Report on Carcinogens (RoC) Concept: Trichloroethylene

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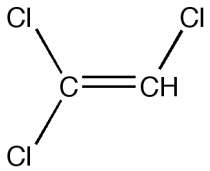

1. Rationale

Trichloroethylene (TCE) is a volatile chlorinated alkene that is primarily used as a metal degreaser. It has been listed in the *Report on Carcinogens* (RoC) as *reasonably anticipated to be a human carcinogen* since 2000. This listing was based on limited evidence of carcinogenicity from studies in humans, sufficient evidence of carcinogenicity from studies in experimental animals, and supporting information from studies on mechanisms of carcinogenesis. Additional cancer studies have been published since the last review, and there is evidence of the continued presence of TCE in the environment, food, numerous consumer products, and the workplace. The U.S. Environmental Protection Agency's (EPA) Integrated Risk Information System recently concluded that TCE is "carcinogenic to humans" based on convincing epidemiologic evidence of a causal association between human exposure and kidney cancer (EPA 2011). The National Research Council (NRC) of the National Academy of Sciences concluded that "there is strong evidence that exposure to high levels of TCE is associated with increased rates of kidney cancer (NRC 2006)." For these reasons TCE has been selected for review for possible change in listing status.[1]

In January 2012, the NTP solicited information on TCE and other nominated substances (77FR2728, see *http://ntp.niehs.nih.gov/go/rocnom* for comments). One comment was received for TCE. The comment did not agree with the U.S. EPA's conclusion of a causal association between TCE exposure in humans and kidney cancer because of limitations in the body of research. The comment cited deficiencies in the exposure assessment, potential unmeasured confounding factors, potential selection biases, and inconsistency across groups of studies. It noted that the magnitudes of the associations in the meta-analyses (conducted by EPA and others) were small, and stated that a series of publications have shown that meta-analysis in general has "serious limitations for the purpose of proving causality." They stated that the NRC report entitled "Contaminated Water Supplies at Camp Lejeune, Assessing Potential Health Effects" concluded that there was limited/suggestive

[1]The scientific evaluation of trichloroethylene will be captured in the draft RoC monograph, which consists of a cancer evaluation component and draft substance profile (for more details see *http://ntp.niehs.nih.gov/go/rocprocess*). The proposed approach, delineated in this concept document, for preparing the cancer evaluation of the draft monograph is tailored to the nature, extent, and complexity of the scientific information on this chemical. This concept document also discusses information supporting the rationale and the proposed approach including (1) data on human exposure, (2) an overview of the nature and extent of the scientific information for evaluating carcinogenicity in humans and/or animals, (3) scientific issues and questions relevant to the evaluation of trichloroethylene carcinogenicity, and (4) the proposed approach for conducting the scientific evaluation including the literature search strategy, the scope and focus of the monograph, and the approaches for obtaining scientific and public input to address the key scientific questions and issues.

evidence from studies in humans for an association between exposure to TCE and kidney cancer (NRC 2009).

The ORoC presented the draft concept document for trichloroethylene to the NTP Board of Scientific Counselors (BSC) at the June 21-22, 2012 meeting[2] which provided an opportunity for written and oral public comments. No public comments were received. The NTP Director approved trichloroethylene as a candidate substance and this concept was finalized based on review of the BSCs comments. The concept may be revised again if new information on trichloroethylene would lead to a change in the proposed approach for conducting the cancer evaluation.

2. Overview of Data Related to Human Exposure

TCE has been produced commercially since the 1920s in many countries, by chlorination of ethylene or acetylene. U.S. production plus imports of TCE totaled between 100 million and 500 million pounds/year between 1986 and 2006 except in 1994 (EPA 2004, 2011). Currently, it is primarily used for degreasing metals; it is also used as a solvent for applications related to adhesives, painting, lacquering, and varnishes. It was commonly used in the dry cleaning industry from the 1930s to the 1950s, and less commonly in the 1960s, but is rarely used today (Bakke *et al.* 2007); its use in cosmetics, drugs, food processing, and pesticides has also been discontinued (EPA 2011, NTP 2011).

