CHAPTER 1. RELEVANCE TO PUBLIC HEALTH

1.1 OVERVIEW AND U.S. EXPOSURES

Endrin [2,7:3,6-dimethanonaphth(2,3-b)oxirene, 3,4,5,6,9,9-hexachloro-1a,2,2a,3,6,6a,7,7a-octahydro-(1aα,2β,2aβ,3α,6α,6aβ,7β,7aα)-, CAS No. 72-20-8] was used as a pesticide until the voluntary cancellation of its registration in 1991. It has not been produced or used in the United States since 1991 (EPA 1984a, 1985a, 1986a, 1993; USDA 1993), which greatly reduces the potential for human exposure. This profile also covers endrin aldehyde and endrin ketone, which were never commercial products, but occurred as impurities of endrin or as degradation products (EPA 1985b; IARC 1974; SRI 1987). Because the United States no longer produces or uses endrin, future levels of endrin, endrin aldehyde, and endrin ketone in environmental media are expected to be low. The most significant route of exposure is most likely ingestion of imported foods contaminated with endrin; however, there may also be some localized risks from exposures near waste disposal sites or from groundwater contaminated with endrin.

Case reports of endrin toxicity in humans suggest that endrin is readily absorbed following ingestion and, as evidenced by accounts in the occupational setting, dermal exposure. Limited data in animals suggest that endrin is also quickly absorbed following inhalation exposure. Endrin is rapidly metabolized and excreted in the urine and feces. However, low concentrations of endrin may remain in adipose tissue following high exposures.

