

**DOH** STATE OF NEW YORK  
DEPARTMENT OF HEALTH

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October 31, 2003

Dale Desnoyers, Director  
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NYS Department of Environmental Conservation  
625 Broadway  
Albany, NY 12233-1080

Dear Mr. Desnoyers:

The New York State Department of Health has derived an air guideline for trichloroethene. Trichloroethene (TCE or trichloroethylene; CAS number 79-01-6) is a chemical commonly found in the environment, including the air (outdoor and indoor) that people breathe. This letter summarizes the important toxicological and epidemiological data we used to evaluate the potential health risks associated with exposure to TCE in air. We have followed the procedures outlined by the National Academy of Sciences and federal agencies such as the United States Environmental Protection Agency (US EPA), the United States Food and Drug Administration and the Agency for Toxic Substances and Disease Registry. These procedures are most recently described in US EPA documents (1994, 2000, 2002, 2003).

**Human Non-Cancer Risks Associated with Exposure to TCE in Air**

For non-cancer effects, points-of-departure (no-observed-effects levels or NOELs, lowest-observed-effects levels or LOELs, benchmark doses) were identified for target organs in humans and animals. Uncertainty factors were applied to the points-of-departure to estimate criteria for long-term exposure of the general population, including subpopulations that may be more vulnerable to TCE than other groups.

Typically, several uncertainty factors (generally, each is 3 or 10) are used to derive an exposure criterion from a point-of-departure. These uncertainty factors are intended to account for:

- the variation in sensitivity among the members of the human population;
- the uncertainty in extrapolating animal data to humans;
- the uncertainty in extrapolating from data obtained in a study with less-than-lifetime exposure to lifetime exposure;
- the uncertainty in extrapolating from a LOEL rather than from a NOEL; and
- the uncertainty associated with extrapolation of results from adult humans or animals to children.

In humans, the central nervous system appears to be a sensitive indicator of TCE exposure, and there is concern that pre-natal TCE exposure may affect fetal development. In animals, TCE damages the central nervous system, liver, and kidneys of adult animals, and disrupts normal fetal development when exposure occurs during gestation. The animal data also suggest that the kidney effects generally occur at higher exposure levels than the other effects noted above.

### **Central Nervous System**

Information on the central nervous system effects of TCE comes from studies of occupationally exposed workers and from studies of animals under controlled experimental conditions. In some occupational studies (Okawa and Bodner, 1973; Rasmussen et al., 1993; Vandervort and Polakoff, 1973), exposure to TCE is associated with effects on the central nervous system, including dizziness, headache, drowsiness, nausea and motor dyscoordination. Confidence in these studies for evaluating dose-response relationships is low because the studies did not provide adequate information on long-term TCE exposure and because the small numbers of workers who were examined were also exposed to chemicals other than TCE. Consequently, these data were not used to derive a potential criterion.

When adult male rats were exposed to TCE at 50 parts per million (ppm or 270 milligrams per cubic meter,  $\text{mg}/\text{m}^3$ ) or more for eight hours per day, five days per week for six weeks, there were electroencephalographic (EEG) changes indicative of decreased wakefulness (Arito et al., 1994). The lowest exposure level in the study was an effect level. This level becomes  $64 \text{ mg}/\text{m}^3$  after adjustment of the experimental exposure level to an equivalent level under conditions of continuous exposure ( $270 \text{ mg}/\text{m}^3 \times 8 \text{ hours}/24 \text{ hours} \times 5 \text{ days}/7 \text{ days} = 64 \text{ mg}/\text{m}^3$ ). Using methods consistent with those recommended in the US EPA (1994) guidelines for deriving air

criteria<sup>1</sup>, the human adult equivalent concentration (HEC) is 64 mg/m<sup>3</sup>. Adjusting the adult HEC to a child's HEC using a child's inhalation rate and body weight and applying an uncertainty factor of 3,000 to the child HEC suggests a potential criterion of about 9 microgram per cubic meter (9 mcg/m<sup>3</sup>). The uncertainty factor was selected to compensate for use of a LOEL for an effect from a subchronic study in rats, human variability, and the potential increased sensitivity of children to TCE. Alternatively, applying a larger uncertainty factor to compensate for the observed effect (and an overall uncertainty factor of 10,000) suggests a potential criterion of 3 mcg/m<sup>3</sup>.

