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Review

Hazard identification of the potential for dieldrin carcinogenicity to humans ☆

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ABSTRACT

Although dieldrin's use in the U.S. was partially banned in the 1970s and its use was completely eliminated in 1987, dieldrin continues to be a common contaminant at hazardous waste sites. The USEPA's current cancer potency estimate for dieldrin was derived in 1987 and is based on the production of mouse liver tumors. Because of its environmental persistence and its relatively high USEPA cancer potency estimate, dieldrin functions as a cleanup "driver" in many hazardous site remediations. Since 1987, new risk assessment perspectives and new data on dieldrin's carcinogenic potential have arisen. This review presents a reassessment of dielrin's human cancer potential in light of these new data and new perspectives.

Based on this reassessment, dieldrin may be carcinogenic through multiple modes of action. These modes of action may operate within the same tissue, or may be specific to individual tissues. Of the several possible carcinogenic modes of action for dieldrin, one or more may be more relevant to human cancer risk than others, but the relative importance of each is unknown. In addition, neither the details of the possible modes of action, nor the shape of the tumor dose–response curves associated with each are sufficiently well known to permit quantitative cancer dose–response modeling. Thus, the mouse liver tumor data used by the USEPA in its 1987 assessment remain the only quantitative data available for cancer dose–response modeling.

1. Background

1.1. The occurrence of dieldrin at NJDEP hazardous waste sites and its implication for site remediation

Dieldrin was used extensively from the 1950s to 1970. All uses of dieldrin were banned in the U.S. in 1970. In 1972, the USEPA relaxed the ban to allow dieldrin to be used as a termiticide. This use continued until 1987, when the registration was voluntarily canceled by the manufacturer.

Despite nearly three decades since its removal from the market, dieldrin is a commonly found contaminant in New Jersey waste sites. Because farmland in New Jersey continues to be converted to residential land and because dieldrin was used extensively in farming from the late 1940s through the mid 1970s, and further, because dieldrin has a long environmental persistence, dieldrin commonly comes to the attention of the New Jersey Department of Environmental Protection (NJDEP) when sites are examined for potential hazardous chemical occurrence. In a database of sites including those with historic pesticide contamination compiled by the NJDEP Site Remediation Program (SRP) from 1997 through 2006, dieldrin was present at 43 of 123 sites (35%). Since this database also includes sites identified solely on the basis of naturally occurring arsenic and no historic pesticide use, the actual proportion of sites with anthropogenic contamination that contain dieldrin is likely considerably larger. Based on its current identification by the USEPA in its Integrated Risk Information System (IRIS) database (last significantly updated in 1993) as a "probable human carcinogen" (category B2 under the, then current 1986 USEPA Guidelines for Carcinogen Risk Asssessment) and its attendant relatively high cancer potency, soil remediation standards for dieldrin in New Jersey are relatively low: 0.040 mg/kg for residential soil, 0.2 mg/kg non-residential soil both based on direct contact and 0.003 mg/kg for impact to groundwater. These factors combine to make dieldrin a cleanup "driver" in a large proportion of waste sites in New Jersey.

Dieldrin's continued occurrence in soil is not limited to New Jersey. Even a cursory sampling of other state environmental departments reveals that dieldrin continues to be present in soil above state mandated clean-up levels in Connecticut (CT Department of Public Health, 2006; New York (NY State DEC), 2007), Texas (TCEQ, 2012), and California (CalEPA, 2011).

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1.2. Current status of USEPA dieldrin cancer risk assessment

In its IRIS cancer assessment for dieldrin, last revised in 1993 (USEPA, 2012), the USEPA classified dieldrin as Group B2, a probable human carcinogen. The basis for this classification is the consistent reporting of hepatocellular carcinomas in mice across 7 studies in 4 strains of mice, both male and female. The USEPA IRIS human equivalent cancer slope factor (potency estimate) is 16 $(mg/kg/day)^{-1}$ day, derived as the average of the relatively narrow range of 7.1–28 $(mg/kg/day)^{-1}$ for slope factors from the 7 studies. The USEPA notes tumors at other sites – pulmonary adenomas and carcinomas, lymphoid tumors, as well as tumors at unspecified "other sites" – in only one of these studies (Walker et al., 1972). The USEPA also states that there was no evidence of carcinogenicity from 7 studies in rats. However, they note that of these 7 studies, only three are considered adequate in design and conduct to add to the overall weight of evidence.

The cancer potency (oral slope factor) for dieldrin currently in IRIS is approximately five times that of benzene, approximately twice that of benzo-a-pyrene, and approximately 11 times that of vinyl chloride. Of the 13 chemicals characterized as either "carcinogenic to humans" or "likely to be carcinogenic to humans" under the criteria in USEPA's 2005 Guidelines for Carcinogen Risk Assessment (USEPA, 2005), the cancer potency for dieldrin is larger than all except one, 1,2,3-trichloropropane, whose potency is approximately twice that of dieldrin.

