA, 1997a) lists a subchronic RfD of 3E-5 mg/kg-day for aldrin adopted from the chronic RfD of the same value listed on IRIS (U.S. EPA, 2003a). The chronic RfD was based on an estimated LOAEL of 0.025 mg/kg-day for liver toxicity (centrilobular histopathology and increased relative organ weight) in rats exposed to aldrin in the diet at a concentration of 0.5 ppm for two years (Fitzhugh et al., 1964). In this derivation, a total uncertainty factor of 1000 (10 to extrapolate from animals to humans, 10 to protect sensitive individuals, and 10 for the use of a LOAEL) was applied to the LOAEL. The chronic RfD is also included in the Drinking Water Standards and Health Advisories List (U.S. EPA, 2002) and the OPP reference dose tracking report (U.S. EPA, 1997b), which includes an identical OPP RfD for aldrin. A Health Effects Assessment (HEA) for aldrin did not derive subchronic or chronic oral RfDs for aldrin because the compound was classified as a carcinogen (U.S. EPA, 1987a).

No other relevant documents were included in the CARA list (U.S. EPA, 1991, 1994a). ATSDR (2002) calculated a chronic oral minimum risk level (MRL) of 3E-5 mg/kg-day for aldrin also using the study of Fitzhugh et al. (1964) and the same uncertainty factors employed in the IRIS derivation. ATSDR (2002) did not derive an intermediate (subchronic) oral MRL because the available studies were not considered to be suitable.

An RfC for aldrin is not listed on the HEAST (1997a) or on IRIS (U.S. EPA, 2003a). The HEA (U.S. EPA, 1987a) indicated that inhalation data for aldrin, limited to monitoring studies in humans, were insufficient to derive an RfC. ATSDR (2002) did not derive inhalation MRLs for aldrin because no suitable quantitative data were available from the existing inhalation studies. The threshold limit value (TLV-TWA) established by ACGIH (2001, 2002), the recommended exposure limit (REL-TWA) set by NIOSH (2002) and the permissible exposure limit (PEL-TWA) established by OSHA (2002) for aldrin are each set at 0.25 mg/m^3, with notations for skin absorption and carcinogenicity (TLV and REL only, see next paragraph); the levels are intended to protect against effects in the liver (increased organ weight, parenchymatous degeneration and necrosis observed in rats), central nervous system (ranging from headache to convulsions in humans), and kidney (parenchymatous degeneration observed in rats and dogs).

The HEAST (1997a) cites IRIS as the primary source for the carcinogenicity assessment of aldrin. On IRIS (U.S. EPA, 2003a), aldrin is classified as a Group B2, possible human carcinogen, based on inadequate evidence in humans and sufficient evidence in mice. A human oral q_1* of 17 $(mg/kg\text{-}day)^{-1}$ for aldrin is presented based on data for hepatic carcinoma in mice; an inhalation unit risk of 4.9E-3 ($\mu g/m^3$) was derived by extrapolation from the oral data (U.S. EPA, 2003a). The source document for this assessment was a Carcinogenicity Assessment (U.S. EPA, 1987b). IARC (1974, 1987, 2002) determined that aldrin is not classifiable as to its carcinogenicity to humans (Group 3) based on an inadequate data in humans and limited data in animals (definitive positive results in mice but not in rats). ACGIH (2001, 2002) included an A3 notation in its TLV assessment for aldrin to indicate the compound's status as a confirmed animal carcinogen with unknown relevance to humans. The NIOSH (2002) REL also noted the carcinogenicity of aldrin to animals in the same organs: lungs, liver, thyroid and adrenal glands.

An Environmental Health Criteria document on aldrin and dieldrin (WHO, 1989), a Health Effects Support Document for Aldrin/Dieldrin (U.S. EPA, 2003b), a toxicity review on chlorinated hydrocarbon pesticides (Bus and Leber, 2001), a review on the long-term health effects of aldrin and dieldrin (de Jong, 1991), an occupational hazard review on aldrin and dieldrin (NIOSH, 1978) and the NTP (2002a, 2002b) management status report and health and safety report for aldrin were consulted for relevant information. Literature searches were conducted for the period from 1999 to October 2002 to identify data relevant for the derivation of a provisional RfD, RfC and cancer assesment for aldrin. The following databases were searched: TOXLINE, MEDLINE, CANCERLIT, NTIS/BIOSIS, RTECS, HSDB, GENETOX,

CCRIS, TSCATS, EMIC/EMICBACK, and DART/ETICBACK. Additional literature searches were conducted by NCEA-Cincinnati from 2002 through May 2004 using TOXLINE, MEDLINE, Chemical and Biological Abstracts databases.

