

## Trichloroacetic acid (TCA); CASRN 76-03-9

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the [IRIS assessment development process](#). Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the [guidance documents located on the IRIS website](#).

### STATUS OF DATA FOR TRICHLOROACETIC ACID (TCA)

**File First On-Line 10/01/1992**

Category (section)	Assessment Available?	Last Revised
<b>Oral RfD (I.A.)</b>	yes	09/30/2011
<b>Inhalation RfC (I.B.)</b>	qualitative discussion	09/30/2011
<b>Carcinogenicity Assessment (II.)</b>	yes	09/30/2011

## I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

### I.A. REFERENCE DOSE (RfD) FOR CHRONIC ORAL EXPOSURE

Substance Name — Trichloroacetic acid (TCA)

CASRN — 76-03-9

Section I.A. Last Revised — 09/30/2011

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the [guidance documents](#) for an elaboration of these concepts. Because RfDs can be

derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

An RfD for TCA was not previously available on the IRIS database.

### IA.1. CHRONIC ORAL RfD SUMMARY

Critical Effect	Point of Departure*	UF	Chronic RfD
Hepatocellular necrosis Male B6C3F <sub>1</sub> mice 60-Week drinking water exposure study DeAngelo et al., <a href="#">2008</a>	BMDL <sub>10</sub> = 18 mg/kg-day	1000	0.02 mg/kg-day

\*Conversion Factors and Assumptions -- The mice in the principal study were exposed continuously via drinking water; therefore, no adjustment for intermittent dosing was required. Doses were estimated from nominal concentrations of TCA in drinking water and measured values for body weight and drinking water consumption.

### IA.2. PRINCIPAL AND SUPPORTING STUDIES

DeAngelo et al. ([2008](#)) exposed male B6C3F<sub>1</sub> mice to nominal concentrations of 0.05, 0.5, or 5 g/L TCA in the drinking water (50/dose at study initiation) for 60 weeks (Study 1); 0 or 4.5 g/L TCA (58 animals/group) for 104 weeks (Study 2); or 0, 0.05, or 0.5 g/L TCA (72/group) for 104 weeks (Study 3). Study design information and results from the 60-week study are provided here. See the *Toxicological Review of Trichloroacetic Acid* ([U.S. EPA, 2011](#)) for additional information on the 104-week studies.

The pH of the dosing solution was adjusted to 6.0–7.1 by the addition of 10 N sodium hydroxide. Mice in the control group in Study 1 received 2 g/L sodium chloride in the drinking water. Body weights and water consumption were measured twice monthly for the first 2 months and then monthly afterwards. In Study 1, groups of five animals from each dose group were examined at necropsy at 4, 15, 31, and 45 weeks.

At interim and terminal necropsies, gross lesions, livers, kidneys, spleens, and testes were examined by a board-certified veterinary pathologist. For all other tissues, a complete pathological examination was performed on five mice from the high-dose and control groups. If the number of any histopathologic lesions in a tissue was significantly increased above that in the control animals, then that tissue was examined in all TCA dose groups. To determine long-term hepatocellular damage during TCA treatment, arterial blood was collected at 30 and 60 weeks, and serum lactate dehydrogenase (LDH) activity was measured. Portions of liver tissue from the interim-sacrifice animals (5/group/duration) were frozen and analyzed for palmitoyl-CoA oxidase (PCO) activity, a marker of peroxisome proliferation.

For Study 1, time-weighted mean doses of 8, 68, and 602 mg/kg-day were calculated by the study authors from nominal TCA concentrations (0.05, 0.5, and 5 g/L, respectively) and drinking water consumption data for the low-, mid-, and high-dose groups. Animals in the mid- and high-dose groups consumed significantly less water than the controls. DeAngelo et al. (2008) also reported measured TCA concentrations in drinking water. Doses calculated by EPA based on those concentrations and reported drinking water consumption were: 7.7, 68.2, and 602.1 mg/kg-day for measured TCA concentrations of 0.05, 0.48, and 5.06 g/L, respectively.

No decrease in animal survival was found at any TCA dose. Exposure to TCA in drinking water decreased body weight by 15% in the high-dose group relative to the control. Significant, dose-related increases in absolute and relative liver weights were observed in the 0.5 and 5 g/L treatment groups at all scheduled sacrifices, with the exception of the 0.5 g/L dose group at 30 days.

Nonneoplastic alterations in the liver and testes were seen at study termination at 60 weeks and appeared to be dose related. The nonneoplastic alterations observed in the liver included hepatocellular cytoplasmic alteration, necrosis, and inflammation. Cytoplasmic alterations were observed in all treatment groups; however, the incidence did not increase monotonically with dose. These lesions were most prominent in the 5 g/L TCA group throughout the study and were most severe after 60 weeks of treatment. The alterations were characterized by an intense eosinophilic cytoplasm with deep basophilic granularity and slight cytomegaly. The distribution ranged from centrilobular to diffuse. Hepatic necrosis was observed in the middle- and high-dose group at all time points and was reported to be most severe at 30–45 weeks. A significant increase in the severity of inflammation was seen in the high-dose group at 60 weeks. A dose-related increase in serum lactate dehydrogenase (LDH) activity (a measure of liver damage) was observed at 30 weeks, and significant increases were measured in the 0.5 and 5.0 g/L dose groups. No change in LDH activity was found in any treatment groups at 60 weeks. No other hepatic changes showed statistically significant increases in

incidence or severity level. An increased incidence of testicular tubular degeneration was seen in the 0.5 and 5 g/L treatment groups. No treatment-related changes were observed in the spleen or kidney.

**Incidence and severity of nonneoplastic lesions in male B6C3F<sub>1</sub> mice exposed to TCA in drinking water for 60 weeks**

Lesion	Treatment	Control	0.05 g/L TCA	0.5 g/L TCA	5 g/L TCA
	Dose	0	8	68	602
Hepatocellular cytoplasmic alteration	Number <sup>a</sup>	30	27	29	29
	Incidence <sup>b</sup>	7%	48% <sup>d</sup>	20.6% <sup>d</sup>	93% <sup>d</sup>
	Severity <sup>c</sup>	0.10 ± 0.40	0.70 ± 0.82	0.34 ± 0.72	1.60 ± 0.62 <sup>d</sup>
Hepatocellular inflammation	Incidence <sup>b</sup>	10%	0	7%	24% <sup>d</sup>
	Severity <sup>c</sup>	0.13 ± 0.40	0	0.07 ± 0.03	0.24 ± 0.44
Testicular tubular degeneration	Incidence <sup>b</sup>	7%	0	14% <sup>d</sup>	21% <sup>d</sup>
	Severity <sup>c</sup>	0.10 ± 0.40	0	0.17 ± 0.47	0.21 ± 0.41

<sup>a</sup>Number of animals examined.