There is the potential for substantial exposure to TCE for people living in the United States. People are exposed to TCE via ingestion of drinking water and food, inhalation of outdoor/indoor air, volatilization of TCE from tap and shower water, or dermal exposure from bathing water and consumer products. Daily estimates of TCE intakes are 18 µg from air, from 2 to 20 µg from drinking water, and 4.96 µg from food (ATSDR 1997, Wu and Schaum 2000).

TCE is ubiquitous in the atmosphere, soil, ground, surface and drinking water, and in food. According to the EPA Emissions Inventory and Toxics Release Inventory (TRI 2011), over 2.9 million pounds of TCE were released in 2009, primarily to the atmosphere. Mean ambient air levels of TCE in the United States were reported to be 0.42 µg/m^3 in rural areas, 1.5 µg/m^3 in urban areas, and 1.6 µg/m^3 in industrial settings. TCE is a common groundwater and drinking-water contaminant. It has been reported in approximately 19% of groundwater samples, 3% of surface water, 9% to 34% of municipal and private wells, and 2.6% of public water systems tested (IARC 1995, ATSDR 1997). It also was identified in 72 food items in the U.S. Food and Drug Administration's Total Diet Study (FDA 2006).

Occupational exposure may occur via inhalational (primarily) or dermal contact in the workplace where TCE is produced or used. A systematic review of industrial hygiene data found that the arithmetic mean (AM) of air measurements across all TCE-related industries (such as metal fabricating, dry cleaning, textiles, electronics, leather, and rubber) and decades was 38.2 ppm; most measurements were made in the 1950s to 1980s. The highest personal and area air levels were reported in vapor degreasing (AM of 44.6 ppm) (Bakke *et al.* 2007).

[2]Information on the NTP BSC June 21-22, 2012 meeting is available at http://ntp.niehs.nih.gov/go/9741.

3. Overview of the Scientific Information Regarding Carcinogenicity

3.1. Human cancer studies

In 2000, the RoC conclusion of limited evidence for the carcinogenicity of TCE from studies in humans was primarily based on excesses in the incidence of non-Hodgkin's lymphoma (NHL) and cancers of the kidney and liver found in several cohort studies with exposure assessments specific for TCE for individual study subjects, and a meta-analysis of these studies (Wartenberg *et al*. 2000; 12th RoC, NTP 2011). The evidence was considered limited rather than sufficient because the studies were based on small numbers of exposed workers, and potential confounding from other solvents could not be ruled out.

Since TCE was last reviewed for the RoC, over 20 human cancer studies (or updates of previous studies) have been published. To date, there are over 75 epidemiologic studies that have evaluated potential cancer hazards from exposure to TCE. These include (1) cohort studies of aircraft and aerospace workers, biomonitoring studies, and studies of TCE-exposed workers in other industries such as electronics, paperboard, or cardboard manufacturers, and of TCE producers, (2) hospital- and population-based case-control studies of occupational exposure to TCE, and (3) geographically based studies of environmental exposure to TCE.

Recently, the EPA conducted a systematic review of these studies, which included a weight of evidence evaluation and meta-analyses for NHL and cancers of the kidney and liver (EPA 2011, Scott and Jinot 2011). The latter were conducted because the individual studies were underpowered to evaluate these relatively rare cancers. As part of their weight of evidence evaluation, the studies were assessed for their ability to inform cancer hazard evaluation using *a priori* guidelines related to study design, conduct, and analysis. Case-control and cohort studies were included in the three meta-analyses if they met a set of *a priori* criteria related to selection of participants, including adequate TCE exposure assessment for individual subjects, and provided risk estimates for incidence or mortality (of the endpoint of interest) that adjusted for possible confounding by age, sex, and race (EPA 2011, Scott and Jinot 2011). Studies included in the meta-analyses were given greater weight in the overall cancer hazard assessment.