REVIEW OF PERTINENT DATA

Human Studies

No data were located for chronic or subchronic toxicity in humans following quantified exposures by the oral route. Acute oral exposures to aldrin have been reported to result in neurological effects that include headache, dizziness, nausea, vomiting, malaise, myoclonic jerks of the limbs, clonic and tonic convulsions, and coma (NIOSH, 1978; U.S. EPA, 1987b; de Jong, 1991; ACGIH, 2001; Bus and Leber, 2001; U.S. EPA, 2003b). A 23-year-old male who ingested 25.6 mg/kg exhibited convulsions within 20 minutes, followed by hematuria and azotemia that lasted 18 days, restlessness, hypothermia and tachycardia that lasted 5 days, and abnormalities in electroencephalograms (generalized cerebral dysrhythmia) that lasted for six months. Estimates for the lowest human lethal dose of aldrin range between 1.25 and 10 mg/kg (de Jong, 1991; U.S. EPA, 2003b).

No data were located for chronic or subchronic toxicity in humans following quantified exposures by the inhalation route. Dermal absorption is presumed to account for the major fraction of the absorption following exposures of unprotected industrial or agricultural workers to aldrin dust, and undoubtedly some oral absorption also occurs under these conditions (de Jong, 1991; Bus and Leber, 2001).

Epidemiological studies have been conducted to evaluate the cancer risk following occupational exposure to aldrin. The IRIS document for aldrin (U.S. EPA, 2003a) indicated that two different epidemiological studies did not quantify exposure in workers and were limited in their ability to detect an excess of deaths from cancer (Van Raalte, 1977; Ditraglia et al., 1981); subjects in both studies had also been exposed to other pesticides in addition to aldrin. Increases (not statistically significant) in standard mortality ratios for a few cancer sites (rectum, esophagus, and lymphatic/hemopoietic cancer) identified in the study of Ditraglia et al. (1981) did not persist in subsequent follow-up studies of the cohort (Brown, 1992; Amoateng-Adjepong et al., 1995). The mortality in these studies was not associated with any cancer events in the rectum, esophagus or lymphatic/hematopoietic system. However, an increase in deaths in male workers from cancer of the liver and biliary tract that was observed in the study of Ditraglia et al. (1981) was found to be significant in the study of Brown (1992). Amoateng-Adjepong et al. (1995) reported that excess deaths from hepatobiliary cancer were significantly increased only for hourly paid workers, but were not correlated with increasing duration of employment.

de Jong (1991) conducted an epidemiological study in Dutch petrochemical workers exposed primarily by dermal contact and inhalation to aldrin and sometimes also to dieldrin. In this study, 570 workers (gender not identified) primarily exposed between January 1954 and January 1970 were followed up for mortality until January 1987. The study used extensive data for industrial hygiene and job histories to assess exposures to aldrin/dieldrin retrospectively. In addition, biological monitoring data, based on blood levels of dieldrin, a persistent metabolite of aldrin, were available for 343 of the workers for the period 1963-1970; data from these workers was used to estimate exposures in workers with similar job histories for which blood data were not available. Estimates of daily and total intakes of dieldrin were calculated for each member of the cohort and three levels of exposure (low, moderate and high) were identified; the average daily intake of dieldrin was calculated as 488 µg/day, ranging from 12 to 7000 µg/day. The standard mortality ratio for the exposed cohort was lower than expected based on the mortality of the general population. No increases were observed in the cancer mortality and no specific cancer sites predominated. In a follow-up study, de Jong et al. (1997) extended analysis of the cohort up to January 1993. Total mortality and total mortality from cancer were lower than expected. The number of deaths (6) from rectal cancer was significantly higher than expected (1.5) (SMR = 390.4 [95% CI:143-850]); however there was not a clear dose relationship (SMR 865 [95% CI: 174-2526], 201 [95% CI :3-1117], and 289 [95% CI: 32-1044] in the low-, moderate- and high-exposure groups, based on 3, 1, and 2 deaths, respectively). Two deaths (one each in the low- and moderate-exposure groups) from liver cancer were not significantly higher than expected (0.9) (SMR = 225 [95% CI: 27-813]). The authors concluded that the study does not provide support for the carcinogenicity of aldrin and dieldrin in exposed workers.