<sup>b</sup>Percentage of animals with alteration.

<sup>c</sup>Severity: 0 = no lesion, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe (reported as the average severity of all animals in the dose group).

<sup>d</sup>Statistically significant from the control group,  $p \leq 0.05$ .

Source: DeAngelo et al. (2008).

**Incidence and severity of hepatocellular necrosis at 30-45 weeks in male B6C3F<sub>1</sub> mice exposed to TCA in drinking water**

Treatment	Control	0.05 g/L TCA	0.5 g/L TCA	5 g/L TCA
Dose (mg/kg-d)	0	8	68	602
Number <sup>a</sup>	10	10	10	10
Incidence <sup>b</sup>	0	0	30.0%	50.0%
Severity <sup>c</sup>	0	0	0.50 ± 0.97	1.30 ± 1.49 <sup>d</sup>

<sup>a</sup>Number of animals examined.

<sup>b</sup>Percentage of animals with alteration.

<sup>c</sup>Severity: 0 = no lesion, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe (reported as the average severity of all animals in the dose group).

<sup>d</sup>Statistically significant from the control group,  $p \leq 0.05$ .

Source: DeAngelo et al. (2008).

Areas of inflammation (at high dose only) and necrosis (at mid- and high dose) were present during the early course of TCA administration, but abated after week 60 in all studies. Similarly, LDH activity was elevated in the mid- and high-dose groups at week 30 but not at week 60. Cytoplasmic alterations occurred as early as week 4 and persisted at all doses, indicating that this effect did not correlate with other nonneoplastic changes in the liver.

For the 60-week study, EPA determined the lowest-observed-adverse-effect level (LOAEL) for effects on the liver (increased liver weight, hepatic necrosis, and serum LDH activity at 30 weeks) and testes (testicular tubular degeneration) to be 0.5 g/L (68 mg/kg-day) and the no-observed-adverse-effect level (NOAEL) to be 0.05 g/L (8 mg/kg-day).

**Methods of Analysis.** Hepatocellular necrosis in male B6C3F<sub>1</sub> mice exposed to TCA in drinking water for 30–45 weeks as reported in the DeAngelo et al. (2008) 60-week study was

identified as the critical effect. All dichotomous models in U.S. EPA's Benchmark Dose Software (BMDS, version 1.4.1) were fit to the incidence data for hepatocellular necrosis. Doses (i.e., benchmark dose [BMD<sub>10</sub>] and 95% lower confidence limit on the benchmark dose [BMDL<sub>10</sub>]) associated with a benchmark response (BMR) of 10% extra risk were calculated. A BMR of 10% is generally used in the absence of information regarding what level of change is considered biologically significant, and also to facilitate a consistent basis of comparison across assessments ([U.S. EPA, 2000](#)). The log-logistic model, which provided the best fit of the hepatocellular necrosis data, yielded a BMD<sub>10</sub> of 40.7 mg/kg-day and a BMDL<sub>10</sub> of 17.9 mg/kg-day. The BMDL<sub>10</sub> or 17.9 mg/kg-day was selected as the point of departure (POD) for the RfD.

### **I.A.3. UNCERTAINTY FACTORS**

UF = 1000

An uncertainty factor (UF) of 10 was selected for interindividual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of TCA in humans.

An UF of 10 was selected for interspecies extrapolation to account for uncertainty in extrapolating from laboratory animals to humans (i.e., interspecies variability) because information was unavailable to quantitatively assess toxicokinetic or toxicodynamic differences between animals and humans for TCA.

An UF of 10 was used to account for database deficiencies. There are no TCA-specific systemic toxicity data in humans. Although subchronic and chronic animal studies of TCA have been conducted in rats and mice, most studies have focused primarily or exclusively on liver lesions and have not examined other organs for microscopic lesions. DeAngelo et al. ([2008](#)) is the only study in mice that included histopathological examination of organs other than the liver; however, complete histopathologic examinations were performed on only five mice from the high-dose and control groups. Other data gaps include lack of a multigeneration reproductive toxicity study. Available developmental studies were conducted at high doses, and did not allow identification of a NOAEL.

An UF for study duration was not required in this assessment because the principal study was of chronic duration.

An UF for LOAEL-to-NOAEL extrapolation was not applied because the current approach is to address this factor as one of the considerations in selecting a BMR for BMD modeling. In

this case, a BMR of 10% increase in the incidence of hepatocellular necrosis was selected under an assumption that it represents a minimally biologically significant change.

#### **I.A.4. ADDITIONAL STUDIES/COMMENTS**

No human epidemiology studies of TCA were located. Case reports and accounts of the medical use of TCA for skin treatment demonstrate its potential for skin corrosion and eye irritation.

In animals, TCA induces systemic, noncancer effects that can be grouped into three general categories: liver toxicity, metabolic alterations, and developmental toxicity. Studies in rats and mice indicate that TCA primarily affects the liver, although effects on the lungs and kidneys have also been noted in rats. Observed hepatic effects in rodents include increased size and weight, collagen deposition, indications of altered lipid and carbohydrate metabolism, histopathologic changes, peroxisome proliferation, evidence of lipid peroxidation, and oxidative damage to hepatic DNA. TCA may influence intermediary carbohydrate metabolism, as shown by altered glycogen content in the livers of mice treated with TCA. Administration of TCA to female rats during pregnancy induced developmental effects in six studies at doses that also resulted in maternal toxicity. Two of these studies are single-dose studies. The observed effects include fetal cardiac malformations, decreased crown-rump length, and reduced fetal body weight. The pattern of observed fetal cardiac malformation effects is not consistent across the available studies.

