Informal Comments of the National Institute for Occupational Safety and Health on the June 2011 Final Agency Interagency Review draft
Toxicological Review of Tetrachloroethylene (Perchloroethylene)
July 19, 2011

The National Institute for Occupational Safety and Health (NIOSH) has reviewed the June 2011 Final Agency/Interagency Review draft ***Toxicological Review of Tetrachloroethylene (Perchloroethylene)*** prepared in support of summary information on the Integrated Risk Information System (IRIS). The following comments are intended to assist EPA in assessing hazards from tetrachloroethylene. NIOSH appreciates the opportunity to comment.

All comments pertain to the Human Studies section of Chapter 4 unless noted; other parts of the draft were not reviewed.

I. Major comment:

The section is a comprehensive and well-considered review of the environmental and occupational epidemiologic literature on tetrachloroethylene. NIOSH recommends two publications for inclusion (copies accompany this response):

·McKernan LT, Ruder AM, Petersen MR, Hein MJ, Forrester CL, Sanderson WT, Ashley DL, Butler MA [2008]. Biological exposure assessment to tetrachloroethylene for workers in the dry cleaning industry. Environ Health 7(1):12.

·Tucker JD, Sorensen KJ, Ruder AM, McKernan LT, Forrester CL, Butler MA [2011]. Cytogenetic analysis of an exposed-referent study: perchloroethylene-exposed dry cleaners compared to unexposed laundry workers. Environ Health 10(1):16.

II. Minor comments:

Calvert GM, Ruder AM, Petersen MR [2011]. Mortality and end-stage renal disease incidence among dry cleaning workers. Occup Environ Med. oem.2010.060665 [pii] 10.1136/oem.2010.060665 [doi] is cited a number of times, sometimes as Calvert et al. "In Press" and sometimes without the "In Press" designation (e.g., pages 4-95, 4-112, 4-183, 4-190, 4-194, 4-201). The article is also listed twice in the bibliography.

Ruder AM, Ward EM, Brown DP [2001]. Mortality in dry-cleaning workers: an update. Am J Ind Med 39(2):121-32, the preceding update in this series is also cited often. On occasion, it seems that these two updates of the same cohort are regarded as separate studies; they are not.

The footnote on page 4-17 refers to two publications as Echeverria et al. 1995; one is Echeverria et al. 1994.

Page 4-18, lines 4-5: the explanation for excluding those who wore glasses seems to be missing. Were subjects who wore glasses and did not bring those glasses to the test location excluded? Perhaps the study author could provide clarification.

Page 4-20, line 34: "…and 13 dry cleaners…compared to 0,…". Compared to zero what or whom?

Page 4-56, lines12-29: limitations of the Schreiber et al. studies (e.g., exposed in New York apartments, unexposed in houses in Albany suburbs, unblinded testing, use of researchers' children as study participants) should be included with study findings.

On page 4-77, line 32, the citation is to Calvert JG 1976, Hydrocarbon involvement in photochemical smog formation in Los Angeles atmosphere…rather than to

> Calvert GM, Ruder AM, Petersen MR [2011]. Mortality and end-stage renal disease incidence among dry cleaning workers. Occup Environ Med. oem.2010.060665 [pii] 10.1136/oem.2010.060665 [doi]

Pages 4-128 —134: in this section, a criterion for the NIOSH study (i.e., Calvert et al.) is repeatedly stated incorrectly as workers having entered the union AFTER 1960. The criterion for all study participants was that they had to have worked for at least one year BEFORE 1960 in a shop where tetrachloroethylene was the main dry cleaning solvent.

Page 4-201, line 23: change "A know risk factor…". to "A known risk factor…".

Page 4-210, line 25: ANCA should be defined here, not just in the table on the following page.

Page 4-262, line 26: change "…period of developmen,…" to "…period of development,…".

Page 4-317, line 24: "(ORc:…". Please check.

Page 4-330, line 36 to page 331, line 1: typo: "In Pressin press".

Page 4-339, entry in reference column of Table 4-37 should be Chang et al., not Change et al.

Page 4-345, lines 19 and 28: Eskenazi citations are unformatted.