Animal Studies

Several subchronic and chronic oral toxicity studies have been conducted in rodents and subchronic studies in dogs exposed to aldrin in the diet (U.S. EPA, 1987a, 2003a,b; WHO, 1989; Bus and Leber, 2001). Hepatotoxicity (hepatomegaly, histopathological degenerative changes) and neurotoxicity (degenerative brain histopathology, hypersensitivity, twitching, tremors and convulsions) were the major effects observed in exposed rats, mice and dogs. Hepatic carcinogenicity was reported in oral studies in mice, but not in rats (U.S. EPA, 1987b, 2003a). The oral database for aldrin also includes developmental toxicity studies in dogs, hamsters, rats and mice, and reproductive toxicity studies in dogs, rats and mice (U.S. EPA, 1987a, 2003b; WHO, 1989; Bus and Leber, 2001). These studies reported reduced fetal survival and/or increases in malformations at doses that were maternally toxic.

Subchronic oral toxicity studies on aldrin examined a limited array of endpoints. Treon and Cleveland (1955) conducted intermediate mortality studies on dogs and rats exposed to aldrin (95% purity) in the diet. Groups of beagle dogs (2-3 male and 2 female) were given diets containing 1, 3, 10, 25 or 50 ppm aldrin for 5 or 6 days per week for up to 15.6 months. Other methods, such as vehicles to dissolve aldrin, were not described systematically, but are inferred

from the reported results. Body weight was recorded weekly. At termination, dogs were necropsied and organ weights were recorded for liver, kidneys, heart, brain, spleen and fat. The liver and kidneys were examined for histopathology. Hemocytology analyses were conducted, but endpoints were not specified. Doses between 0.9 and 9.1 mg/kg-day (10-50 ppm levels) were lethal to all dogs. All dogs that received doses between 0.9 and 1.8 mg/kg-day (10 ppm group) died within 6.7 months. No deaths occurred among dogs exposed to 3 ppm (0.12-0.25 mg/kg-day) or 1 ppm (0.043-0.091 mg/kg-day) for up to 15.6 months. Aldrin had no effect on body weight or hemocytology parameters (not specified). Treatment at ≥3 ppm increased the absolute and relative liver weights in both sexes. Histopathology of the liver (local hyaline droplet degeneration) and kidneys (renal tubular degeneration or vacuolization) was observed in male dogs at ≥3 ppm and female dogs at ≥1 ppm. Male and female dogs that died (that is, those exposed at ≥10 ppm or ≥0.9 mg/kg-day) had diffuse degenerative changes in the liver, kidneys and brain. The 1 ppm dietary level (0.043-0.091 mg/kg-day) was a LOAEL for renal histopathology in female dogs. A NOAEL was not identified.

NCI (1978) conducted subchronic range-finding feeding bioassays on aldrin (technical grade, >85% purity) to establish maximum tolerated doses for carcinogenicity studies in rats and mice. Groups of Osborne-Mendel rats (5/sex/group) were given diets containing 0, 40, 80, 160 or 320 ppm of aldrin for six weeks and observed for an additional two weeks. Using reference values for body weight and food consumption (U.S. EPA, 1988), doses are estimated as 0, 3, 7, 14 and 28 mg/kg-day for male and 0, 4, 8, 16 and 32 mg/kg-day for female rats. Dose-related mortality was observed in both sexes at ≥160 ppm. Body weight gain was depressed consistently in males at 320 ppm. No additional information was provided. No effects were observed at the 80 ppm dietary level (7 or 8 mg/kg-day in male or female rats respectively), based on limited evaluations.

In the subchronic range-finding assay in $B6C3F_1$ mice (5/sex/group), NCI (1978) provided diets containing 0, 2.5, 5, 10, 20, 40 or 80 ppm of aldrin technical grade, >85% purity) for six weeks and then control diets for two weeks. Using reference values for body weight and food consumption (U.S. EPA, 1988), doses are estimated as 0, 0.5, 1, 2, 4, 7 and 14 mg/kg-day in male and 0, 0.5, 1, 2, 4, 8 or 16 mg/kg-day in female mice. Dose-related increases in mortality were observed in both sexes at ≥20 ppm. Aldrin had no effect on body weight gain. No additional information was provided. No effects were observed at the 10 ppm dietary level (4 mg/kg-day) in male or female mice, based on limited evaluations.