*For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.8 \(PDF\)](#).*

#### **I.A.5. CONFIDENCE IN THE CHRONIC ORAL RfD**

Study — Medium

Database — Medium

RfD — Medium

The overall confidence in this RfD assessment is medium. Confidence in the principal study ([DeAngelo et al., 2008](#)) is medium. The study was well designed and studied, with a study duration of 60 weeks, and well conducted. Only male mice were tested. Quantitative data for the incidence and severity of the various endpoints were included in the published paper. Complete histopathologic examination was conducted for control and high-dose groups, but only on five animals. Confidence in the database is medium. Human data are limited primarily to case reports of skin or eye effects associated with medical treatments, and information on systemic toxicity is lacking. Significant gaps in the animal database include the absence of a multigeneration reproductive toxicity study.

*For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6 \(PDF\)](#).*

## I.A.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC ORAL RfD

Source Document — *Toxicological Review of Trichloroacetic Acid* ([U.S. EPA, 2011](#)).

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Trichloroacetic Acid* ([U.S. EPA, 2011](#)). [To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition \(PDF\)](#)

Agency Completion Date -- 09/30/2011

## I.A.7. EPA CONTACTS

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (email address).

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## I.B. REFERENCE CONCENTRATION (RfC) FOR CHRONIC INHALATION EXPOSURE

Substance Name — Trichloroacetic acid (TCA)

CASRN — 76-03-9

Section I.B. Last Revised — 09/30/2011

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrapulmonary effects). The inhalation RfC (generally expressed in units of  $\text{mg}/\text{m}^3$ ) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (possibly threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* ([U.S. EPA, 1994](#)). Because RfCs

can also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

An inhalation RfC for TCA was not previously available on the IRIS database.

### **I.B.1. CHRONIC INHALATION RfC SUMMARY**

No inhalation studies adequate for the derivation of an RfC were located. The respiratory tract has not been examined in oral studies of TCA. Because the liver is the critical target organ for oral toxicity and a first-pass effect by the liver is expected following oral administration, the route of exposure may influence the hepatic response to TCA. Physiologically based pharmacokinetic (PBPK) models that would support route-to-route extrapolation for TCA have not been published. Thus, the available information is inadequate for extrapolation of oral toxicity data to the inhalation pathway. For these reasons, an RfC for TCA was not derived.

### **I.B.2. PRINCIPAL AND SUPPORTING STUDIES**

Not applicable.

### **I.B.3. UNCERTAINTY FACTORS**

Not applicable.

### **I.B.4. ADDITIONAL STUDIES/COMMENTS**

Not applicable.

*For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.8 \(PDF\)](#).*

### **I.B.5. CONFIDENCE IN THE CHRONIC INHALATION RfC**

Not applicable.

*For more detail on Characterization of Hazard and Dose Response, exit to [the toxicological review, Section 6 \(PDF\)](#).*

### **I.B.6. EPA DOCUMENTATION AND REVIEW OF THE CHRONIC INHALATION RfC**

Source Document — *Toxicological Review of Trichloroacetic Acid* ([U.S. EPA, 2011](#)).

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Trichloroacetic Acid* ([U.S. EPA, 2011](#)). [To review this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition \(PDF\)](#)

Agency Completion Date -- 09/30/2011

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## **II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE**

Substance Name — Trichloroacetic acid (TCA)

CASRN — 76-03-9

Section II. Last Revised — 09/30/2011

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005a](#)) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* ([U.S. EPA, 2005b](#)). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The “oral slope factor” is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a “unit risk” is a plausible upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water

(see Section II.B.1.) or per  $\mu\text{g}/\text{m}^3$  air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

In the previous IRIS assessment (posted in 1996), TCA had a classification of C (possible human carcinogen). The previous IRIS assessment did not provide quantitative estimates of carcinogenic risk from oral or inhalation exposure.

## II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

### II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Under the *Guidelines for Carcinogen Risk Assessment* (Cancer Guidelines) ([U.S. EPA, 2005a](#)), there is *suggestive evidence of carcinogenic potential* for TCA based on significantly increased incidences of liver tumors in male B6C3F<sub>1</sub> mice exposed via drinking water for 52–104 weeks ([DeAngelo et al., 2008](#); [Bull et al., 2002](#); [Bull et al., 1990](#); [Herren-Freund et al., 1987](#)) and female B6C3F<sub>1</sub> mice exposed for 51 or 82 weeks ([Pereira, 1996](#)), and lack of treatment-related tumors in a study of male F344/N rats following lifetime exposure in drinking water ([DeAngelo et al., 1997](#)).

There are no studies of TCA in humans. In animals, the scope of carcinogenicity testing has been limited. The only lifetime studies (104 weeks) are of TCA administered in drinking water to male F344/N rats and to male B6C3F<sub>1</sub> mice. TCA did not induce tumors at any site in male rats ([DeAngelo et al., 1997](#)), but in mice TCA induced a statistically significant increase in hepatocellular adenomas and carcinomas at the high dose (0.5 g/L in drinking water) ([DeAngelo et al., 2008](#)).

There are several less-than-lifetime studies (51-82 weeks) of TCA-induced liver cancer following administration in drinking water to male and female B6C3F<sub>1</sub> mice. In all studies in male mice, TCA induced hepatocellular carcinomas ([DeAngelo et al., 2008](#); [Bull et al., 2002](#); [Bull et al., 1990](#)). It is noteworthy that the high background rate of liver tumors observed in male B6C3F<sub>1</sub> mice at 104 weeks was not reported in these less-than-lifetime studies. Bull et al. (1990) reported no liver tumors in female mice in a 52-week study. However, this result is outweighed by an 82-week study ([Pereira, 1996](#)) that found no tumors in female mice at a comparable dose administered in drinking water for 51 weeks but reported hepatocellular carcinomas at a higher dose at 51 weeks and at the highest two doses by 82 weeks.

Taking the results of these studies together, TCA: 1) has consistently tested positive in males in one strain of mouse in one lifetime and several less-than-lifetime studies; 2) has not been tested in lifetime studies in females, and was shown to induce tumors in one less-than-lifetime

study but did not produce tumors in another; and 3) has tested negative in one lifetime study that was conducted in male rats only. Therefore, there are consistent observations of tumor formation in male mice, however, the overall weight of evidence is tempered due to a lack of studies on female animals in general and the negative results in male rats.