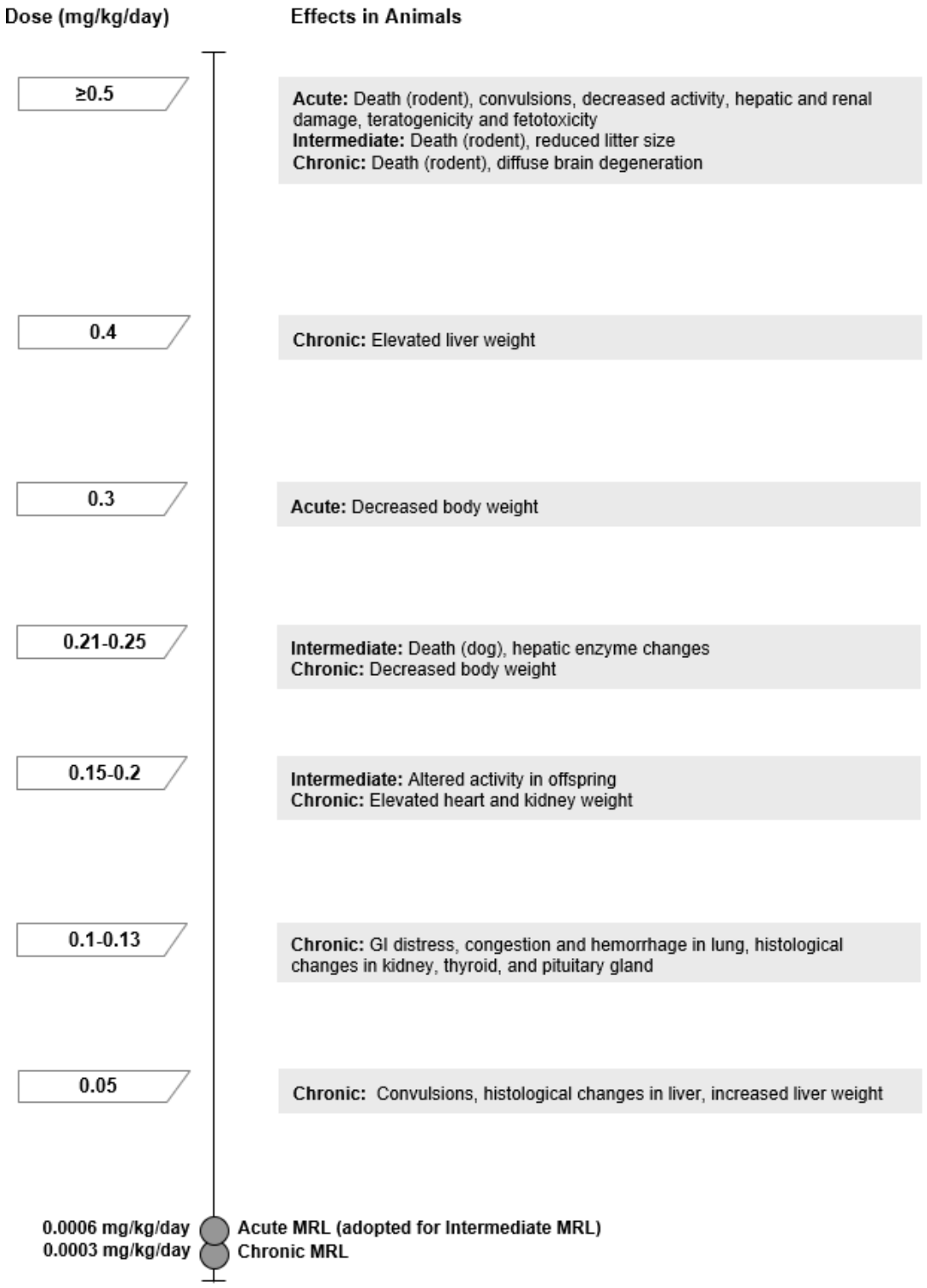
1.2 SUMMARY OF HEALTH EFFECTS

Information on the noncancer toxicity of endrin comes primarily from oral studies in animals; however, several occupational surveys and case reports in exposed humans contribute to the identification of primary toxicity targets. Sixty-three laboratory animal toxicity studies with health effects data have been identified: 2 inhalation, 57 oral, and 4 dermal.

As illustrated in Figure 1-1, the most sensitive effects in laboratory animals appear to be neurological effects (e.g., altered activity, convulsions) and hepatic toxicity. Other noncancer toxicity effects are generally only observed at doses associated with lethality, including diffuse organ damage (lungs, heart, kidney, endocrine glands) and body weight effects. With the exception of altered locomotor activity in offspring, developmental effects were only observed at doses that caused significant maternal mortality and/or toxicity. Data regarding these effects are discussed briefly below. Available data following exposure to endrin in humans and animals are inadequate to determine the potential for adverse effects in

the gastrointestinal, hematological, musculoskeletal, ocular, dermal, immunological, or reproductive systems.

Figure 1-1. Health Effects Found in Animals Following Oral Exposure to Endrin



Neurological Effects. Based on human reports, the central nervous system is the primary target system of endrin. Acute human poisonings by endrin were characterized by symptoms of central nervous system toxicity such as jerking of arms and legs, twitching facial muscles, tonic and clonic contractions, convulsions and sudden collapse, and death (Carbajal-Rodriquez et al. 1990; Coble et al. 1967; Curley et al. 1970; Davies and Lewis 1956; Rowley et al. 1987; Runhaar et al. 1985; Waller et al. 1992; Weeks 1967). Numerous case reports of convulsions following acute, high-level exposure have been reported in workers that manufacture endrin; changes in electroencephalogram (EEG) patterns were usually observed in these cases (Hoogendam et al. 1962, 1965).

Neurological effects occurred consistently in animals exposed to endrin via inhalation, oral, and dermal exposure. Reported findings included behavioral effects (e.g., altered activity) and frank neurotoxic effects (e.g., tremors and convulsions) (Chernoff et al. 1979; Deichmann et al. 1970; Gaines 1960; Kavlock et al. 1981; Kettering 1969, 1971; Lawrence et al. 1968; Mehrotra et al. 1989; NCI 1979; Pandy 1978; Speck and Maaske 1958; Treon et al. 1955), with altered EEG and diffuse brain lesions observed at lethal levels (Ressang et al. 1959; Speck and Maaske 1958; Treon et al. 1955). Altered activity levels have also been reported in rat and hamster offspring following maternal exposure to endrin (Gray et al. 1981).

