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To: Kirsten Vice

From: Vickie Tatum

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Re: CIIT Acrolein Studies and Their Potential Impact on Ambient Air Quality Standard Development in Ontario

The Chemical Industry Institute of Toxicology (CIIT) was formed as a non-profit research organization in the 1970s by the chemical industry. Today, it is a part of The Hamner Institutes, which is, according to their web site, an "independent, nonprofit coalition of universities, foundations, government agencies, and private sector businesses engaged in environmental risk assessment and biomedical sciences research and development." CIIT researchers are highly regarded among the toxicology community and have been at the forefront of toxicology research for several decades. A quick review of US EPA risk assessment-related documents will reveal widespread acceptance and use of CIIT research. A number of the Reference Doses/Concentrations (RfDs, RfCs) in the US EPA's Integrated Risk Information System (IRIS) are based on research carried out at CIIT.

One area in which CIIT researchers have been at the forefront in nasal dosimetry research. About 30% of US EPA IRIS RfCs are based on nasal effects and most of the human risk assessments for inhaled substances are based on the results of testing with laboratory animals, typically rats. However, the anatomy and airflow patterns of rodents are significantly different from those of humans, and most of the RfCs based on nasal effects are derived using extrapolation techniques that don't consider most of these differences. CIIT researchers have conducted extensive research in order to develop models of human, monkey, and rat nasal passages that allow them to realistically estimate doses of airborne contaminants to humans using data from laboratory animals. The use of these computational fluid dynamics (CFD) models provides much more accurate risk assessments for humans.

CIIT researchers have recently completed research on the nasal effects of acrolein. This research was funded by the American Forest and Paper Association and was designed to improve human risk assessment for acrolein. The current US EPA RfC for acrolein is based on a 1978 study that provided incomplete data, in that effects were observed at all of the tested exposure concentrations. The absence of a no-effect level (NOAEL) results in increased uncertainty in the human risk assessment. Uncertainty in the current RfC is also increased by the use of a dosimetry adjustment based on relative minute volume to upper respiratory tract (URT) surface area ratios between the rat and the human, an extrapolation that does not consider potential differences in airflow and vapor uptake in the nasal passages. The recent CIIT research included testing at exposure levels lower than those previously used in order to determine the NOAEL for nasal effects in rats. In addition, data was collected to support the use of a CFD model-based dosimetry adjustment.

The three manuscripts describing CIIT's research on the nasal effects of acrolein have just been published in the journal *Inhalation Toxicology* and can be referenced as follows:

> Dorman, D. C., Struve, M. F., Wong, B. A., Marshall, M. W., Gross, E. A., and Willson, G. 2008. Respiratory tract responses in male rats following subchronic acrolein inhalation. *Inhal. Toxicol*. 20:205-216.
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> Schroeter, J. D., Kimbell, J. S., Gross, E. A., Willson, G. A., Dorman, D. C., Tan, Y. M., and Clewell, H. J. IIII. 2008. Application of physiological computational fluid dynamics models to predict interspecies nasal dosimetry of inhaled acrolein. *Inhal. Toxicol*. 20:227-243.
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> Struve, M. F., Wong, V. A., Marshall, M. W., Kimbell, J. S., Schroeter, J. D., and Dorman, D. C. 2008. Nasal uptake of inhaled acrolein in rats. *Inhal. Toxicol*. 20:217-225.

The Schroeter et al. manuscript includes both the derivation of a computational fluid dynamics (CFD) model-based human equivalent concentration (HEC) for the NOAEL and a proposed inhalation RfC[1] based on that $NOAEL_{HEC}$. All three of these publications are enclosed for your reference. The discussion of the derivation of the proposed inhalation RfC may be found on page 240 of the Schroeter et al. paper.

In brief, use of the CFD model yields a $NOAEL_{HEC}$ of 8 ppb. Then, in order to derive an RfC, they suggest the application of a composite uncertainty factor of 30 (10 for human variability and 3 for interspecies extrapolation), which yields an RfC of 0.27 ppb.

This approach differs from the Ontario air standard derivation process in several ways. The Ontario process (1) uses the LOAEL from some older studies rather than the NOAEL from the new CIIT study; (2) uses a dosimetry adjustment based on relative minute volume to upper respiratory tract (URT) surface area ratios between the rat and the human rather than the CFD model; and (3) applies an uncertainty factor of 3 to account for the lack of a NOAEL. In addition, the Ontario process applies an uncertainty factor of 3 to account for extrapolating from subchronic to chronic exposure. Schroeter et al. do not believe the use of this uncertainty factor is warranted. They point out that previous studies have shown that there is little or no progression of olfactory epithelial lesions, such as caused by acrolein, after the first 3-12 months of exposure, even when exposures continue through a two year chronic study.

Aside from the argument of Schroeter et al. for omitting the uncertainty factor of 3 for subchronic to chronic extrapolation, eliminating this factor from the Ontario derivation process is appropriate simply because of the nature of the standard being developed. Typically, the uncertainty factor for extrapolation from subchronic is applied when a subchronic study is used to derive a standard that applies to a longer duration, such as the US EPA RfC, which is a lifetime exposure guideline. However, the Ontario AAQC and POI for acrolein are short-term limits, 24-hr and 30 minutes, respectively. Since the duration of the subchronic study (13 weeks) is considerably longer than the time period covered by the AAQC or POI, it serves as a more than protective basis for the standards and no adjustment for study duration is necessary.

If the Ontario ambient air quality criteria were derived using the approach adopted by Schroeter et al., the 24-hr AAQC would be 0.27 ppb, based on a $NOAEL_{HEC}$ of 8 ppb and a composite uncertainty factor of 30 (10 to address intraspecies variability and 3 to account for interspecies extrapolation). The half-hour POI for acrolein would be three times the 24-hr AAQC, or 0.81 ppb.

Table 1 Comparison of the Ontario MOE and Proposed CIIT Derivations of Ambient Air Quality Criteria for Acrolein

	Existing Derivation	CIIT Derivation
Starting Point	LOAEL for nasal lesions in rodents	NOAEL for nasal lesions in rodents
Adjustment for Non-Continuous Exposure	6 hrs/24 hrs X 5 days/7 days	6 hrs/24 hrs X 5 days/7 days
Derivation of Human Equivalent Dose (HEC)	Application of Regional Gas Dose Ratio	Application of Computational Fluid Dynamics Model
HEC	$LOAEL_{HEC}$ = 23 ug/m^3	$NOAEL_{HEC}$ = 18 ug/m^3
Uncertainty Factor for Use of LOAEL Instead of NOAEL	3	Not Necessary[1]
Uncertainty Factor for Interspecies Variation (rat to human)	3	3
Uncertainty Factor for Intraspecies Variation (Sensitive Subpopulations)	10	10
Uncertainty Factor for Subchronic to Chronic Extrapolation	3[2]	Not Necessary[3]
Total Uncertainty Factor	300	30
24-hr AAQC	0.08 ug/m^3	0.62 ug/m^3
½ hr POI (AAQC x 3)	0.24 ug/m^3	1.86 ug/m^3

1. Not necessary because the CIIT study provides a NOAEL
2. Although the AAQC is a 24-hour standard rather than a chronic (lifetime) standard, this factor was included as an extra level of conservatism.
3. This factor is not necessary for two reasons. First, the increased quality of the underlying data and derivation process reduce the need for any added level of conservatism. Second, research on a number compounds that produce nasal lesions has demonstrated that there is little progression as exposures are increased from subchronic to chronic.