EPA's Cancer Guidelines ([U.S. EPA, 2005a](#)) emphasize the importance of weighing all of the evidence in reaching conclusions about the human carcinogenic potential of agents. Each cancer descriptor may be applicable to a variety of potential data sets and represent points along a continuum of evidence. The available tumorigenic evidence for TCA could be considered a borderline case between two descriptors - *likely to be carcinogenic to humans* and *suggestive evidence of carcinogenic potential*. For example, TCA has tested positive in more than one sex of B6C3F<sub>1</sub> mice, which minimally corresponds to one of the examples provided in EPA's Cancer Guidelines ([U.S. EPA, 2005a](#)) for the descriptor *likely to be carcinogenic to humans*. The example states that supporting data for this descriptor may include "an agent that has tested positive in animal experiments in more than one species, sex, strain, site, or exposure route, with or without evidence of carcinogenicity in humans."

In evaluating this borderline case, EPA considered Section 2.5 of the Cancer Guidelines which states that the descriptor *likely to be carcinogenic to humans* is appropriate when "the weight of evidence is adequate to demonstrate carcinogenic potential to humans but does not reach the weight of evidence for the descriptor *carcinogenic to humans*." The Cancer Guidelines further state that the descriptor *suggestive evidence of carcinogenic potential* is appropriate when "the weight of evidence is suggestive of carcinogenicity, a concern for potential carcinogenic effects is raised, but the data are not judged sufficient for a stronger conclusion."

Thus, although either descriptor is plausible and the consistent positive evidence in B6C3F<sub>1</sub> mice raises a concern for carcinogenic effects in humans, this assessment attaches greater weight to the lack of evidence in other strains or species than to the replication of positive results in this one strain. Accordingly, this assessment concludes that there is *suggestive evidence of carcinogenic potential* for TCA.

In choosing a cancer descriptor, consideration was also given to the nature of the only tumor type induced by TCA, i.e., liver tumors (hepatocellular adenomas and carcinomas). The mouse, and in particular the B6C3F<sub>1</sub> mouse, is relatively susceptible to liver tumors, and the background incidence of this tumor is generally high. For these reasons, use of mouse liver tumor data in risk assessment has been a subject of controversy ([King-Herbert and Thayer, 2006](#)). The less-than-lifetime drinking water bioassays of TCA in the B6C3F<sub>1</sub> mouse ([DeAngelo et al., 2008](#); [Bull et al., 2002](#); [Pereira, 1996](#); [Bull et al., 1990](#)) reported relatively low incidences of liver adenomas and carcinomas in control animals (ranging from 0 to 13%), thereby minimizing the possible confounding of compound-related liver tumors. In the only

lifetime (104-week) study in the male B6C3F<sub>1</sub> mouse (females were not tested), however, the incidence of spontaneous liver tumors was 55%, an incidence that was higher than the liver tumor incidence in the low-dose group in this study.

EPA's Cancer Guidelines ([U.S. EPA, 2005a](#)) indicate that for tumors occurring at a site other than the initial point of contact, the weight of evidence for carcinogenic potential may apply to all routes of exposure that have not been adequately tested, unless there is convincing toxicokinetic data that absorption does not occur by other routes. For TCA, systemic tumors were observed in mice following oral exposure, but carcinogenicity studies of TCA by the inhalation or dermal routes in humans or animals have not been conducted. There is some evidence of rapid absorption of TCA through the skin, but no studies of uptake following inhalation exposure (see Section 3.1). Because TCA is highly soluble in water, it is reasonable to assume that TCA can be absorbed and taken up into the blood via the inhalation route. Moreover, the drinking water studies demonstrate that TCA acts systemically rather than only at the site of first contact. In the absence of information to indicate otherwise, there is *suggestive evidence of carcinogenic potential* for TCA by all routes of exposure.

In view of widespread human exposure to TCA as a water chlorination byproduct and as a metabolite of several commonly used chlorinated solvents, there is a need for further testing of TCA in experimental models other than the B6C3F<sub>1</sub> mouse.

As discussed in more detail in Section 4.7.3, the MOA for TCA-induced liver carcinogenesis has not been established. The available data collectively provide limited evidence of genotoxic potential of TCA. In mouse liver tumor promotion assays, also conducted exclusively in the B6C3F<sub>1</sub> strain, TCA induced liver tumors with and without pre-treatment with an initiator (see Table 4-3). GGT-positive foci (closely linked to the subsequent development of tumors) were observed following TCA promotion of Sprague-Dawley rats that had undergone prior partial hepatectomy and DEN initiation ([Parnell et al., 1988](#)). Tumor induction appears to include perturbation of cell growth, both through growth inhibition of normal cells and proliferation of selected cell populations. Specific mechanisms of altered growth control that have been investigated for TCA include activation of the PPAR $\alpha$  pathway, global DNA hypomethylation, reduced intercellular communication, and oxidative stress. Of these, PPAR $\alpha$  agonism has been advanced as the most likely MOA contributing to the development of liver tumors. However, significant gaps in the understanding of the hypothesized PPAR $\alpha$  MOA exist. Specifically, Ito et al. ([2007](#)) showed that the peroxisome proliferator, DEHP, induced liver tumors in PPAR $\alpha$ -null mice. Yang et al. ([2007](#)) demonstrated that transgenic mice with PPAR $\alpha$  activation constitutively in hepatocytes did not develop liver tumors. These data challenge the hypothesis that PPAR $\alpha$  agonism is necessary and sufficient for hepatocarcinogenesis. As such, the formation of liver tumors cannot be sufficiently accounted for by the proposed PPAR $\alpha$  MOA and the existence of other contributing MOA(s) is assumed.

As noted above, EPA concluded that there is *suggestive evidence of carcinogenic potential* for TCA. The *Guidelines for Carcinogen Risk Assessment* ([U.S. EPA, 2005a](#)) state: "When there is suggestive evidence, the Agency generally would not attempt a dose-response assessment, as the nature of the data generally would not support one; however, when the evidence includes a well-conducted study, quantitative analyses may be useful for some purposes, for example, providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities. In each case, the rationale for the quantitative analysis is explained, considering the uncertainty in the data and the suggestive nature of the weight of evidence. These analyses generally would not be considered Agency consensus estimates."

In this case, although there are no epidemiologic studies that have evaluated the carcinogenicity in humans, the carcinogenicity of TCA has been evaluated in several studies in both rats and mice. These studies are well-conducted studies showing evidence of increased incidence of tumors in both sexes of one species at multiple exposure levels. The data from these studies are adequate to support a quantitative cancer dose-response assessment. Considering these data and uncertainty associated with the suggestive nature of the tumorigenic response, EPA concluded that quantitative analyses may be useful for providing a sense of the magnitude of potential carcinogenic risk. Based on the weight of evidence, a dose-response assessment of the carcinogenicity of TCA is deemed appropriate.