Hepatic Effects. Human data on endrin-related hepatic effects are limited. The available human data consist of an occupational survey of endrin workers reporting a few cases of increased serum levels of liver enzymes (Hoogendam et al. 1965). However, only limited conclusions should be drawn from these results, as the levels were within normal limits at subsequent evaluations (1 week–3 months later), despite continued occupational exposure. Moreover, the study did not control for concurrent exposure to other chemicals or alcohol. Studies involving several species of laboratory animals have consistently reported hepatic effects following inhalation, oral, or dermal exposure at or near lethal levels. Effects included increased liver weight, altered liver serum enzymes, diffuse degenerative lesions, necrosis, vacuolation, fatty degeneration, and lipid peroxidation (Ali and Shakoori 1993; Bagchi et al. 1992a, 1992b, 1992c; Hassan et al. 1991; Hassoun et al. 1993; Kavlock et al. 1981; Lawrence et al. 1968, Treon et al. 1955; Young and Mehendale 1986). Chronic-duration oral studies in rats and dogs reported hepatic effects at sublethal doses, including increased liver weight and/or cloudy swelling of centrilobular cells (Deichmann et al. 1970; Kettering 1969; Treon et al. 1955).

Renal Effects. No human studies that assessed renal effects following endrin exposure were found. Inhalation, oral, and dermal exposure to lethal levels of endrin caused diffuse degenerative lesions in the

kidneys of various species (Treon et al. 1955). Available laboratory animal studies have reported inconsistent renal effects at sublethal exposure levels. A single study involving acute exposure to a high dose reported renal histopathologic effects in rats, mice, and hamsters, including moderate tubular necrosis and congestion, inflammation, and interstitial edema (Hassan et al. 1991). One chronic-duration oral study in rats reported renal effects (cloudy swelling of tubule epithelial cells) at sublethal levels (Deichmann et al. 1970). However, a 2-year bioassay did not observe any pathological renal effects in rats or mice (NCI 1979) or dogs (Kettering 1969) following sublethal chronic doses.

Endocrine Effects. Several epidemiological studies have examined the potential relationship between environmental endrin exposure and thyroid hormone levels in highly contaminated regions. In general, only weak (if any) relationships were observed, and findings are inconsistent between studies, sexes, and age groups (Freire et al. 2011, 2012, 2013; Piccoli et al. 2016). A potential increase in risk for Type I diabetes was observed in children with high serum endrin levels; however, the study did not adjust for any confounders, including other detectible pesticides (El Morsi et al. 2012). In laboratory animals, thyroid hyperplasia and pituitary cysts were observed in rats, but not in mice or dogs, in chronic bioassay studies with endrin administered in the feed (Kettering 1969; NCI 1979).

Respiratory Effects. Limited human and animal data showed respiratory effects following endrin exposure. Increased deaths due to pneumonia and other nonmalignant respiratory diseases were observed in workers at one of two plants that manufactured endrin (Ditraglia et al. 1981). However, simultaneous exposure to other chemicals occurred, and increased respiratory disease was not observed in the second endrin manufacturing facility. Pulmonary edema was observed in a patient poisoned with endrin, but was thought to be due to chemical pneumonitis from aspiration of aromatic hydrocarbons contained in the formulation (Runhaar et al. 1985). Some rats chronically exposed to low dietary doses exhibited focal hemorrhage and congestion of the lungs (Deichmann et al. 1970). Other histopathologic effects were only observed in animals at lethal doses and were attributed to widespread systemic failure at lethal exposure levels.