Meta-analyses have also been conducted by Exponent Health Sciences for exposure to TCE and risks for NHL (Mandel *et al.* 2006), leukemia (Alexander *et al.* 2006), multiple myeloma (Alexander *et al.* 2006), and cancers of the liver (Alexander *et al.* 2007) and kidney (Kelsh *et al*. 2010). These analyses classified cohort studies into two groups (Group I – higher quality and Group II – lower quality) based on the quality of the exposure assessment; case-control studies were either considered separately or combined with the Group II studies.

3.2. Cancer studies in experimental animals

TCE has been tested for carcinogenicity by inhalation exposure in mice (4 studies), rats (3 studies), and hamsters (1 study) and by gavage exposure in rats (6 studies) and mice (2 studies). The NTP concluded in 2000 that studies in experimental animals – which found that TCE caused tumors in mice and rats at different tumor sites and by different routes of exposure – provide sufficient evidence of the carcinogenicity of TCE (12th RoC, NTP 2011). In mice, exposure to TCE by inhalation or by gavage caused liver tumors in both sexes; inhalation exposure also caused lung tumors in both sexes and lymphoma in females. In rats,

exposure to TCE by inhalation or by gavage caused kidney cancer (tubular adenocarcinoma) and testicular tumors (interstitial-cell tumors) in males.

Two additional cancer studies were identified (from a preliminary literature search) that were published after the 2000 listing of TCE in the RoC. One study found an increase in the incidences of liver tumors in male $B6C3F_1$ mice exposed to TCE in drinking water (Bull *et al.* 2002). In the second study, no increase in the incidences of tumors was observed in male or female $B6C3F_1$ mice exposed to TCE by intraperitoneal injection as neonates (Von Tungeln *et al.* 2002).

3.3. Mechanistic and other relevant data

TCE is rapidly absorbed from the stomach, intestines, and lungs. It is distributed throughout the body and concentrates in fatty tissues, such as the liver, brain, and body fat. Metabolism in humans and rodents occurs by two major pathways: (1) oxidation by cytochrome P450, primarily via CYP2E1 to chloral or TCE oxide and (2) conjugation with glutathione (GSH) to form *S*-dichlorovinyl glutathione (DCVG) (Chiu *et al.* 2006, EPA 2011). Downstream metabolites of the oxidation pathway include chloral hydrate, trichloroethanol (TCOH), trichloroacetic acid (TCA), and dichloroacetic acid (DCA); downstream metabolites of the glutathione pathway are *S*-dichlorovinyl-cysteine (DCVC) and *N*-acetyl-*S*-dichlorovinyl-L-cysteine (NAcDCVC). Chloral hydrate, DCA, and TCA are associated with liver and lung toxicity and cause liver tumors in rodents, and DCVC is associated with kidney toxicity (EPA 2011). TCA, DCA, TCOH, NAcDCVC, and DCVG have been detected in blood and/or urine in humans and rodents; DCVG, DCVC, and NAcDCVC have also been detected in the kidneys of rats. DCVC and DCVG are mutagenic in bacteria.

There is a large database of studies in experimental systems or humans evaluating potential mechanisms for TCE-induced kidney and liver cancer. Several modes of action have been proposed, such as mutagenicity, cytotoxicity, oxidative damage, peroxisome proliferation-activated receptor alpha activation (PPARα), and α_{2u}-globulin-related nephropathy. There are also studies measuring mutations in the von Hippel-Lindau tumor-suppressor gene in renal tumors from TCE-exposed and non-exposed people. There is a paucity of mechanistic data for TCE-induced lymphoma in rodents and humans (NRC 2006, EPA 2011). There are numerous studies in humans and laboratory animals evaluating immune effects of TCE, and TCE has been shown to play a role in autoimmune disease including autoimmune hepatitis (EPA 2011). Altered immunity is proposed to be a risk factor for NHL (Grulich *et al.* 2007) and may be important in the development of other cancers.