*For more detail on Dose-Response Assessments, exit to [the toxicological review, Section 6 \(PDF\)](#).*

*For more detail on Susceptible Populations, exit to [the toxicological review, Section 4.8 \(PDF\)](#).*

## **II.A.2. HUMAN CARCINOGENICITY DATA**

None. There are no epidemiological studies of TCA carcinogenicity in humans. Most of the human health data for chlorinated acetic acids concern components of complex mixtures of water disinfectant byproducts. These complex mixtures of disinfectant byproducts have been associated with increased potential for bladder, rectal, and colon cancer in humans [reviewed by Boorman et al. ([1999](#)); Mills et al. ([1998](#))].

### II.A.3. ANIMAL CARCINOGENICITY DATA

The experimental database for carcinogenicity of TCA consists of studies in rats and mice. Studies in mice indicate that TCA is a complete carcinogen that significantly increased the incidence of liver tumors in male B6C3F<sub>1</sub> mice exposed via drinking water for 52–104 weeks ([DeAngelo et al., 2008](#); [Bull et al., 2002](#); [Bull et al., 1990](#); [Herren-Freund et al., 1987](#)) and female B6C3F<sub>1</sub> mice exposed for 51 or 82 weeks ([Pereira, 1996](#)). Incidence of tumors increased with increasing TCA concentrations ([DeAngelo et al., 2008](#); [Bull et al., 2002](#); [Pereira, 1996](#); [Bull et al., 1990](#)). Results from the less-than-lifetime studies were obtained under conditions where the background incidence of tumors in control animals was generally low. The development of tumors in animals exposed to TCA progressed rapidly, as evident from the observation of significant numbers of tumors in less-than-lifetime studies of ≤82 weeks. Positive evidence for tumor promotion by TCA (following exposure to known tumor initiators) has been reported for liver tumors in B6C3F<sub>1</sub> mice ([Bull et al., 2004](#); [Pereira et al., 2001](#); [Pereira et al., 1997](#); [Pereira and Phelps, 1996](#); [Herren-Freund et al., 1987](#)) and for gamma-glutamyl transferase (GGT)-positive foci in livers of partially hepatectomized Sprague-Dawley rats ([Parnell et al., 1988](#)).

In contrast to the results observed for mice, treatment-related tumors were not observed in a study of male F344/N rats exposed to TCA via drinking water for 104 weeks ([DeAngelo et al., 1997](#)). The carcinogenicity of TCA has not been evaluated in female rats or in other species of experimental animals. However, treatment of primary cultures of male Long-Evans rat hepatocytes with 0.01–1.0 mM TCA for 10–40 hours did not induce proliferation of the cultured hepatocytes ([Walgren et al., 2005](#)).

### II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Evidence for genotoxic activity of TCA is inconclusive. No mutagenicity was reported in *Salmonella typhimurium* strain TA100 in the absence of metabolic activation ([Rapson et al., 1980](#)) or in an alternative protocol using a closed system ([DeMarini et al., 1994](#)), but a mutagenic response was induced in this same strain in the Ames fluctuation test reported by Giller et al. ([1997](#)). Mutagenicity in mouse lymphoma cells was only induced at cytotoxic concentrations ([Harrington-Brock et al., 1998](#)). Measures of DNA-repair responses in bacterial systems are similarly inconclusive, with induction of DNA repair reported in *S. typhimurium* ([Ono et al., 1991](#)) but not in *Escherichia coli* ([Giller et al., 1997](#)). Although positive results were reported for unneutralized TCA in three in vivo cytogenetic assays by Bhunya and Behera ([1987](#)), later in vitro studies by Mackay et al. ([1995](#)), using neutralized TCA, reported negative results, suggesting that TCA-induced clastogenicity may occur secondary to pH changes. Some evidence for TCA-induction of hepatic DNA strand breaks and chromosome damage has been reported ([Harrington-Brock et al., 1998](#); [Giller et al., 1997](#);

[Nelson and Bull, 1988](#)); however, these effects have not been uniformly reported ([Chang et al., 1992](#); [Styles et al., 1991](#)) and may be related to low pH when TCA was not neutralized. TCA induced oxidative DNA damage in the livers of mice following a single dose ([Austin et al., 1996](#)), but not following repeated dosing over 3 or 10 weeks ([Parrish et al., 1996](#)).

## II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

### II.B.1. SUMMARY OF RISK ESTIMATES

#### II.B.1.1. Oral Slope Factor -- $6.7 \times 10^{-2} \text{ (mg/kg-day)}^{-1}$ rounded to $7 \times 10^{-2} \text{ (mg/kg-day)}^{-1}$

The oral slope factor is derived from the LED<sub>10</sub>, the 95% lower bound on the exposure associated with an 10% extra cancer risk, by dividing the risk (as a fraction) by the LED<sub>10</sub>, and represents an upper bound, continuous lifetime exposure risk estimate:

LED<sub>10</sub>, lower 95% bound on exposure at 10% extra risk – 1.5 mg/kg-day  
ED<sub>10</sub>, central estimate of exposure at 10% extra risk – 5.7 mg/kg-day

The slope of the linear extrapolation from the central estimate ED<sub>10</sub> is  $0.1/(5.7 \text{ mg/kg-day}) = 1.8 \times 10^{-2}$  per mg/kg-day.

The slope factor for TCA should not be used with exposures exceeding the POD (1.5 mg/kg-day), because above this level the fitted dose-response model better characterizes what is known about the carcinogenicity of TCA.

#### II.B.1.2. Drinking Water Unit Risk\* -- $2 \times 10^{-6}$ per µg/L

Drinking water concentrations at specified risk levels

Risk Level	Lower Bound on Concentration Estimate*
E-4 (1 in 10,000)	50 µg/L
E-5 (1 in 100,000)	5 µg/L
E-6 (1 in 1,000,000)	0.5 µg/L

\* The unit risk and concentration estimates assume a water consumption of 2 L/day by a 70-kg human.

### II.B.1.3. Extrapolation Method

Multistage model with linear extrapolation from the POD (LED<sub>10</sub>).

