Adjustment factors used in the trichloroethylene IRIS assessment to estimate combined cancer risk

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Introduction

- The Integrated Risk Information System (IRIS) assessment for trichloroethylene (TCE) found that TCE was *carcinogenic to humans*, with the strongest evidence supporting the development of renal cancers but also with evidence suggesting that TCE exposure increases the risk of non-Hodgkin's lymphoma (NHL) and liver cancer (U.S. EPA, 2011)
- Human data were sufficient to develop an inhalation unit risk (IUR) for renal cell carcinoma (RCC) specifically (Charbotel et al. 2005). Data on the other cancers were not sufficient for IUR development
- The IRIS assessment used a combination of two different approaches to address this uncertainty, by adjusting the estimate derived for RCC to include risk for other cancers in the final IUR

Methods

- In the TCE IRIS assessment, an **adjustment factor** was developed and applied to the IUR to account for risk of two other cancers with substantial human evidence of hazard: NHL and liver cancer
- This adjustment was calculated from two different data sets:
  - meta-analyses of human epidemiologic data for the three cancer types
  - large cohort study with relative risk (RR) estimates for all three cancer types

Adjustment factor calculations used in the IRIS TCE assessment

1. Use RR estimates and lifetime background risk estimates in unexposed population (Ro) to calculate lifetime risk in exposed population (Rx) for each tumor type

   Ro estimates: *RCC: from life-table analysis*
   NHL and liver: from National Cancer Institute SEER statistics

1. Estimate extra risk from TCE exposure for each tumor type (Rx = RR × Ro)
2. Sum extra risks across three cancer types and calculate ratio of the sum to extra risk for RCC alone (Extra risk = (Rx – Ro)/(1 – Ro))

Results

- The factor developed and applied in the TCE IRIS assessment accounted for the relative contributions of the three cancer types combined in contrast to the extra risk for RCC alone
- Calculations based on two different data sets yielded comparable values for the adjustment factor (both within 25% of the selected factor of 4)

Table 1. Relative contributions to extra risk for cancer incidence from TCE exposure for multiple cancer types (U.S. EPA, 2011)

	RR	Ro	Rx	Extra risk	Ratio to kidney value
Calculation #1: using RR estimates from the meta-analysis					
Kidney (renal cell carcinoma)	1.27	0.0107	0.01359	0.002920	1
Non-Hodgkin's lymphoma	1.23	0.0202	0.02485	0.004742	1.62
Liver (and biliary) cancer	1.29	0.0066	0.008514	0.001927	0.66
			sum	0.009589	**3.28***
Calculation #2: using RR estimates from Rasschou-Nielsen et al., 2003					
Kidney (renal cell carcinoma)	1.20	0.0107	0.01284	0.002163	1
Non-Hodgkin's lymphoma	1.24	0.0202	0.02505	0.004948	2.29
Liver (and biliary) cancer	1.35	0.0066	0.008910	0.002325	1.07
			sum	0.009436	**4.36***

Ro = lifetime risk in an unexposed population; Rx = lifetime risk in the exposed population = RR X Ro
* = Adjustment factor

Conclusion

- Relative contributions to extra risk were estimated in the absence of cancer-specific dose-response data by calculating an adjustment factor for the additional risk of NHL and liver cancer, in addition to RCC alone
- The use of two data sets analyzed by different methods provided more robust support for the use of the factor of 4 to estimate the IUR in the IRIS TCE assessment, based on high-quality epidemiological data

Triangulation

- Triangulation brought together information on the three cancer types using two different dataset and statistical approaches. This enabled the use of human data to estimate an adjustment factor and address uncertainty in the IRIS assessment IUR derived for RCC to include risk for other cancers associated with TCE exposure with substantial human evidence of hazard

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