4. Key Scientific Questions and Issues Relevant for the Cancer Evaluation

There is an extensive database on TCE exposure and cancer, including several comprehensive reviews of the epidemiological data, toxicological data, metabolism, genotoxicity, and potential modes of action (IOM 2003, NRC 2006, EPA 2011), and several recent meta-analyses of epidemiological studies (Mandel *et al.* 2006, NRC 2006, Alexander *et al.* 2006, 2007, Kelsh *et al.* 2010, EPA 2011). These reviews have identified NHL and cancers of the liver and kidney as cancer sites of concern in humans. There is site concordance for these cancers in experimental animals. The RoC concluded that there was sufficient evidence from studies in experimental animals, and no new studies or reviews were identified to question this conclusion. The key questions and relevant issues for the reevaluation of TCE concern the review of epidemiologic, metabolic, and mechanistic data for NHL, kidney cancer, and liver tumors. These are as follows:

Questions related to the evaluation of human cancer studies

- What is the level of evidence (sufficient, limited) for the carcinogenicity of TCE from studies in humans?
- What are the major strengths and limitations in the individual studies and how do they affect the findings?
- Are the associations between exposure to TCE and non-Hodgkin's lymphoma and cancers of the kidney and liver observed in some studies, and in the meta-analyses, credible? Can bias, chance, or confounding be ruled out with reasonable confidence?

Questions related to the evaluation of mechanistic data

- What are the potential mechanisms by which TCE may cause lymphoma and cancers of the kidney and liver?
- Is there evidence that the mechanisms by which TCE causes cancer in experimental animals may not occur in humans? If so, what is the level of evidence (strong, moderate, weak)? Of special interest is whether the TCE-induced liver tumors in mice are relevant to humans.
- Is there mechanistic evidence in humans that would support the associations observed in some human cancer studies? If so, what is the level of evidence (strong, moderate, weak)? Of special interest is the level of evidence for mutagenic and cytogenetic modes of action for kidney cancer.
- Is there any evidence that TCE-induced immunologic effects are related to cancer (such as lymphoma or liver cancer) development?

5. Proposed Approach for Conducting the Cancer Evaluation

5.1. Scope and focus of the draft RoC monograph

The ORoC will prepare the draft RoC monograph on TCE, which will consist of two parts, the cancer evaluation and the substance profile. The cancer evaluation component of the draft monograph will review and assess the scientific literature, provide a discussion of scientific issues, assess and integrate the relevant scientific evidence, and apply the RoC listing criteria to reach a preliminary recommendation on whether the listing classification of TCE should be changed. The substance profile of the draft monograph will give the NTP's preliminary listing recommendation and a summary of the key supportive evidence. Details on the methods for writing the draft RoC monograph and topics typically covered in the monograph are outlined in the NTP process for the preparation of the RoC (*http://ntp.niehs.nih.gov/go/rocprocess*).

The goal of the NTP cancer evaluation component of the draft monograph is to conduct an independent assessment to determine the appropriate listing category for TCE utilizing information from the extensive reviews conducted by other agencies and scientific panels to focus the deliberations. Key topics are the assessment of the evidence from human cancer studies and mechanistic and other related data such as metabolism, genotoxicity, and toxicity. The RoC monograph will not re-evaluate whether there is sufficient evidence in experimental animals, but will assess the evidence from any new studies and integrate the conclusions into the overall synthesis of cancer studies in humans and mechanistic data. The monograph will limit its assessment to non-Hodgkin's lymphoma and cancers of the kidney and liver. As mentioned above, there is site concordance between these cancers in humans and experimental animals. In addition, there is a large database of studies

evaluating potential modes of action for specific cancer sites. Thus, the monograph will be organized by the three types of cancer rather than by topics (e.g., human cancer studies experimental animals studies, etc. as is the usual convention). Details on the approach for writing the monograph are outlined in the NTP process for preparation of the RoC (*http://ntp.niehs.nih.gov/go/rocprocess*), and the preliminary literature search for this approach is in Appendix 1.