### II.B.2. DOSE-RESPONSE DATA

Tumor Type — Hepatocellular adenomas or carcinomas

Test species — Male B6C3F<sub>1</sub> mice

Route — Oral (drinking water)

Reference — DeAngelo et al. (2008)

#### Incidence of hepatocellular adenomas, carcinomas, or adenomas and carcinomas combined in male B6C3F<sub>1</sub> mice exposed to TCA in drinking water for 104 weeks

TCA concentration (g/L)	Estimated intake <sup>a</sup> (mg/kg-day)	Human lifetime equivalent dose <sup>b</sup> (mg/kg-day)	Incidence of adenomas <sup>c</sup>	Incidence of carcinomas <sup>c</sup>	Incidence of adenomas or carcinomas <sup>c</sup>
0	0	0	10/56	26/56	31/56
0.05	6.7	1	10/48	15/48	21/48
0.5	81.2	12.8	20/51	32/51	36/51

<sup>a</sup>Estimated daily intakes were calculated with the mean measured TCA concentrations reported by DeAngelo et al. (2008) where available; if not, the nominal concentration for the dose group was used. See Appendix D, Table D-1 of the *Toxicological Review of Trichloroacetic Acid* (U.S. EPA, 2011) for details.

<sup>b</sup>Estimated daily intakes of TCA from the mouse study were converted to human equivalent doses for continuous lifetime exposure using an interspecies body weight scaling factor (body weight to the <sup>3</sup>/<sub>4</sub> power) and exposure time adjustment factors.

<sup>c</sup>Individual animal data were obtained through the study author (email dated February 1, 2010, from Anthony DeAngelo, National Health and Environmental Effects Research Laboratory

(NHEERL), Office of Research and Development (ORD), U.S. EPA, to Diana Wong, National Center for Environmental Assessment (NCEA), ORD, U.S. EPA). Because the first liver tumors were found at the interim sacrifice (52 weeks), adenoma or carcinoma data for all mice examined histopathologically between weeks 52 and 104 were included.

Source: DeAngelo et al. (2008).

### II.B.3. ADDITIONAL COMMENTS

In addition to the 104-week study of TCA in male B6C3F<sub>1</sub> mice that served as the basis for the TCA cancer slope factor, four other bioassays in B6C3F<sub>1</sub> mice exposed to TCA in drinking water were selected for analysis and derivation of candidate oral slope factor for TCA. These four bioassays consisted of two 52-week studies in male mice (Bull et al., 2002; Bull et al., 1990), a 60-week study in male mice (DeAngelo et al., 2008), and an 82-week study in female mice (Pereira, 1996). The candidate oral cancer slope factors derived from these four bioassays in mice ranged from  $2.1 \times 10^{-2}$  to  $1.1 \times 10^{-1}$  (mg/kg-day)<sup>-1</sup>.

Consideration was also given to whether the liver tumor incidence data from the three bioassays conducted by DeAngelo et al. (2008) could be combined to derive an oral cancer slope factor. Statistical analysis revealed that two liver tumor data sets from DeAngelo et al. (2008), i.e., the 60-week study and the multi-dose 104-week study, were statistically compatible to be combined for multistage Weibull (MSW) time-to-tumor modeling. The cancer slope factor derived from the combined data set was  $7.2 \times 10^{-2}$  (mg/kg-day)<sup>-1</sup>, and was similar to the cancer slope factor of  $6.7 \times 10^{-2}$  (mg/kg-day)<sup>-1</sup> rounded to  $7 \times 10^{-2}$  (mg/kg-day)<sup>-1</sup> derived from male mouse liver tumor data from the 104-week DeAngelo et al. (2008) study using the multistage model in BMDS.

### II.B.4. DISCUSSION OF CONFIDENCE

Confidence in the oral slope factor and extrapolation of cancer risks to low doses would be increased with the identification of precursor events for TCA-induced liver tumors and additional information concerning tumor responses in mice to drinking water concentrations <0.05 g/L TCA (the lowest tested concentration in the mouse bioassays).

## **II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE**

No inhalation unit risk (IUR) for TCA was derived. Cancer bioassays involving inhalation exposure to TCA are not currently available, and PBPK models that could be used to support route-to-route extrapolation for TCA have not been published. In the absence of a PBPK model, route-to-route extrapolation (from oral to inhalation) is not recommended because the liver is the critical target organ for oral toxicity, and first-pass effect by the liver is expected following oral administration. Furthermore, the respiratory tract has not been evaluated in oral exposure studies. Therefore, an IUR for TCA was not derived.

### **II.C.1. SUMMARY OF RISK ESTIMATES**

Not applicable.

### **II.C.2. DOSE-RESPONSE DATA**

Not applicable.

### **II.C.3. ADDITIONAL COMMENTS**

Not applicable.

### **II.C.4. DISCUSSION OF CONFIDENCE**

Not applicable.

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## **II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)**

### **II.D.1. EPA DOCUMENTATION**

Source document -- *Toxicological Review of Trichloroacetic Acid* ([U.S. EPA, 2011](#)).

This document has been provided for review to EPA scientists, interagency reviewers from other federal agencies and White House offices, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of Trichloroacetic Acid* ([U.S. EPA, 2011](#)). [To review](#)

[\*this appendix, exit to the toxicological review, Appendix A, Summary Of External Peer Review And Public Comments And Disposition \(PDF\)\*](#)

## **II.D.2. EPA REVIEW**

Agency Completion Date -- 09/30/2011

## **II.D.3. EPA Contacts (Carcinogenicity Assessment)**

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or [hotline.iris@epa.gov](mailto:hotline.iris@epa.gov) (email address).

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**III. [reserved]**

**IV. [reserved]**

**V. [reserved]**

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## **VI. Bibliography**

Substance Name — Trichloroacetic acid (TCA)  
CASRN — 76-03-9

### **VI.A. Oral RfD References**

[DeAngelo, AB; Daniel, FB; Wong, DM; George, MH.](#) (2008) The induction of hepatocellular neoplasia by trichloroacetic acid administered in the drinking water of the male B6C3F<sub>1</sub> mouse. J Toxicol Environ Health A 71: 1056-1068.  
<http://dx.doi.org/10.1080/15287390802111952>.

