Brief Review of Trichloroethylene (TCE) Developmental Risks

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The Connecticut Department of Public Health is relying upon the USEPA 2011 review of trichloroethylene developmental effects to make a determination that there is an acute risk of cardiac defects and impaired immunity from encountering TCE during pregnancy (USEPA IRIS 2011; USEPA 2011). As summarized below, USEPA's analysis provides an assessment of both the strength of evidence for this effect as well as TCE's potency to produce this effect.

USEPA developed an IRIS profile for TCE in 2011 and summarized this analysis in a subsequent publication (USEPA IRIS, 2011; Chiu et al. 2013). These documents detail the animal and human evidence for TCE developmental effects and provide the Agency's analysis of its potency. The potency estimate is captured in the reference dose or RfD which in this case is derived based upon the dose response for TCE-induced increases in cardiac defects as seen in rat studies. USEPA's review found there to be strong evidence for TCE-induced cardiac defects from gestational exposure on the basis of: 1) suggestive epidemiological studies (Goldberg et al. 1990; Bove et al. 2002; Forand et al. 2011) in which a National Academy of Sciences review found that although the studies were of limited value when viewed individually, as a whole showed relatively consistent elevations of cardiac malformations (NRC 2006); 2) limited studies in rats indicating TCE cardiac teratogenesis, although these studies are not entirely consistent (Johnson et al. 2003; Dawson et al. 1993; Fisher et al. 2001); 3) extensive studies in the developing chick model showing TCE perturbation of heart development (Drake et al. 2006, Loeber et al. 1988; Rufer et al. 2010); 4) multiple mechanistic studies showing that TCE affects gene expression and biochemical events in heart tissue (Caldwell et al. 2008; Ou et al. 2003; Mishima et al. 2006); 5) independent studies of the TCE metabolites dichloroacetic acid and trichloroacetic acid which also show cardiac teratogenesis (Johnson et al. 1998).

These various lines of evidence led USEPA to select the rodent developmental study of Johnson et al. 2003 for RfD derivation (USEPA IRIS 2011). In this study, pregnant rats were exposed to TCE via drinking water on gestation days 1-22 at water concentrations spanning a range from 0.0025 ppm to 1,100 ppm. Cardiac defects were elevated at 0.25 ppm and above. Atrial and ventricular septal defects were the primary findings. A probit analysis by these authors of the percentage of fetuses with abnormal hearts showed a classical sigmoidal dose response pattern. The RfD derived from USEPA's analysis of these data is based upon a benchmark dose lower limit (BMDL) of 0.005 mg/kg/d after taking into account toxicokinetic differences across species and toxicokinetic variability across the human population. This BMDL was divided by a 10 fold uncertainty factor to account for toxicodynamic differences across species and across individuals within a species to yield an RfD based upon cardiac defects of 0.0005 mg/kg/d. This RfD was converted via toxicokinetic modeling to an RfC of 2 $\mu g/m^3$.

CT DPH recognizes a number of uncertainties in this analysis, particularly with respect to the presence of well conducted rodent studies which did not show evidence of the cardiac defect effect. For example, Fisher et al. (2001) failed to find any increase in cardiac defects from gestational exposure to a single TCE dose level (500 mg/kg/day) via gavage administration. While cardiac defects were noted they were not elevated relative to the concurrent soy oil control group. The National Academy of Sciences review stated

that the high incidence of cardiac defects in the soy oil control group may have decreased the sensitivity of the study to find a TCE-related effect. Further, use of a single dose level does not allow for a full exploration of the TCE effects. An inhalation study by Carney et al. (2006) failed to find cardiac effects at TCE inhaled concentrations as high as 600 ppm. While there are obvious design differences between the positive and negative cardiac studies (dose route, strain of rat, dose levels used), there is no clear explanation for the difference in results. Increasing confidence in the cardiac effects of TCE are the 5 lines of evidence mentioned above such that the rat teratogenesis studies are just one aspect of a much larger body of evidence that supports this finding. Increasing confidence further is the finding that the same type of cardiac defect was found in both the rat and avian developmental studies (septal defects).

TCE produces other developmental effects with developmental immunotoxicity a particular concern. TCE is known to inappropriately modulate the immune system, decreasing normal responses and increasing autoimmunity (Chiu et al. 2013). When TCE was dosed to pregnant mice via drinking water during both the prenatal and postnatal periods, offspring mice had an impaired ability to produce antibodies to a standard immunologic stimulus and they had an increased delayed hypersensitivity response to an allergenic stimulus (Peden-Adams et al. 2006). This developmental endpoint was also used by USEPA in establishing the IRIS RfD. The RfD derived for developmental immunotoxicity was nearly identical to that for cardiac defects indicating that maintaining the oral dose below 0.0005 mg/kg/d and the inhalation dose below 2 $\mu g/m^3$ during pregnancy will protect against both the cardiac and immunologic effects of TCE. It also shows that while the acute concern from TCE exposure during pregnancy is driven by evidence of cardiac defects, this concern is further supported by the evidence of TCE-induced developmental immunotoxicity.

In summary, CT DPH finds that TCE is a low dose developmental risk such that exposures to pregnant women and women of childbearing age should be avoided or at least mitigated to below targets associated with the RfD (if in drinking water) or RfC (if in indoor or outdoor air).

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