### **Liver**

Trichloroethene is also toxic to the liver of laboratory animals. Increases in absolute and relative liver weights were observed in male and female mice exposed continuously to 37 ppm (200 mg/m<sup>3</sup>) or more for 30 days (Kjellstrand et al., 1983). We modeled the dose-response data for absolute liver weights and identified 13 ppm (70 mg/m<sup>3</sup>) as the lowest air concentration corresponding to the lower bound on a 10% increase in liver effects in either male or female mice (essentially equivalent to a LOEL). Using methods consistent with those recommended in the US EPA (1994) guideline for deriving air criteria, the adult HEC is 70 mg/m<sup>3</sup>. Adjusting the adult HEC to a child's HEC using a child's inhalation rate and body weight and applying an uncertainty factor of 3,000 to the child HEC suggests a potential criterion of about 9 mcg/m<sup>3</sup>. The uncertainty factor was selected to compensate for use of a LOEL from a subchronic study in mice, human variability, and the potential increased sensitivity of children to TCE.

### **Developmental/Reproductive Effects**

An epidemiological investigation (Goldberg et al., 1990) found an association between mothers living in areas where public drinking water wells were contaminated (primarily with TCE) and an increased incidence of cardiac malformations in their children. Whether or not prenatal TCE exposure played a role in producing these cardiac effects is unclear; however, this study raises concerns that developmental effects may be an important toxicological endpoint for TCE in humans.

In animals, Dawson et al. (1990, 1993) showed that exposure to TCE in drinking water during pregnancy caused a statistically significant increase in cardiac malformations in fetal rats at doses as low as 0.2 mg/kg/day. Applying an uncertainty factor of 1,000 to the animal LOEL and assuming

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<sup>1</sup> For extrarrespiratory effects of Type 3 chemicals such as TCE, the HEC equals the animal exposure concentration x an adjustment factor, which typically is a default value of 1 (US EPA, 1994).

that the inhaled and ingested doses of TCE (as mg/kg/day) are equivalent suggests a potential criterion of about 0.7 mcg/m<sup>3</sup>. The uncertainty factor was selected to compensate for use of a LOEL in rats and human variability in the general population. Confidence in this potential criterion is lower than for those based on other animal studies.

### **Human Cancer Risks Associated with Exposure to TCE in Air**

TCE is an animal carcinogen via the oral and inhalation routes of exposure, and evidence from occupational studies and drinking-water studies suggests that TCE is a risk factor for several types of cancer, including kidney, liver, and cancers of the lympho-hematopoietic systems (e.g., Non-Hodgkin's lymphoma (NHL) and Hodgkin's disease) (ATSDR, 1997; US EPA, 2001; Wartenberg et al., 2000). The National Toxicology Program has classified TCE as "*reasonably anticipated to be a human carcinogen.*" Similarly, the International Agency for Research on Cancer classifies TCE "*as probably carcinogenic to humans.*" In both cases, the determination was based on "limited evidence" of carcinogenicity from studies in humans and "sufficient evidence" of carcinogenicity from studies in experimental animals. In short, epidemiological studies suggest, but do not conclusively prove, that TCE increases the incidence of some types of cancer in humans, animal bioassay studies show unequivocally that oral or inhaled doses of TCE cause cancer at several sites in rats and mice, and mode-of-action data suggest that the way TCE causes cancer in animals may be relevant to humans.

For cancer effects, we identified the important human and animal studies on the carcinogenicity of TCE in air, and determined the appropriateness of each study for use in estimating the human TCE air concentration associated with an excess lifetime human cancer risk of one-in-one million. In both the qualitative and quantitative evaluation, we used procedures and methods consistent with the US EPA guidelines for carcinogen risk assessment (US EPA, 2003).

We evaluated four epidemiological studies to determine their usefulness to estimate the TCE air level (mcg/m<sup>3</sup>) associated with an excess lifetime human cancer risk of  $1 \times 10^{-6}$  (i.e., a TCE  $1 \times 10^{-6}$  air level). Three of the studies (Anttila et al., 1995; Cohn et al., 1994; Henschler et al., 1995) did not meet minimal requirements (see Hertz-Picciotto, 1995) for use in dose-response assessment, largely because each study did not characterize adequately the duration and/or magnitude of exposure to TCE. The fourth study (Hansen et al., 2001) provided estimates of TCE air levels in the workplace and of the average duration of occupational exposures and was used to derive estimates of TCE  $1 \times 10^{-6}$  air levels.

Using the relative risk data (from Hansen et al., 2001), exposure data from occupational studies (Hansen et al., 2001; Raaschou-Nielsen et al., 2002) and an average relative risk model recommended by the World Health Organization (WHO, 1996), our estimates of the TCE  $1 \times 10^{-6}$  air levels range from about 0.06 to about 1 mcg/m<sup>3</sup> under a standard exposure scenario (continuous exposure for 70 years, 70-kg person, and inhalation rate of 20 m<sup>3</sup>/day), and vary with choice of cancer site, measure of relative risk, the TCE workplace air level, and years of employment. Confidence in these estimates is low because of the small number of cases, the inability to adequately control the potential influence of confounders, unavoidable uncertainties in the exposure estimates, and the lack of clear dose-response relationship. Thus, these estimates were used to check the plausibility of animal-based estimates of  $1 \times 10^{-6}$  TCE air level (see below).