[U.S. EPA](#) (U.S. Environmental Protection Agency). (2000). Benchmark dose technical guidance document [external review draft]. (EPA/630/R-00/001). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum.  
<http://www.epa.gov/raf/publications/benchmark-dose-doc-draft.htm>

[U.S. EPA](#) (U.S. Environmental Protection Agency). (2011). Toxicological review of Trichloroacetic acid. (EPA/635/R-09/003F). Washington, DC.  
<http://www.epa.gov/iris/toxreviews/0655tr.pdf> (270 pp, 1.89M).

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## VI.B. INHALATION RfC REFERENCES

[U.S. EPA](#). (U.S. Environmental Protection Agency). (1994). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. (EPA/600/8-90/066F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Research and Development, Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office. <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993>.

[U.S. EPA](#). (U.S. Environmental Protection Agency). (2011). Toxicological review of Trichloroacetic acid. (EPA/635/R-09/003F). Washington, DC.  
<http://www.epa.gov/iris/toxreviews/0655tr.pdf> (270 pp, 1.89M).

---

## VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

[Austin, EW; Parrish, JM; Kinder, DH; Bull, RJ](#). (1996). Lipid peroxidation and formation of 8-hydroxydeoxyguanosine from acute doses of halogenated acetic acids. *Fundam Appl Toxicol* 31: 77-82. <http://dx.doi.org/10.1006/faat.1996.0078>.

[Bhunya, SP; Behera, BC](#). (1987). Relative genotoxicity of trichloroacetic acid (TCA) as revealed by different cytogenetic assays: Bone marrow chromosome aberration, micronucleus and sperm-head abnormality in the mouse. *Mutat Res Genet Toxicol Environ Mutagen* 188: 215-221. [http://dx.doi.org/10.1016/0165-1218\(87\)90092-9](http://dx.doi.org/10.1016/0165-1218(87)90092-9).

[Boorman, GA](#). (1999). Drinking water disinfection byproducts: Review and approach to toxicity evaluation. *Environ Health Perspect* 107: 207-217.

[Bull, RJ; Sanchez, IM; Nelson, MA; Larson, JL; Lansing, AJ](#). (1990). Liver tumor induction in B6C3F<sub>1</sub> mice by dichloroacetate and trichloroacetate. *Toxicology* 63: 341-359.  
[http://dx.doi.org/10.1016/0300-483X\(90\)90195-M](http://dx.doi.org/10.1016/0300-483X(90)90195-M).

[Bull, RJ; Orner, GA; Cheng, RS; Stillwell, L; Stauber, AJ; Sasser, LB; Lingohr, MK; Thrall, BD](#). (2002). Contribution of dichloroacetate and trichloroacetate to liver tumor induction in

mice by trichloroethylene. *Toxicol Appl Pharmacol* 182: 55-65.  
<http://dx.doi.org/10.1006/taap.2002.9427>.

[Bull, RJ; Sasser, LB; Lei, XC.](#) (2004). Interactions in the tumor-promoting activity of carbon tetrachloride, trichloroacetate, and dichloroacetate in the liver of male B6C3F<sub>1</sub> mice. *Toxicology* 199: 169-183. <http://dx.doi.org/10.1016/j.tox.2004.02.018>.

[Chang, LW; Daniel, FB; DeAngelo, AB.](#) (1992). Analysis of DNA strand breaks induced in rodent liver in vivo, hepatocytes in primary culture, and a human cell line by chlorinated acetic acids and chlorinated acetaldehydes. *Environ Mol Mutagen* 20: 277-288.  
<http://dx.doi.org/10.1002/em.2850200406>.

[DeAngelo, AB; Daniel, FB; Most, BM; Olson, GR.](#) (1997). Failure of monochloroacetic acid and trichloroacetic acid administered in the drinking water to produce liver cancer in male F344/N rats. *J Toxicol Environ Health* 52: 425-445.  
<http://dx.doi.org/10.1080/00984109708984074>.

[DeAngelo, AB; Daniel, FB; Wong, DM; George, MH.](#) (2008). The induction of hepatocellular neoplasia by trichloroacetic acid administered in the drinking water of the male B6C3F<sub>1</sub> mouse. *J Toxicol Environ Health A* 71: 1056-1068.  
<http://dx.doi.org/10.1080/15287390802111952>.

[DeMarini, DM; Perry, E; Shelton, ML.](#) (1994). Dichloroacetic acid and related compounds: Induction of prophage in *E. coli* and mutagenicity and mutation spectra in *Salmonella* TA100. *Mutagenesis* 9: 429-437. <http://dx.doi.org/10.1093/mutage/9.5.429>.

[Giller, S; Le Curieux, F; Erb, F; Marzin, D.](#) (1997). Comparative genotoxicity of halogenated acetic acids found in drinking water. *Mutagenesis* 12: 321-328.

[Harrington-Brock, K; Doerr, CL; Moore, MM.](#) (1998). Mutagenicity of three disinfection by-products: Di- and trichloroacetic acid and chloral hydrate in L5178Y(+/-) --3.7.2C mouse lymphoma cells. *Mutat Res Genet Toxicol Environ Mutagen* 413: 265-276.

[Herren-Freund, SL; Pereira, MA; Khoury, MD; Olson, G.](#) (1987). The carcinogenicity of trichloroethylene and its metabolites, trichloroacetic acid and dichloroacetic acid, in mouse liver. *Toxicol Appl Pharmacol* 90: 183-189. [http://dx.doi.org/10.1016/0041-008X\(87\)90325-5](http://dx.doi.org/10.1016/0041-008X(87)90325-5).

[Ito, Y; Yamanoshita, O; Asaeda, N; Tagawa, Y; Lee, CH; Aoyama, T; Ichihara, G; Furuhashi, K; Kamijima, M; Gonzalez, FJ; Nakajima, T.](#) (2007). Di(2-ethylhexyl)phthalate induces

hepatic tumorigenesis through a peroxisome proliferator-activated receptor alpha-independent pathway. *J Occup Health* 49: 172-182.

[King-Herbert, A; Thayer, K.](#) (2006). NTP workshop: Animal models for the NTP rodent cancer bioassay: Stocks and strains - Should we switch? *Toxicol Pathol* 34: 802-805.  
<http://dx.doi.org/10.1080/01926230600935938>.

[Mackay, JM; Fox, V; Griffiths, K; Fox, DA; Howard, CA; Coutts, C; Wyatt, I; Styles, JA.](#) (1995). Trichloroacetic acid: Investigation into the mechanism of chromosomal damage in the in vitro human lymphocyte cytogenetic assay and the mouse bone marrow micronucleus test. *Carcinogenesis* 16: 1127-1133. <http://dx.doi.org/10.1093/carcin/16.5.1127>.

