March 22, 2013

Benjamin J. Ericson
Assistant Commissioner
Bureau of Waste Site Cleanup
Massachusetts Department of Environmental Protection
One Winter Street
Boston, MA 02108

Re: Adoption of Current EPA Toxicity Information for Perchloroethylene (PCE)

Dear Commissioner Ericson:

The LSP Association is submitting this second letter regarding the treatment of tetrachloroethylene (or perchloroethylene, "PCE") under the Massachusetts Contingency Plan (MCP). In an earlier letter dated April 4, 2012, on the topic of BWSC's regulatory reform proposals, the LSP Association urged MassDEP to adopt the more current toxicity information published by the US Environmental Protection Agency (EPA) in 2012. This letter provides additional supporting documentation for your consideration, and reiterates our prior request to proceed with application of the new PCE values.

The EPA published cancer and non-cancer toxicity values for PCE in its Integrated Risk Information System (IRIS) database on February 10, 2012 (http://www.epa.gov/iris/subst/0106.htm and USEPA 2012). EPA had previously published an oral reference dose for PCE on the IRIS database in 1998, but had not provided an inhalation reference concentration or oral or inhalation cancer toxicity values for use in evaluating human health risk. The EPA's publication of an oral reference dose, reference concentration, oral cancer slope factor, and inhalation unit risk in 2012 followed a four-year process of evaluation and review by both EPA and the National Research Council (NRC), as well as review and input from members of the public.

To date, MassDEP has not officially accepted the IRIS cancer inhalation unit risk (UR) value of 3×10^{-7} per ug/m^3 for PCE, instead relying on its own derived cancer toxicity values as presented in the MassDEP Office of Research and Standards 2008 document, *Revised MassDEP Cancer Unit Risk for Tetrachloroethylene*. An interim UR of 1×10^{-5} per ug/m^3 was developed by MassDEP, recognizing the absence of IRIS values and the need for toxicity values to evaluate health risks, and given the prevalence of PCE sites.

However, since the MassDEP interim UR value was published, the EPA toxicological review of PCE has undergone a peer-review process, and has incorporated additional scientific information to support development of the current IRIS toxicity values. There are three major factors that support the use of the IRIS cancer UR value over the MassDEP UR; these are broadly summarized below.

1. Choice of Endpoint

The two critical cancer PCE toxicity studies considered by EPA evaluated mononuclear cell leukemia (MCL) and hepatic cancer as endpoints. The MassDEP UR is based on MCL as an endpoint, which yielded the most conservative UR. However, EPA and NRC noted the following issues with use of MCL as an endpoint:

- There is a high background (unrelated to PCE) incidence of MCL in the study organism (F344 rats);
- MCL may not be a particularly relevant endpoint for human health; and
- There is a high uncertainty with respect to the mode of action of PCE and incidence of MCL.

For these reasons, and per the recommendation of the majority of the NRC peer review panel, EPA used hepatic cancer (in the mouse) as the target endpoint. Use of this endpoint results in a less conservative UR than one derived using MCL as a cancer endpoint, but EPA and NRC believed that there is less uncertainty associated with this UR, and that hepatic cancer is more relevant to human health than is MCL. We believe that using the current IRIS toxicity data allows for a more realistic estimation of the human health risk posed by PCE and would not result in underestimation of the risk of harm to human health.

2. Extrapolation of Data From Animals to Humans

Extrapolation of toxicological data from animal studies to estimate adverse effects on human health has always been subject to significant uncertainties that often result in the overestimation of the risk of harm to human health. In deriving its toxicity values for PCE, MassDEP used the "metabolized dose" approach instead of physiologically based pharmacokinetic (PBPK) models for extrapolation of the UR from rodent studies to humans. At the time that MassDEP evaluated PCE, there was a high uncertainty regarding the use of the then-available PBPK models.

In recent studies, the EPA and NRC acknowledged these model uncertainties and limitations and developed a harmonized PBPK model that takes into account multiple exposure routes, metabolic pathways and tissue components for dose metric estimation, allowing for a more accurate estimation of the risk of harm to human health. The current EPA harmonized PBPK model addresses many of the limitations of the previous models; MassDEP should incorporate this advance in the science of risk assessment into its own standards.

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3. Differences in Supporting Studies

The two major PCE inhalation studies evaluated by both MassDEP and EPA for deriving cancer toxicity values are the National Toxicology Program study (NTP; 1986) and the Japan Industrial Safety Association study (JISA; 1993). MassDEP used and gave equal weight to both studies, which yielded similar UR values for the hepatic cancer endpoint but a more conservative UR based on MCL as an endpoint (see point #1 above). However, EPA based the UR on only the JISA study, because it used a larger number of dose groups, used lower exposure concentrations, and evaluated toxicity in both rats and mice. Thus, the JISA study yielded a dataset for the derivation of toxicity values that is more relevant to the evaluation of the risk of harm to human health.

In summary, the LSP Association believes that the EPA Unit Risk is more appropriate to use for the characterization of cancer risk than the current MassDEP value. The development of this toxicity value reflects a significant evaluation and review by a number of highly qualified and competent toxicologists, which has resulted in a toxicity value that reflects the most current, and still conservative, scientific approach. The EPA Unit Risk also has reduced uncertainty due to use of better exposure modeling, more realistic exposure levels and a more biologically relevant cancer endpoint. In light of the rigorous evaluation and review process undertaken by the EPA, and the current state of the science of risk evaluation, the LSP Association recommends that MassDEP adopt the IRIS toxicity values for PCE.

We appreciate the opportunity to comment on this matter of importance to the practice. As always, please feel free to contact us if you have any questions regarding our comments, or if we can be of further assistance.

Sincerely,

The LSP Association

Cole E. Worthy, III, LSP
LSPA President

Wendy Rundle
LSPA Executive Director

References:

Japan Industrial Safety Association. (1993). Carcinogenicity study of tetrachloroethylene by inhalation in rats and mice. Hadano, Japan.

National Toxicology Program (1986). Toxicology and carcinogenesis studies of tetrachloroethylene (perchloroethylene) (CAS no. 127-18-4) in F344/N rats and B6C3F1 mice (inhalation studies). (NTP TR 311). Research Triangle Park, NC: U.S. Department of Health and Human Services, National Toxicology Program. http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr311.pdf (pp 199, 8.44M).

United States Environmental Protection Agency (2012). Toxicological Review of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4) in Support of Summary Information on the Integrated Risk Information System (IRIS). http://www.epa.gov/iris/toxreviews/0106tr.pdf#page=503