1.3. Carcinogenicity assessments for dieldrin from other sources

Although ATSDR does not include quantitative risk assessments for carcinogenic effects or derive cancer slope factors in their Toxicological Profiles, ATSDR (2002) qualitatively evaluated the relevance of the mouse cancer data (essentially the same studies as evaluated by the USEPA in developing the IRIS slope factor). ATSDR concluded that the preponderance of evidence supported the hypothesis that dieldrin produces liver tumors in mice through the promotion of spontaneous foci of transformed hepatocytes, but does not function in the induction of carcinogenicity. ATSDR further hypothesizes that this promotional activity occurs through non-mutagenic mechanisms that are specific to the mouse, specifically oxidative stress and inhibition of gap junction communication.

With respect to rat tumors, an increased incidence of liver tumors as well as tumors at other sites in a reassessment of the chronic dietary study of Fitzhugh et al. (1964). Fitzhugh et al. (1964) was one of the studies cited by the USEPA as showing no evidence of dieldrin carcinogenicity in the rat. ATSDR also cites two studies showing increases in thyroid follicular cell tumors in rats. However, the tumor incidence in these studies did not follow a dose–response relationship. ATSDR cites a re-analysis of the mouse data of Walker et al. (1972) referenced by the USEPA IRIS cancer assessment relative to pulmonary and lymphoid tumors (as well as liver tumors) as indicating that the reported excess of pulmonary and lymphoid tumors was due to errors in data reporting (Hunt et al., 1975). The USEPA did not reference this re-analysis and the appropriateness of its conclusion is unclear.

WHO (1987) addressed dieldrin in 1987 under the International Agency for Research on Cancer (IARC) concluding that the evidence regarding the carcinogenicity of dieldrin to humans was "inadequate" and the evidence regarding the carcinogenicity of dieldrin to animals was "limited." In 1989, WHO addressed dieldrin under its International Program on Chemical Safety (IPCS) (WHO, 1989) concluding that "…for practical purposes," dieldrin makes "very little contribution, if any, to the incidence of cancer in human beings."

1.4. Rationale for re-examination of the potential for human cancer risk from dieldrin

The current USEPA IRIS assessment of dieldrin is based on pre-1990 studies. The ATSDR assessment, based on more recent studies, concludes that the mouse tumors that form the basis for the IRIS assessment result from a non-mutagenic, epigenetic mechanism that does not proceed through direct DNA damage. Much of the existing scientific literature bearing on dieldrin carcinogenicity post-dates the 1987 USEPA IRIS assessment and some potentially critical studies post-date the 2002 ATSDR Toxicological Profile. In addition, risk assessment methodology and policy have evolved since both the USEPA and ATSDR assessments. In particular, the USEPA's Guidelines for Carcinogen Risk Assessment (USEPA, 2005) have provided a more nuanced approach to consideration of human cancer risk than the earlier USEPA guidelines. Thus, given the continuing and important role that dieldrin plays in environmental regulation and given the availability of new data and new risk assessment perspectives, a re-examination of dieldrin's potential to pose a risk to humans through environmental exposure is warranted.

2. Brief summary of relevant chemical and toxicokinetic information

2.1. Structure, environmental chemistry and environmental persistence in soil

Dieldrin (Fig. 1) has a molecular weight of 380.91. It has low solubility in water, but is highly soluble in organic solvents (ATSDR, 2002). Dieldrin is structurally very similar to aldrin (Fig. 2). Aldrin differs only in lacking an oxygen bridging two carbons atoms with an expoxide linkage. In place of the oxygen, aldrin links these two carbons in a double bond. In the environment and in the human body, aldrin readily transforms to dieldrin (ATSDR, 2002).

The half-life of dieldrin in soil is widely reported to be 5 years in temperate soils and much less in tropical soils (ATSDR, 2002). However, shorter values of 175 days-3 years are also reported for the U.S. (USEPA, 1989). The half-life of aldrin in soil was estimated at 53 days (ATSDR, 2002). However, the loss of aldrin is largely due to its transformation to dieldrin. The reported persistence of dieldrin in soil in New Jersey and elsewhere may appear to reflect a significant resistance to loss and/or degradation. Nonetheless, the fact that dieldrin continues to trigger environmental remediations is consistent with its moderately short half-life in soil. Assuming a half-life of 5 years with first order exponential decay kinetics and assuming application in 1987 (the latest possible year

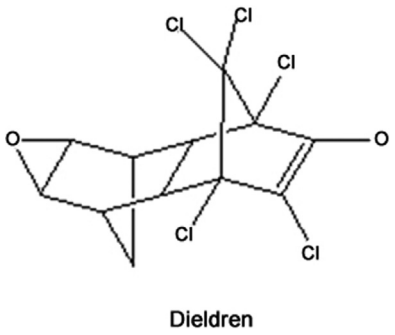

Fig. 1. Molecular structure of dieldrin.