A single new oral study was located in the literature search. Paul et al. (1992) evaluated the effect of subchronic oral exposure to aldrin or endosulfan on muscle coordination, learning and memory in rats. Groups of Wistar rats (10/sex/group) were given 0 or 1 mg/kg-day of aldrin by gavage in an aqueous suspension with tragacanth powder daily for 90 days. Motor coordination (balancing on a moving rod) was measured prior to exposure and on every 15^{th} day of treatment. Unconditioned and conditioned avoidance tests were conducted after 90 days of

treatment. Rats were tested for their ability to learn the correct behavior (pole climbing) for avoiding a buzzer/shock in 15 trials; subsequently (the next day) the time for their conditioned response to the buzzer alone was measured in 15 trials. The authors reported that treatment with aldrin had no effect on growth or behavior but did not report any methods or data for these endpoints. Treatment reduced the ability of male and female rats to remain balanced on a moving rod, indicating impairment of motor coordination; male were more severely affected than females. Treated male and female rats demonstrated an inhibition in the ability to learn the correct avoidance behavior compared to controls; 6 trials were needed before all controls were successful, whereas 12 trials were needed before all treated rats were successful. The responding time of all rats to a conditioned stimulus declined with each repetition, reaching a constant value after the 7th trial; however, the response time was slightly slower (about four seconds longer) for treated rats compared to controls. This study identifies a LOAEL of 1 mg/kg-day for neurological impairment (reduced motor coordination, learning ability and delayed response to conditioned stimulus) in rats exposed by gavage for 90 days.

No additional chronic oral animal data were found in the literature search beyond those studies already reviewed by U.S. EPA (1987a, 2003a). Thus, there is no new information to challenge the basis for the chronic RfD on IRIS, namely, the estimated LOAEL of 0.025 mg/kg-day in the 2-year dietary study in rats (Fitzhugh et al., 1964).

Reproduction studies in dogs did not establish no-effect levels for aldrin (WHO, 1989; U.S. EPA, 2003b). Deichmann et al. (1971) administered aldrin (95% purity) by capsule to groups of beagles at doses of 0.15 mg/kg-day (4 females) or 0.3 mg/kg-day (4 males, 3 females) 5 days/week for 14 months. Dogs were mated and the viability of pups recorded. Estrous cycles were delayed 7 to 12 months in treated females and some males exhibited a depressed sexual drive. Mammary development and milk production were severely depressed in treated females. A dose-related decrease in pup survival at weaning was observed: 85, 75 and 44% in the control, low- and high-dose groups, respectively. The low dose of 0.15 mg/kg-day is a LOAEL for reproductive effects (reduced pup survival) in dogs.

In another reproduction study in dogs, Kitselman (1953) fed aldrin (99% purity) in dosed meatballs to groups of mongrel dogs (1-2/sex/group) at doses of 0, 0.2, 0.6 or 2.0 mg/kg-day for one year. Aldrin had no apparent effect on fertility or pregnancy rates. In all treated groups, pups were born with no obvious defects, but died within three days and exhibited degenerative changes in the liver and renal tubules. Treated females also exhibited degenerative changes in the liver. The low dose of 0.2 mg/kg-day in this study is a LOAEL for reproductive toxicity (hepatic and renal toxicity in pups exposed during gestation and hepatic toxicity in bitches).

Reproductive and developmental oral toxicity studies for aldrin were also conducted in rodents (WHO, 1989; U.S. EPA, 2003b). In a three-generation study, Treon and Cleveland (1955) fed groups of male and female Carworth rats (group sizes not reported) diets containing

0, 2.5, 12.5 or 25 ppm of aldrin. U.S. EPA (2003b) estimated doses as 0, 0.125, 0.624 and 1.25 mg/kg-day. Two litters were produced for each generation. Treatment had no effect on numbers of live pups per litter or pup weights at weaning (postnatal day 21), but reduced the viability of pups during lactation in a dose-specific manner. The low dose of 0.125 mg/kg-day is a LOAEL for reduced viability in rat pups.