Page 4-346, line 33: Lagakos and Aschengrau citations are melded.

Page 4-361 and subsequent pages: the Tucker et al. [2011] paper (see major comment above) should be described in this section.

List of Abbreviations and Acronyms***:*** NIOSH is the "National Institute for Occupational Safety and Health", not "National Institutes of Occupational Safety and Health".

III. Generic issues about epidemiologic studies

We note that Appendix B lists strengths and limitations of the studies. These general comments are provided for consideration of additional issues that may apply to studies of perchloroethylene-exposed workers.

1. Concurrent exposures

Multiple exposures are a frequent problem in occupational settings and particularly with solvent exposures because the solvents are used to dissolve something. In the retail laundry setting, the

dissolved material is uncharacterized and presumably includes oils, greases, and waxes of biological origin. However, exposure to specific classes of materials may exist in industrial laundries that handle work clothes or other process-related items. The workers with autoimmune-related conditions (pages 4-209, 210) could have been handling spent solvent laden with whatever substances the laundry was removing. In specific process environments, such as electronics, plastics, metalworking, aerospace, or printing, solvent exposures may be associated with high concentrations of very specific chemical classes ranging from resins to dyes. In some applications, solvent evaporation is used to aerosolize less volatile surface contaminants. These potentially confounding exposures could deform an otherwise clear exposure-response to the solvent or create false associations; they may add to the apparent variability in estimates across studies.

2. Noninhalation exposure

Systemic uptake of perchloroethylene via liquid and vapor phase dermal contact typically was not assessed in studies of perchloroethylene health effects. This route of exposure may vary widely across and within industrial processes, including laundry dry cleaning, and could account for variability in estimated effects.

3. Healthy worker effect (HWE)

In occupational studies with general population reference groups (i.e., external comparisons), non-comparability arises from the "healthy worker" selection bias inherent in employed populations. This effect is stronger for disease outcomes related to respiratory capacity, but is also present for malignancies that often have standardized mortality ratios (SMRs) < 1.0 in exposure-free worker populations. The draft review mentions potential socioeconomic confounding, but not specifically HWE confounding which could be important for most mortality outcomes using SMRs and possibly for morbidity outcomes using standardized incidence ratios (SIRs). Some of the variability in effect estimates within tables may arise from HWE bias.

4. Duration trends

In the absence of actual exposure history, duration of exposure can be a good second choice except when the exposures themselves influence employment duration. For example, when work occurs in adverse environments, workforce turnover is sometimes driven by those exposures, producing a consistent negative, statistically significant association between a health outcome and duration (i.e., workers with the highest cumulative exposures can have shorter durations.) Therefore, such negative results/trends should not automatically lead to the inference that there is no exposure-association with the studied outcome.

5. Relative risk in non-smokers

In studies restricted to non-smokers, a choice used mainly with smoking-related outcomes such as lung cancer, relative risks are calculated against a low background risk. However, in studies that do not exclude smokers, the attributable or excess cases are compared to a much higher background and hence result in a much lower relative risk. The relative risks estimated in these two designs cannot be compared directly; the statistical power is enhanced by studying (the same number of) non-smokers.

6. Kidney disease

Page 4-62 of the kidney disease section describes a study that linked subjects to a database of individuals receiving Medicare benefits for end-stage renal disease (ESRD). It is important to consider that many of those recipients may have had other environmental risk factors, notably but not exclusively, occupational lead exposure (probably not likely in laundry work). Thus, the excess risk for the perchloroethylene-exposed workers was not measured against a general (unexposed) population background, which would tend to reduce the standardized incidence ratio and make elevations less significant.

IV. Format suggestion for human studies section of future drafts

Many of the reviewed studies examined multiple endpoints. Rather than repeating a brief description of a study for each finding, an alternative would be to present all findings of a study, then add those results to outcome-specific tables. The order of presentation might begin with the most important studies (e.g., Calvert et al.; Blair et al.) and perhaps proceed chronologically to lesser studies or by endpoint for single-focus studies.

Enclosures: McKernan et al. [2008]; Tucker et al. [2011]