When relevant, the recent EPA and NRC reports on TCE will be used as resources, especially for issues where there is consensus in the peer-reviewed literature. For the human cancer studies, there is reasonable agreement on which studies are the most useful for informing cancer evaluation and on the overall risk estimates found in the meta-analyses conducted by EPA and Exponent Health Sciences. As per the NRC (2006) recommendations, studies of dry cleaning workers will not be included in the review because it is unlikely that substantial numbers of these workers were frequently exposed to high enough levels of TCE. The draft monograph will focus on whether the associations between exposure to TCE and cancer are credible and whether bias, chance, or confounding can be ruled out.

There is evidence suggesting that the toxicity and carcinogenicity of TCE are mediated by its metabolites. The monograph will also review toxicity and genotoxicity data on the major TCE metabolites. The NAS and EPA reports have identified several potential modes of action for liver and kidney cancer (see Section 3.3). These modes of action include some which have been proposed not to be relevant to humans (such as PPARα activation) and others that might support an association between cancer and exposure to TCE, such as mutagenicity. The cancer evaluation component of the monograph will also discuss data on immunomodulation because these data may be relevant to evaluating potential mechanisms for lymphoma and other cancers. The monograph will focus its assessment on these specific modes of action and integrate the findings with its assessment of cancer studies in humans and experimental animals to reach a preliminary listing recommendation.

5.2. Proposed approach for obtaining scientific and public input

Public comments on scientific issues have been requested on TCE at several times prior to the development of the draft RoC monograph including the request for information on the nomination, and the request for comment on the draft concept. The ORoC will consider this information and experts suggested by the public[3] in drafting the cancer evaluation component of the draft monograph. The ORoC will also use variety of sequential approaches to receive relevant advice public and expert advisory inputs to address scientific issues important in the cancer assessment.

The ORoC will create a webpage for the candidate substances currently under review. The webpage will typically include the following: (1) RoC documents related to the review of the substance as available (e.g., concept document, draft RoC monograph), (2) citations for references identified from literature searches, (3) public comments, (4) an input box for the public to provide information (such as new literature) or comments (such as the identification of additional scientific issues), and (5) information on public meetings or listening sessions. The NTP will communicate when new information is added or updated (such as updated literature searches) to the website via the NTP list serve[4].

[3]Federal Register notice and public comments are available at *http://ntp.niehs.nih.gov/go/rocnom*.

[4]Persons can subscribe to the NTP list serve free-of-charge at *http://ntp.niehs.nih.gov/go/getnews*.

The first step the ORoC will take in obtaining scientific input is to identify appropriate technical advisors, external or internal to the government, with expertise in TCE and/or target organs (e.g., kidney, liver, or the hematopoietic system) who will serve as consultants in developing the monograph. Sources for identification of these experts include, but are not limited to, peer-reviewed literature databases and recommendations from the scientific community and the public.

Next, the ORoC will post on the website a preliminary outline (e.g., specific topics discussed, such as specific modes of action) for the cancer evaluation component of the monograph on TCE, in addition to its preliminary list of references (as stated above), and will convene a listening session to receive public comments. The focus of the listening session will be on the inclusion of topics and literature in the monograph, and the identification of any additional scientific issues. The listening session will be announced via a *Federal Register* notice, the RoC website, and the NTP list serve and other NTP publications. These announcements will also invite identification of potential speakers for several web-based symposiums as described below.

Subsequent steps are to tentatively convene three web-based symposiums, one for each of the three cancer sites of interest (non-Hodgkin's lymphoma and cancer of the liver and kidney) identified above. These symposiums will be announced via *Federal Register* notices and other NTP media options (see above), and will focus on both the epidemiologic and toxicologic/mechanistic data. Each symposium will include presentations by invited speakers providing their views on the strength of the evidence for the association observed between exposure to TCE and cancer, and a discussion of the key issues led by ORoC technical advisors and staff. Symposium speakers may be from industry, environmental advocacy groups, academia, unions, research organizations, or government agencies. Any real or apparent conflicts of interest will be disclosed. The public will be invited to listen to the symposium (via the web) and there will an opportunity for the public to submit questions for the speakers.