Inhalation studies using laboratory animals provide scientifically-sound, dose-response datasets showing a statistically significant relationship between TCE exposure levels and an increased incidence of tumors (Fukuda et al., 1983; Henschler et al., 1980; Maltoni et al., 1986). These data have been used by the US EPA (1987, 2001), CA EPA (1999, 2002), WHO (1996), Health Canada (1993), and Rhomberg (2000) to derive estimates of the TCE  $1 \times 10^{-6}$  air level.

We evaluated published estimates and derived additional estimates based on considerations of the quality of the animal data and the use of recommended dose metrics and cross-species extrapolation factors. The estimates considered in our evaluation were based on dose-response data from rats and mice for four cancer sites (liver, lung, testes, and lymph system) using three dose metrics (lifetime average daily exposure as TCE mg/m<sup>3</sup>; lifetime average daily metabolized TCE dose as mg TCE metabolized/kg/day; or lifetime average daily internal dose of trichloroacetic acid (TCA) in plasma or tissue as TCA-area-under-curve (mg-hr)/liter), and two cross-species scaling methods (equal risk at equal exposure or equal risk at exposure scaled by body weight<sup>0.75</sup>). The range of estimates of the TCE  $1 \times 10^{-6}$  air level is about 0.2 to about 4 mcg/m<sup>3</sup> under a standard exposure scenario (continuous exposure for 70 years, 70-kg person, and inhalation rate of 20 m<sup>3</sup>/day). Because there is a lack of scientific consensus on the appropriate animal surrogate and cancer sites, dose metric, and the method for scaling dose across species, no single estimate is preferred. These estimates are similar to the estimates obtained from the human data.

## Summary

We have evaluated the non-cancer effects associated with TCE exposure in air, and focused our attention on those studies that identified sensitive human and animal responses to TCE exposures. Three types of effects observed in animals were used: central nervous system (Arito et al., 1994), liver (Kjellstrand et al., 1983), and developmental (Dawson et al., 1990, 1993). Using methods consistent with latest US EPA guidelines, the potential criteria range from about 1 mcg/m<sup>3</sup> to about 10 mcg/m<sup>3</sup>.

In developing these potential criteria, uncertainties that limit our ability to estimate the human non-cancer effects of low-dose exposures (i.e., use of subchronic studies to evaluate chronic exposures, use of an effect level rather than a no-observed-effect level, interspecies extrapolations, and human variability) and factors necessary when considering children (respiration rate and body weight of children and the potential increased sensitivity of children to TCE exposures) were taken into account.

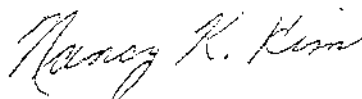
We have evaluated the cancer effects associated with TCE exposure in air, and focused our attention on those human and animal studies that showed significant relationships between estimated or measured TCE exposure and increased rates of cancers. We did not find any human studies strong enough to support potential criteria (i.e., TCE  $1 \times 10^{-6}$  air levels) based on cancer effects, although one study (Hansen et al., 2001) was used for checking the plausibility of criteria based on animal studies.

We derived estimates of the TCE air level associated with an excess lifetime human cancer risk of  $1 \times 10^{-6}$  using data from inhalation studies using animals (Fukuda et al., 1983; Henschler et al., 1980; Maltoni et al., 1986). Given the lack of consensus on the appropriate data, we developed estimates based on two different species, four cancer sites, three different methods of estimating dose, and two different methods for scaling dose across species. Using methods consistent with latest US EPA guidelines, the potential criteria range from about 0.2 to about 4 mcg/m<sup>3</sup>. This range reflects the uncertainty surrounding our ability to estimate the human cancer effects of low-dose exposures. The animal-based estimates are similar to the human-based estimates.

After reviewing the data on the non-cancer and cancer effects of TCE and the potential criteria for long-term exposure of the general populations based on these effects, the New York State Department of Health has set an air guideline for TCE of 5 mcg/m<sup>3</sup>. The margins-of-exposure between this guideline and the TCE air levels known to cause non-cancer effects in animals are consistent with recommended procedures and are adequate when

considered in conjunction with the limitations of the different studies. Similarly, the estimated increased human cancer risks associated with lifetime continuous exposure to 5 mcg/m<sup>3</sup> are in the risk range (1 x 10<sup>-6</sup> to 1 x 10<sup>-4</sup>) that is generally used by regulatory agencies when making decisions. We continue to update, review, and refine our evaluation of the potential health risks associated with TCE.

Sincerely,



Nancy K. Kim, Ph.D., Director  
Division of Environmental Health Assessment

Enclosure

cc: R. Tramontano  
C. Johnson

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