In a six-generation study, Keplinger et al. (1970) fed Swiss white mice (4 males and 14 females per group) diets containing 0, 3, 5, 10 or 25 ppm of aldrin (purity not reported). U.S. EPA (2003b) estimated doses as 0, 0.45, 0.75, 1.5 or 3.75 mg/kg-day. The 3.75 mg/kg-day dose was discontinued because of high litter mortality. Reduced pup survival during lactation was observed in the 0.75 and 1.5 mg/kg-day groups. No effects on fertility, viability or gestation were observed in the 0.45 mg/kg-day group. The lowest dose of 0.45 mg/kg-day was a NOAEL and 0.75 mg/kg-day was a LOAEL for reduced pup survival during lactation in mice.

Ottolenghi et al. (1974) conducted developmental toxicity studies in which pregnant mice (groups of 10) or hamsters (groups of 41-43) were given a single gavage dose of aldrin (in corn oil) at half the median lethal dose during gestation; the studies included both untreated and vehicle-only controls. In pregnant CD-1 mice, treatment with aldrin at 25 mg/kg-day on gestational day (GD) 9, had no effect on fetal survival or body weight. However, the number of live fetuses with malformations (webbed feet, cleft palate and open eyes) was significantly increased (33%). Maternal toxicity was observed. In pregnant Syrian golden hamsters, treatment with 50 mg/kg-day on GD 7, 8 or 9 significantly reduced the number of live fetuses and fetal weight and increased the incidence of fetal abnormalities (webbed feet, cleft palate and open eyes).

No adequate inhalation toxicity studies in animals were found in the review documents or the literature search. According to ATSDR (2002), Treon et al. (1957) exposed animals to unknown concentrations of aldrin vapor/particles generated by sublimating aldrin at 200°C; however, these studies are confounded by the presence of uncharacterized thermal decomposition products.

Other Studies

Absorption of aldrin in humans or animals occurs following exposure by any route (ATSDR, 2002). Since aldrin is readily metabolized in both humans and animals, it is rarely detected in distribution studies; the metabolite dieldrin is the primary marker for aldrin exposure. Based on studies in volunteers and human cadavers, the relative steady-state distribution of dieldrin in human whole blood, brain gray matter, brain white matter, liver and adipose tissue is estimated as 1, 2.8, 4.2, 22.7 and 136, respectively (U.S. EPA, 2003b). Dieldrin persists in the body with a mean half-life of ~8 months (de Jong, 1991). In humans and rodents, dieldrin has

been detected in breast milk and has been shown to pass through the placenta (ATSDR, 2002; U.S. EPA, 2003b).

The biotransformation of aldrin to dieldrin has been detected in the liver, lung and skin, (ATSDR, 2002; U.S. EPA, 2003b). Mixed function oxidases (cytochrome P-450) are responsible for the epoxidation of aldrin to dieldrin in mammalian hepatocytes; rates of conversion are higher in male rats and mice than in females. *In vitro* studies suggest that the conversion of aldrin in tissues with a low cytochrome P-450 content is carried out by an arachadonic acid-dependent prostaglandin endoperoxide synthase pathway (ATSDR, 2002; U.S. EPA, 2003b). 9-Hydroxydieldrin has been identified as a fecal metabolite in humans and animals. Other metabolites include pentachloroketone, 6,7-trans-dihydroxydihydroaldrin (and its glucuronide conjugate), the glucuronide conjugate of 9-hydroxydieldrin, and aldrin dicarboxylic acid. The relative proportion of the metabolites varies by species, strain and sex (U.S. EPA, 2003b).

In humans and rodents, excretion following oral exposure is primarily in the feces via the bile, with smaller amounts in the urine (ATSDR, 2002). Excretion via lactation has also been described in for humans and rodents (ATSDR, 2002; U.S. EPA, 2003b).

Neurological effects of aldrin have been attributed to alterations in brain neurotransmitters, specifically GABA (γ-aminobutyric acid) (Ecobichon, 2002). Treatment of rats with single gavage doses between 2 and 10 mg/kg or with 2 mg/kg-day for 12 days altered GABA parameters in the brain and increased locomotor activity within two hours of administration (Jamaluddin and Poddar, 2001a,b). The increased locomotor activity was attributed to an activation of glutamate and concomitant inhibition of the GABA system in the cerebellum, hypothalamus and pons-medulla. In a biophysical study, aldrin was demonstrated to change the fluidity of model phospholipid bilayers, increasing the fluidity of bilayers enriched with cholesterol (Demétrio et al., 1998). The results of this study suggest that *in vivo*, intercalation of aldrin into the hydrophobic layer of neuronal cell membranes may contribute to the perturbed function of embedded proteins such as the GABA receptor.