In general, each symposium will include at least two talks that address the epidemiologic evidence and two talks that address the mechanistic data. The speakers discussing the epidemiologic evidence will be asked (1) to identify and evaluate the evidence for potential random errors, systematic biases, or sources of confounding in the individual studies and (2) to discuss how each specific bias or confounder might affect observed associations in the studies for a specific endpoint (For example, would evidence of selection bias in a given study most likely lead to an over- or underestimate of the risk estimate or is the effect of the bias unknown?). The presentation and discussion of mechanistic data at each symposium will focus on the level of evidence for specific modes of action for the respective cancer sites. For example, the symposium on kidney cancer may focus on the level of evidence in humans for mutagenic or cytotoxic modes of action, and the symposium on liver cancer may focus on whether the findings in experimental animals are relevant to humans. The specific topics (e.g., modes of actions) will be decided after the listening session.

6. Public Release and Peer Review of the Draft Monograph

Once completed, the draft RoC monograph on TCE will undergo interagency review followed by release for public comment and public peer review. The NTP will convene an

external scientific panel[5] to peer review the draft monograph in a public forum. The panel will have expertise in disciplines related to the cancer evaluation of TCE such as epidemiology, exposure assessment, kidney, liver or hematopoietic cancer, toxicology, metabolism, immunology, and mechanisms of carcinogenesis. The NTP will set aside time at the peer-review meeting for a discussion of scientific issues raised in the public comments.

[5]NTP panels are federally chartered technical and scientific advisory groups convened as needed to provide advice on specific scientific issues and peer review. Members of NTP panels are scientists with relevant expertise and knowledge from the public and private sectors. The final selection of membership is based upon providing a balanced and unbiased group of highly qualified individuals and is made in accordance with Federal Advisory Committee Act and HHS implementing guidelines; *http://ntp.niehs.nih.gov/go/166*.

References

1. Alexander D, Mink P, Mandel J, Kelsh M. 2006. A meta-analysis of occupational trichloroethylene exposure and multiple myeloma or leukaemia. *Occup Med (Lond)* 56: 485-493.
2. Alexander D, Mink P, Adami H, Chang E, Cole P, Mandel J, Trichopoulos D. 2007. The non-Hodgkin lymphomas: A review of the epidemiologic literature. *Int J Cancer* 120: 1-39.
3. ATSDR. 1997. *Toxicological Profile for Trichloroethylene*. Agency for Toxic Substances and Disease Registry. 335 pp. *http://www.atsdr.cdc.gov/toxprofiles/tp19.pdf*.
4. Bakke B, Stewart PA, Waters MA. 2007. Uses of and exposure to trichloroethylene in U.S. industry: a systematic literature review. *J Occup Environ Hyg* (5): 375-90.
5. Bull R, Orner G, Cheng R, Stillwell L, Stauber A, Sasser, L, Lingohr M, Thrall B. 2002. Contribution of dichloroacetate and trichloroacetate to liver tumor induction in mice by trichloroethylene. *Toxicol Appl Pharmacol* 182: 55-65.
6. Chiu WA, Okino MS, Lipscomb JC, Evans MV. 2006. Issues in the pharmacokinetics of trichloroethylene and its metabolites. *Environ Health Perspect* 114(9): 1450-1456.
7. EPA. 2004. *Non-confidential IUR Production Volume Information*. U.S. Environmental Protection Agency. *http://www.epa.gov/iur/tools/data/2002-comp-chem-records.html* and search on CAS number or chemical name.
8. EPA. 2011. Toxicological Review of Trichloroethylene. Chapter 2. (CAS No. 79-01-6) In Support of Summary Information on the Integrated Risk Information System (IRIS). EPA/635/R-09/011F. U.S. Environmental Protection Agency. 24 pp.
9. FDA. 2006. *Total Diet Study Market Baskets 1991-3 through 2003-4*. U.S. Food and Drug Administration. *http://www.fda.gov/Food/FoodSafety/FoodContaminantsAdulteration/TotalDietStudy/ucm184293.htm*.
10. Grulich AE, Vajdic CM, Cozen W. 2007. Altered immunity as a risk factor for non-Hodgkin lymphoma. Cancer *Epidemiol Biomarkers Prev* 16(3): 405-408.
11. IARC. 1995. Trichloroethylene. In *Dry Cleaning, Some Chlorinated Solvents and Other Industrial Chemicals*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 63. Lyon, France: International Agency for Research on Cancer. pp. 75-158.
12. IOM. (Institute of Medicine). 2003. Gulf war and health: Volume 2. Insecticides and solvents. pp. 616. Washington, DC: National Academies Press. *http://www.nap.edu/catalog.php?record_id=10628*.
13. Kelsh MA, Alexander DD, Mink PJ, Mandel JH. 2010. Occupational trichloroethylene exposure and kidney cancer: a meta-analysis. *Epidemiology* 21(1): 95-102.
14. Mandel J, Kelsh M, Mink P, Alexander D, Kalmes R, Weingart M, Yost L, Goodman M. 2006. Occupational trichloroethylene exposure and non-Hodgkin's lymphoma: A meta-analysis and review. *Occup Environ Med* 63: 597-607.
15. NRC. (National Research Council). 2006. Assessing the human health risks of trichloroethylene: Key scientific issues. Washington, DC: The National Academies Press. *http://books.nap.edu/openbook.php?record_id=11707&page=1.*
16. NRC. (National Research Council). 2009. Contaminated water supplies at Camp Lejeune: Assessing potential health effects. Washington, DC: National Academies Press. *http://books.nap.edu/openbook.php?record_id=12618&page=1.*
17. NTP. 2011. Trichloroethylene. In *Report on Carcinogens*. 12th ed. Research Triangle Park, NC: National Toxicology Program. pp. 420-423.