Cardiovascular Effects. Only limited reports of cardiovascular toxicity of endrin in animals were located. Diffuse degenerative lesions of the heart were observed in some dogs administered lethal doses of endrin, and enlarged hearts were observed at sublethal doses (Lawrence et al. 1968; Treon et al. 1955). The health significance of these finding is unclear, as the effects were not observed in other animal species.

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Body Weight Effects. No specific effects on body weight have been noted in humans. Decreases in body weight in animals were usually associated with administration of lethal doses and were not observed in chronic toxicity studies (Chernoff et al. 1979; Deichmann et al. 1970; Goldenthal 1978a; Kavlock et al. 1981; NCI 1979; Treon et al. 1955).

Developmental Effects. Available evidence in humans is inadequate to determine if endrin is associated with adverse birth outcomes or male reproductive development (Fernandez et al. 2007; Samra and Selim 2009); however, one study reported an association between endrin exposure and cord blood thyroid hormone levels (Freire et al. 2011). Prenatal exposure of animals to concentrations of endrin sufficient to cause maternal toxicity has resulted in a statistically significant increase in the incidence of fused ribs, cleft palate, exencephaly, meningoencephaloceles, and open eyes in hamsters and mice (Chernoff et al. 1979; Kavlock et al. 1981, 1985; Ottolenghi et al. 1974). Effects were not necessarily reproducible between studies (Goldenthal 1978b), and were not observed in rats (Goldenthal 1978a). Increased motor activity has been observed in hamster offspring after gestational exposure to maternally toxic doses (Gray et al. 1981). Adverse developmental effects generally have not been observed in rats (Kavlock et al. 1981), except for a transient increase in locomotor activity of pups at low doses that were not toxic to the dam (Gray et al. 1981) and delayed ossification at doses that resulted in maternal toxicity (Goldenthal 1978a).

Cancer. Studies of endrin-exposed workers have not detected significant increases in mortality due to cancer (Ribbens 1985). In two industries manufacturing endrin, small excesses of certain cancers were reported, including malignant neoplasms of the esophagus, rectum, liver, and lymphatic and hematopoietic systems (Ditraglia et al. 1981). However, these findings were not statistically significant, and the studies were limited by concurrent exposure to other chemicals. Endrin was reported to be noncarcinogenic in animal studies (Deichmann et al. 1970; NCI 1979; Treon et al. 1955). Reuber (1979) reported that endrin is carcinogenic; however, multiple reporting inconsistencies were identified, observed tumors did not show a dose-related response, and Reuber's criteria for classifying tissues as tumorigenic were not consistent with those of other investigators (IRIS 2002).

The U.S. Environmental Protection Agency (EPA) has classified endrin in Group D, not classifiable as to carcinogenicity in humans (IRIS 2002). The International Agency for Research on Cancer (IARC) has classified endrin in Group 3, not classifiable as to its carcinogenicity in humans (IARC 1987). The Department of Health and Human Services (HHS) has not classified the potential for endrin to cause cancer in humans (NTP 2016).

1.3 MINIMAL RISK LEVELS (MRLs)

MRLs for inhalation exposure to endrin, endrin aldehyde, and endrin ketone were not derived for any duration category because data are insufficient.

The oral database was considered adequate for deriving an acute-duration MRL and a chronic-duration MRL. An MRL was not derived for intermediate-duration oral exposure because the MRL derived from the available data in the limited database would be higher than the acute-duration MRL. The acute-duration MRL is expected to be protective of intermediate-duration exposures; therefore, the acute oral MRL is adopted as the intermediate oral MRL. As presented in Figure 1-2, the available oral data for endrin suggest that the central nervous system and liver effects are the most sensitive targets of toxicity in laboratory animals; other potential sensitive targets include body weight, respiratory, renal, and endocrine effects.

The MRL values are summarized in Table 1-1 and discussed in greater detail in Appendix A.