Daily subcutaneous administration of aldrin to pregnant Wistar rats at a dose of 1 mg/kg-day throughout gestation had no teratogenic effect and no effect on body weights in pups, although subtle effects were observed in pups postnatally (Castro et al., 1992). Treated pups showed significant changes in the average timing of certain developmental landmarks; the appearance of incisor eruption was accelerated (on day 4.4 compared to 6.6 for controls), whereas the descent of the testes was delayed (day 31.5 compared to 21.0 for the controls). The timing of pinna detachment, fur development, ear opening and eye opening were not significantly affected. Treated pups also showed significantly higher scores in locomotor frequency tests conducted at 21 and 90 days. Histological examination of brain sections did not reveal overt changes in brain structure that could have contributed to the behavioral effects.

Genotoxicity assays for aldrin were primarily negative in bacteria, but were occasionally positive in mammalian systems, possibly reflecting a requirement for bioactivation. In several studies, aldrin did not induce reverse mutations in *Salmonella typhimurium* (strains TA98, TA100, TA1535, TA1537 or TA1538), *Escherichia coli* or *Bacillus subtilis*, with or without metabolic activation (U.S. EPA, 1987b, 2003a,b; ATSDR, 2002). With or without metabolic activation, aldrin did not cause gene conversion, but did induce reverse mutations in *Saccharomyces cerevisiae* (U.S. EPA, 2003b). In a mouse dominant lethal mutation assay, aldrin reduced the levels of implantations, but the results were not statistically significant (U.S. EPA, 2003b). Aldrin did not induce heritable sex-linked recessive lethal mutations in *Drosophila melanogaster* (U.S. EPA, 2003b). Aldrin induced chromosomal aberrations in human lymphocytes *in vitro* and rat and bone marrow cells of orally-exposed mice, but only at cytotoxic concentrations (U.S. EPA, 2003a,b; ATSDR, 2002). Results of assays for unscheduled DNA synthesis were negative in primary rat hepatocytes and human lymphocytes, but were positive in transformed human fibroblasts *in vitro* (U.S. EPA, 2003b). Aldrin did not induce breakage of plasmid DNA in *E. coli* in the absence of metabolic activation but did induce DNA breakage in rat hepatocytes (U.S. EPA, 2003b).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR ALDRIN

A **chronic RfD of 3E-5 mg/kg-day** is listed for aldrin on IRIS (U.S. EPA, 2003a), based on a LOAEL of 0.025 mg/kg-day for hepatotoxicity (centrilobular lesions and increased liver weight) in rats exposed to 0.5 ppm of aldrin in the diet for two years (Fitzhugh et al., 1964). The presence of a chronic RfD on IRIS precludes derivation of a provisional chronic RfD for this chemical.

The data were reviewed in order to determine the most suitable basis for derivation of a subchronic RfD. Neurotoxicity is the primary effect of aldrin exposure in humans. Aldrin intoxication has been observed following exposures that resulted in a dieldrin concentration in blood higher than 200 ng/mL (de Jong, 1991). The body-burden of dieldrin, which persists in fatty tissue, determines whether a particular exposure would increase the blood concentration of dieldrin above the critical level. Induction of liver enzymes in humans has a lower threshold for dieldrin in blood: 105 ng/mL (de Jong, 1991). Hepatic and neurological changes have been described in rodents orally exposed to aldrin. Hepatic effects (increased organ weight, enlarged centrilobular hepatocytes) were observed in Osborne-Mendel rats exposed to aldrin at a dietary concentration of 0.5 ppm for two years, and nephritis was observed at higher exposure levels (Fitzhugh et al., 1964); the study did not establish a NOAEL. This LOAEL, estimated at 0.025 mg/kg-day, was the lowest effect-level identified among the numerous oral toxicity studies

reviewed by U.S. EPA (1987a, 2003a) and, as mentioned above, was the basis for the chronic RfD of 3E-5 mg/kg-day on IRIS, as well as the subchronic RfD in the HEAST (U.S. EPA, 1997).