18. Scott CS, Jinot J. 2011. Trichloroethylene and cancer: systematic and quantitative review of epidemiologic evidence for identifying hazards. *Int J Environ Res Public Health*. 8(11): 4238-4272.
19. TRI. 2011. *TRI Explorer Chemical Report*. U.S. Environmental Protection Agency. *http://www.epa.gov/triexplorer* and select trichloroethylene. Last accessed: 9/22/11.
20. Von Tungeln LS, Yi P, Bucci TJ, Samokyszyn VM, Chou MW, Kadlubar FF, Fu PP. 2002. Tumorigenicity of chloral hydrate, trichloroacetic acid, trichloroethanol, malondialdehyde, 4-hydroxy-2-nonenal, crotonaldehyde, and acrolein in the B6C3F(1) neonatal mouse. *Cancer Lett* 185(1): 13-19.
21. Wartenberg D, Reyner D, Scott CS. 2000. Trichloroethylene and cancer: epidemiologic evidence. *Environ Health Perspect* 108 (Suppl. 2): 161-176.
22. Wu C, Schaum J. 2000. Exposure assessment of trichloroethylene. *Environ Health Perspect* 108 (Suppl. 2): 359-363.

Appendix 1

Preliminary Literature Search Strategy: Trichloroethylene

This document identifies the data sources, search terms and preliminary search strategies for identifying literature for the draft monograph on trichloroethylene. The literature search will be updated approximately every three months, and prior to submitting the draft monograph for interagency review. Additional literature searches will be conducted as needed to identify information to address scientific issues that arise during the review. Citations retrieved from literature searches will be uploaded to web-based systematic review software and screened using inclusion and exclusion criteria. Multi-level reviews of the literature are conducted, with initial reviews based on titles and abstracts only, and later reviews based on full-text.