Figure 1-2. Summary of Sensitive Targets of Endrin – Oral

The central nervous system and liver are the most sensitive targets of endrin oral exposure.
Numbers in circles are the lowest LOAELs for all health effects in animals.
No reliable dose response data were available for humans.

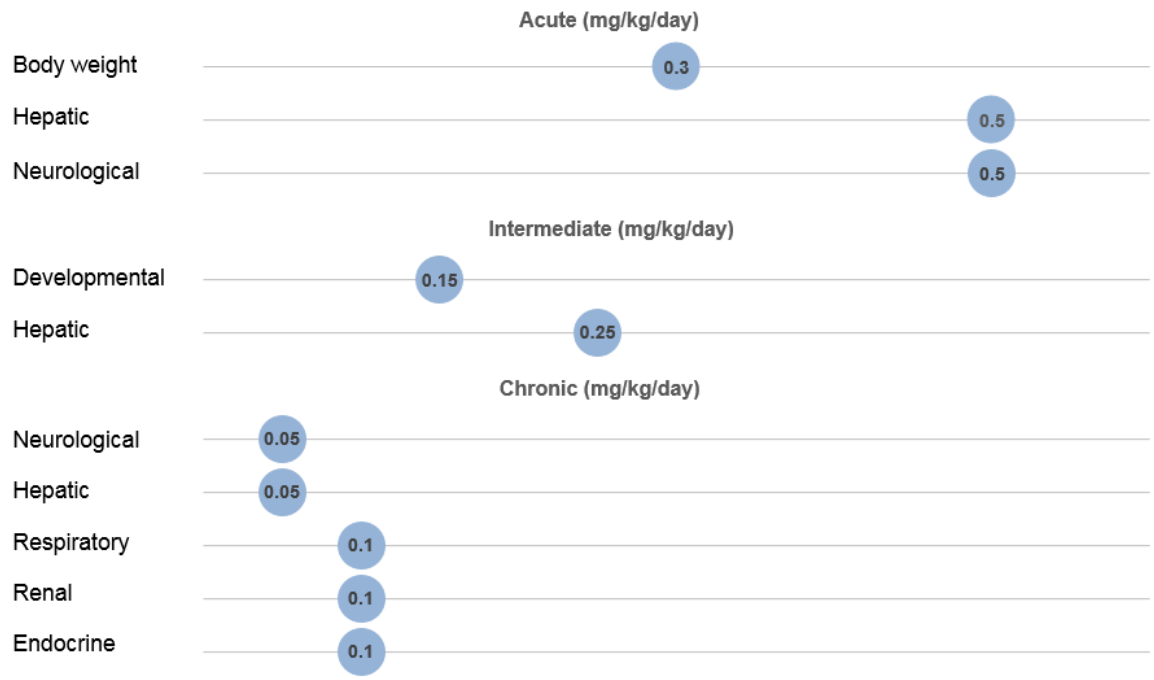

Table 1-1. Minimal Risk Levels (MRLs) for Endrin[a]

Exposure duration	MRL	Critical effect	Point of departure	Uncertainty factor	Reference
Inhalation exposure (ppm)					
Acute	Insufficient data for MRL derivation				
Intermediate	Insufficient data for MRL derivation				
Chronic	Insufficient data for MRL derivation				
Oral exposure (mg/kg/day)					
Acute	**0.0006**	Decreased locomotor activity	$BMDL_{1SD}$: 0.057	100	Kavlock et al. 1981
Intermediate	**0.0006**	Acute MRL is adopted as the intermediate MRL			
Chronic	**0.0003**	Convulsions, hepatic vacuolation	NOAEL: 0.025	100	Kettering 1969

[a]See Appendix A for additional information.

BMDL = 95% lower confidence limit on the benchmark dose (subscripts denote benchmark response: i.e., 1SD = exposure concentration associated with 1 standard deviation change in outcome); NOAEL = no-observed-adverse-effect level