Most of the available subchronic toxicity information for aldrin is in studies that were conducted prior to the establishment of current standard protocols. A LOAEL of 0.043 mg/kg-day was identified for renal toxicity (renal tubular degeneration) in beagles exposed to aldrin at a dietary concentration of 1 ppm for nearly 16 months (Treon and Cleveland, 1955). Renal and hepatic effects (degenerative lesions) were observed at the 3 ppm dietary level (0.12-0.25 mg/kg-day) and degenerative lesions in brain, liver and kidneys were observed in dogs fed at or above the 10 ppm level (≥0.9 mg/kg-day). The only newly-located study reported changes in neurobehavioral parameters (impairments in motor coordination, learning and conditioned response times) in rats given 1 mg/kg-day of aldrin by gavage for 90 days (Paul et al., 1992). The NCI (1978) 6-week range-finding studies in rats and mice did not evaluate any endpoints aside from mortality and body weight effects; therefore, the apparent NOAELs in these assays (8 mg/kg-day in rats and 4 mg/kg-day in mice) are not supported by histopathology data. Aldrin had adverse effects on reproduction in dogs exposed in the diet at doses of 0.15 mg/kg-day or higher (Deichmann et al., 1971): delayed estrus and reduced mammary development and milk production in females, reduced sex drive in males, and reduced pup survival at weaning. Another reproductive study reported no effects on fertility or pregnancy rates in dogs at ≥0.2 mg/kg-day, but increases in degenerative hepatic lesions in bitches and increased postnatal mortality of pups, concomitant with degenerative hepatic and renal lesions (Kitselman, 1953). In a 3-generation feed study in rats, reduced pup survival at weaning was observed at ≥0.125 mg/kg-day (Treon and Cleveland, 1955). In a 6-generation study in mice, 0.45 mg/kg-day was a NOAEL and 0.75 mg/kg-day was a LOAEL for reduced pup survival during lactation (Keplinger et al., 1970). A single gavage dose of 25 mg/kg during gestation increased the incidence of fetal abnormalities but did not affect fetal survival or body weight in mice (Ottolenghi et al., 1974). In hamsters, a single gavage dose of 50 mg/kg during gestation reduced fetal survival and body weight and increased the incidence of fetal abnormalities (Ottolenghi et al., 1974). Reproductive and developmental effects of aldrin appear to occur at maternally-toxic doses.

The LOAEL of 0.043 mg/kg-day for renal lesions in the 16-month toxicity study in beagles (Treon and Cleveland, 1955) can serve as the basis for the subchronic RfD for aldrin. Since developmental studies indicate that fetal effects of aldrin occur at maternally-toxic doses, an RfD based on this LOAEL should be protective against fetal effects (U.S. EPA, 2003b). The provisional **subchronic RfD of 4E-5 mg/kg-day for aldrin** is derived by applying an uncertainty factor of 1000 (10 to extrapolate from dogs to humans, 10 to protect sensitive individuals and 10 for the use of a LOAEL) to the dog LOAEL of 0.043 mg/kg-day, as follows:

subchronic p-RfD = subchronic LOAEL / UF
= 0.043 mg/kg-day / 1000
= 0.00004 or 4E-5 mg/kg-day

Confidence in the critical subchronic study is low because, although it evaluated a range of doses, and included examinations for histopathology and hemocytology, it had relatively small group sizes, omitted some toxicological endpoints (clinical chemistry, and urinalysis), did not identify a NOAEL, and was poorly documented. Confidence in the database is medium since reproductive studies were available, but NOAELs were lacking for some supporting studies. Low-to-medium confidence in the provisional subchronic RfD for aldrin results.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR ALDRIN

No human or animal inhalation data were located, precluding derivation of a subchronic or chronic p-RfC for aldrin.

DERIVATION OF A PROVISIONAL CARCINOGENICITY ASSESSMENT FOR ALDRIN

A cancer assessment, including derivation of an oral slope factor of 17 per mg/kg-day and an inhalation unit risk 4.9E-3 per $\mu g/m^3$, is available for aldrin on IRIS (U.S. EPA, 2003a), precluding derivation of a provisional carcinogenicity assessment for this chemical.

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