1. Data Sources

Identification of synonyms and metabolites for trichloroethylene (CASRN 79-01-6); chemical class = chlorinated alkenes, halogenated alkenes

- *Synonyms*- IARC (1995) and National Library of Medicine databases (e.g., ChemIDplus, Hazardous Substances Data Bank)
- *Metabolites*- IARC (1995), EPA (2011)

Citation databases (searches for titles, abstracts, and key words)

- PubMed
- Web of Science
- Scopus

Additional data sources:

- EPA. 2011. Toxicological Review of Trichloroethylene
- National Research Council 2006. Assessing the human health risks of trichloroethylene: Key scientific issues.
- National Research Council 2009. Contaminated water supplies at Camp Lejeune: Assessing potential health effects.
- Other authoritative reviews or general sources for exposure and other information (e.g., Toxnet; U.S. Government agencies websites, publications and databases; International Agency for Research on Cancer)
- Citations in authoritative reviews or in primary references located by literature search
- QUOSA library of occupational case-control studies (full text search for trichloroethylene)

2. Preliminary Literature Searches:

Literature searches in the three databases (see Data Sources, Section 1) are conducted using search terms specific for trichloroethylene (synonyms, chemical class, metabolites, and exposure scenario) and for the topics covered by the monograph (See Table 1).

As mentioned in the concept document for TCE, the monograph will focus on human cancer studies and mechanistic data related to non-Hodgkin's lymphoma, and cancers of the

liverand kidney. Searches will also be conducted for studies of cancer in experimental animals published TCE was last reviewed for the RoC (2000). In addition, the draft monograph will utilize information, including the extensive list of cited references in several comprehensive reviews. Literature searches will be conducted to update the information in those reviews (latest review 2011, update from 2009) and to identify literature that might not be covered in those review. However, there will be no date restrictions for literature searches to identify cancer studies in humans.

Searches for human cancer studies are somewhat unique because they involve the identification of search terms for exposure scenarios in which people may be exposed to trichloroethylene in addition to search terms specific for trichloroethylene. TCE is primary used as a metal degreaser and is mainly used in industries such as metal fabricating, electronics, aircraft carriers, and dry cleaning. As mentioned in the concept document, studies on drycleaners will not be included in the review because it is unlikely that substantial numbers of them were frequently exposed to sufficient amounts of TCE. Exposure scenario-related search terms are provided in Table 1.

In addition to the human cancer studies identified from the above searches, a full-text search for trichloroethylene is conducted using a QUOSA library of occupational case-control studies published since 2000.

Table 1. Preliminary literature search approach for TCE

Topic[a]	Combined with	Date/limits
Human exposure	*TCE synonyms*: [(1,1,2 or 1,2,2)-trichloroethylene, 79-01-6, TCE, trichloroethene, acetylene trichloride, ethylene trichloride]	Authoritative reviews Other reviews since 2009
Human cancer studies	*TCE synonyms* *Exposure scenario-related terms*: [degreasers; aircraft, aerospace, or aircraft-maintenance workers; metal workers; and electronic workers]	No date limits
Studies in experimental animals	*TCE synonyms* *TCE metabolites (for mechanistic information)*: [trichloroethanol, trichloroacetic acid, dichloroacetic acid, chloral hydrate, *S*-(1,2-dichlorovinyl)glutathione (DCVG), *S*-(1,2-dichlorovinyl)-L-cysteine (DCVC), *N*-acetyl-1,2-*S*-(1,2-dichlorovinyl-L-cysteine (NAcDCVC), *S*-(1,2-dichlorovinyl)thiol (DCVSH)]	Primary literature since 2000 Authoritative reviews Primary literature since 2009
ADME and Toxicokinetics	*TCE synonyms* *TCE metabolites*	Authoritative reviews Primary literature since 2009
Genotoxicity	*TCE synonyms* *TCE metabolites*	Authoritative reviews Primary literature since 2009
Toxicity (liver, kidney, and immune)	*TCE synonyms* *TCE metabolites*	Authoritative reviews Primary literature since 2009
Mechanisms	*TCE synonyms* *TCE metabolites*	Authoritative reviews Primary literature since 2009

Appendix 1

Topic[a]	Combined with	Date/limits
	Chemical class: [chlorinated alkenes, halogenated alkenes]	

ADME = adsorption, distribution, metabolism and excretion.

[a]Search terms for each of these topics have been developed in consultation with an information specialist.