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Review

A systematic evaluation of the potential effects of trichloroethylene exposure on cardiac development

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ABSTRACT

The 2011 EPA trichloroethylene (TCE) IRIS assessment, used developmental cardiac defects from a controversial drinking water study in rats (Johnson et al. [51]), along with several other studies/endpoints to derive reference values. An updated literature search of TCE-related developmental cardiac defects was conducted. Study quality, strengths, and limitations were assessed. A putative adverse outcome pathway (AOP) construct was developed to explore key events for the most commonly observed cardiac dysmorphologies, particularly those involved with epithelial-mesenchymal transition (EMT) of endothelial origin (EndMT); several candidate pathways were identified. A hypothesis-driven weight-of-evidence analysis of epidemiological, toxicological, in vitro, in ovo, and mechanistic/AOP data concluded that TCE has the potential to cause cardiac defects in humans when exposure occurs at sufficient doses during a sensitive window of fetal development. The study by Johnson et al. [51] was reaffirmed as suitable for hazard characterization and reference value derivation, though acknowledging study limitations and uncertainties.

Contents

Abbreviations: AOP, adverse outcome pathway; BMD, benchmark dose; BMDS, Benchmark Dose Software; BMDL, 95% lower confidence limit on the benchmark dose; BMR, benchmark response; CHD, congenital heart defects; CI, confidence interval; DCA, dichloroacetic acid; IRIS, Integrated Risk Information System; EPA, U.S. Environmental Protection Agency; MGI, Mouse Genome Informatics; NTP, National Toxicology Program; POD, point of departure; TCA, trichloroacetic acid; TCE, trichloroethylene; WOE, weight of evidence (evidence integration).

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1. Introduction

Trichloroethylene (TCE), CAS No. 79-01-6, is a volatile chemical and widely used chlorinated solvent that is frequently found in ground water and in soil at contaminated sites across the U.S. TCE ranks 16th among hazardous substances most commonly found at facilities on the federal National Priorities List [4]. At sites where groundwater is contaminated and depending upon site-specific circumstances, TCE exposures and accompanying human health risks may arise from: (1) movement of TCE vapors from subsurface locations into the indoor air of overlying and nearby buildings (i.e., vapor intrusion) [5]; and/or (2) use of groundwater as a source of drinking water, process water, or irrigation water. A number of health effects have been observed after exposure to TCE during development, e.g., decreased fetal survival, impaired growth, alterations in immune and nervous system function, and structural defects, including ocular and cardiac malformations [16]. Here we report on a focused review of the published literature, conducted to update the information and critically evaluate the available data relevant to the potential for cardiac defects resulting from developmental exposures to TCE. This effort was initiated because of concerns raised about study quality and application of the reference value to short term and pregnancy exposure scenarios.

EPA completed an IRIS Toxicological Review of TCE in September 2011 [87]. The most sensitive types of noncancer health effects identified in this assessment were developmental, renal, and immunological. A reference concentration (RfC)[2] of 0.0004 ppm (0.4 ppb or 2 μg/m^3) is derived in U.S. EPA [87], based on route-to-route extrapolated results from oral studies for the critical effects of heart malformations in rats and immunotoxicity in mice, further supported by route-to-route extrapolated results from an oral study of nephropathy in rats. The reference dose (RfD) for noncancer effects of 0.0005 mg/kg-day is based on the critical effects in oral studies of heart malformations in rats, adult immunological effects in mice, and developmental immunotoxicity in mice. The RfD is further supported by results from an oral study for the effect of toxic nephropathy in rats and route-to-route extrapolated results from an inhalation study for the effect of increased kidney weight in rats ([87]; pages 6–43).

After the final IRIS document was released, EPA and others realized that because fetal adverse outcomes could potentially result from short-term exposures or peaks in exposure during pregnancy, one of the two endpoints used to derive the RfC (the fetal cardiac defects) is particularly important when evaluating whether TCE exposure poses an immediate potential hazard and whether peak exposures are a potential health concern. A study by Johnson et al. [51], which reports the results of research on TCE in drinking water, including the findings of Dawson et al. [20], is included in the group of studies on which the reference values are based in the 2011 IRIS assessment, and is one of several lines of evidence regarding the hazard potential for developmental toxicity of TCE. Concerns have been raised about the Johnson et al. [51] study and EPA's use of this study for risk evaluation [1,90,38]. Specific needs to resolve these concerns include: (1) a systematic evaluation of study quality; (2) more details in the description of the study design (e.g., the source of concurrent controls); (3) a reexamination of the dose-response relationship for cardiac defects; and (4) an evaluation of the study results in light of other studies that did not observe cardiac defects after in utero exposures. In addition, concerns have been raised regarding the interpretation of the epidemiological database for cardiac defects associated with TCE exposures [13,1,90,38].

An updated literature search and analysis of the developmental cardiac toxicity data for TCE was conducted to address the identified issues and to provide a focused, rigorous, systematic scientific review of the available data on associations between exposure to TCE and fetal cardiac defects. The scope of this update and analysis was limited to the fetal cardiac defects observed following gestational exposures to TCE and/or its oxidative metabolites, dichloroacetic acid (DCA) and trichloroacetic acid (TCA), which have been specifically associated with cardiac malformations in rats [51,49,20,27,79,78], and does not include an update on other developmental effects after TCE exposure, i.e., fetal growth retardation, embryolethality, ocular malformations, developmental neurotoxicity, and developmental immunotoxicity. This update of the fetal cardiac effects includes (1) a systematic search to identify any recently published literature; (2) a detailed evaluation of the available data; (3) a hypothesis-driven assessment of the weight of evidence (evidence integration) for the association of TCE exposures with cardiac malformations; (4) a reexamination of the dose-response relationship for cardiac malformations; and (5) a transparent description of the evaluation. This process is aligned

[2] A reference concentration (RFC) or dose (RfD) is an estimate of a continuous inhalation exposure (daily oral exposure) for a chronic duration (up to a lifetime) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.