[Mills, CJ; Bull, RJ; Cantor, KP; Reif, J; Hrudey, SE; Huston, P.](#) (1998). Workshop report. Health risks of drinking water chlorination by-products: Report of an expert working group. *Chronic Dis Can* 19: 91-102.

[Nelson, MA; Bull, RJ.](#) (1988). Induction of strand breaks in DNA by trichloroethylene and metabolites in rat and mouse liver in vivo. *Toxicol Appl Pharmacol* 94: 45-54.  
[http://dx.doi.org/10.1016/0041-008X\(88\)90335-3](http://dx.doi.org/10.1016/0041-008X(88)90335-3).

[Ono, Y; Somiya, I; Kawamura, M.](#) (1991). The evaluation of genotoxicity using DNA repairing test for chemicals produced in chlorination and ozonation processes. *Water Sci Technol* 23: 329-338.

[Parnell, M; Exon, J; Koller, L.](#) (1988). Assessment of hepatic initiation-promotion properties of trichloroacetic acid. *Arch Environ Contam Toxicol* 17: 429-436.  
<http://dx.doi.org/10.1007/BF01055507>.

[Parrish, JM; Austin, EW; Stevens, DK; Kinder, DH; Bull, RJ.](#) (1996). Haloacetate-induced oxidative damage to DNA in the liver of male B6C3F<sub>1</sub> mice. *Toxicology* 110: 103-111.  
[http://dx.doi.org/10.1016/0300-483X\(96\)03342-2](http://dx.doi.org/10.1016/0300-483X(96)03342-2).

[Pereira, MA.](#) (1996). Carcinogenic activity of dichloroacetic acid and trichloroacetic acid in the liver of female B6C3F<sub>1</sub> mice. *Fundam Appl Toxicol* 31: 192-199.  
<http://dx.doi.org/10.1006/faat.1996.0091>.

[Pereira, MA; Phelps, JB.](#) (1996). Promotion by dichloroacetic acid and trichloroacetic acid of N-methyl-N-nitrosourea-initiated cancer in the liver of female B6C3F<sub>1</sub> mice. *Cancer Lett* 102: 133-141. [http://dx.doi.org/10.1016/0304-3835\(96\)04156-0](http://dx.doi.org/10.1016/0304-3835(96)04156-0).

[Pereira, MA; Li, K; Kramer, PM.](#) (1997). Promotion by mixtures of dichloroacetic acid and trichloroacetic acid of N-methyl-N-nitrosourea-initiated cancer in the liver of female B6C3F<sub>1</sub> mice. *Cancer Lett* 115: 15-23. [http://dx.doi.org/10.1016/S0304-3835\(97\)04699-5](http://dx.doi.org/10.1016/S0304-3835(97)04699-5).

[Pereira, MA; Kramer, PM; Conran, PB; Tao, L.](#) (2001). Effect of chloroform on dichloroacetic acid and trichloroacetic acid-induced hypomethylation and expression of the c-myc gene and on their promotion of liver and kidney tumors in mice. *Carcinogenesis* 22: 1511-1519. <http://dx.doi.org/10.1093/carcin/22.9.1511>.

[Rapson, WH; Nazar, MA; Butsky, VV.](#) (1980). Mutagenicity produced by aqueous chlorination of organic compounds. *Bull Environ Contam Toxicol* 24: 590-596. <http://dx.doi.org/10.1007/BF01608160>.

[Styles, JA; Wyatt, I; Coutts, C.](#) (1991). Trichloroacetic acid: Studies on uptake and effects on hepatic DNA and liver growth in mouse. *Carcinogenesis* 12: 1715-1719. <http://dx.doi.org/10.1093/carcin/12.9.1715>.

[U.S. EPA](#) (U.S. Environmental Protection Agency). (2005a). Guidelines for carcinogen risk assessment. (EPA/630/P-03/001F). Washington, DC. <http://www.epa.gov/cancerguidelines/>.

[U.S. EPA](#) (U.S. Environmental Protection Agency). (2005b). Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens. (EPA/630/R-03/003F). Washington, DC: U.S. Environmental Protection Agency, Risk Assessment Forum. <http://www.epa.gov/cancerguidelines/guidelines-carcinogen-supplement.htm>.

[U.S. EPA](#) (U.S. Environmental Protection Agency). (2011). Toxicological review of Trichloroacetic acid. (EPA/635/R-09/003F). Washington, DC. <http://www.epa.gov/iris/toxreviews/0655tr.pdf> (270 pp, 1.89M).

[Walgren, JL; Kurtz, DT; McMillan, JM.](#) (2005). Lack of direct mitogenic activity of dichloroacetate and trichloroacetate in cultured rat hepatocytes. *Toxicology* 211: 220-230. <http://dx.doi.org/10.1016/j.tox.2005.03.009>.

[Yang, Q; Ito, S; Gonzalez, FJ.](#) (2007). Hepatocyte-restricted constitutive activation of PPAR alpha induces hepatoproliferation but not hepatocarcinogenesis. *Carcinogenesis* 28: 1171-1177. <http://dx.doi.org/10.1093/carcin/bgm046>.

## VII. Revision History

Substance Name — Trichloroacetic acid (TCA)

CASRN — 76-03-9

File First On-Line 10/01/1992

Date	Section	Description
10/01/1992	I.A.	RfD added.
02/01/1996	II.	Carcinogenicity assessment added.
09/30/2011	I., II., VI.	RfD and cancer assessment sections updated; RfC discussion added.

## VIII. Synonyms

Substance Name — Trichloroacetic acid (TCA)

CASRN — 76-03-9

Section VIII. Last Revised — 09/30/2011

- 76-03-9
- Acetic acid, trichloro-
- TCA
- Aceto-Caustin
- Acide trichloracetique [French]
- Acido tricloroacetico [Italian]
- Acido tricloroacetico [Spanish]
- AI3-24157
- Amchem Grass Killer
- Caswell No. 870
- EPA Pesticide Chemical Code 081002
- HSDB 1779
- Kyselina trichloroctova [Czech]
- Trichloorazijnzuur [Dutch]
- Trichloressigsäure [German]
- Trichloroethanoic acid