# DRAFT Dichloroacetic Acid HEAC Health-Based Assessment and Recommendation

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## I. IDENTIFICATION

Chemical Name: Dichloroacetic Acid

Synonyms/Tradenames: acetic acid, dichloro; 2,2-dichloroacetic acid; dichloroethanoic acid; bichloroacetic acid, dichlorethanoic acid, DCA, Dichloracetic acid

CAS Number: 79-43-6

Molecular Formula: C2H2Cl2O2 / CHCl2COOH

Structural Formula:


## II. CHEMICAL AND PHYSICAL PROPERTIES

Physical State and Appearance: liquid at room temperature

Odor Description: Pungent

Odor Threshold: 0.04 ppm (CHEMINFO)

Molecular Weight: 128.94

Conversion Factors at 25 oC and 760 mm/Hg:

 1 ppm = 5.27 mg/m3

 1 mg/m3 = 0.19 ppm

Vapor Pressure: 1 mm Hg at 44°C (111.2oF)

Melting Point: 9.7 °C (45 oF)

Freezing Point: -4 °C

Boiling Point: 193-194 °C

Flammability Limits: Not a fire hazard

Flash Point: NA

Solubility: Soluble in water and miscible with alcohol and ether

Special physical characteristics if any: highly corrosive, attacks metals, releases HCl gas

## Ill. USES/APPLICATIONS/OCCURRENCE/EXPOSURES:

Dichloroacetic acid is produced in small quantities for use as an intermediate in the production of glyoxylic acid, dialkyloxy, and diaryloxy acids and sulfonamides ((IARC) 1995). Human exposures may occur during commercial production and use of DCA and from drinking chlorinated water. Therapeutic agent for lactic acidosis, hyperglycemia, hypercholesteremia and an investigational drug for treatment of stroke. DCA has also been shown to have a protective effect against myocardial ischemic damage (Wahr et al, 1994). In the 1970's, this compound was investigated as a vasodilator and hypotensive agent (Grant & Schuman, 1993).

## IV. CURRENT EXPOSURE GUIDELINES

| **Organization/Country**  | **TWA** **(ppm)**  | **Notations/Other Info**  |
| --- | --- | --- |
| ACGIH TLV® | 0.5 ppm TWA | Eye and upper respiratory tract irritation and testicular damageSkinA3 Confirmed animal carcinogen with unknown relevance to humans (ACGIH 2005) |
| OSHA PEL | -- | None Established for Dichloroacetic acid  Trichloroacetic Acid PEL – 1 ppm TWA8 |
| NIOSH REL | -- |  |
| AIHA  | --  |  |
| Belgium | 0.5 ppm TWA; 2.7 mg/m3 TWA |  |
| Bulgaria | 4.0 mg/m3 TWA STEL |  |
| Canada:* British Columbia
* Manitoba
* Nova Scotia
* Ontario
 | 0.5 ppm TWA | Skin |
| Columbia | 0.5 ppm TWA |  |
| Israel | 0.5 ppm TWA |  |
| Latvia | 4 mg/m3 TWA STEL |  |
| Lithuania | 4 mg/m3 TWA STEL |  |
| Portugal | 0.5 ppm TWA | Skin |
| Russia | 4 mg/m3 MAC STEL (aerosol and vapor) |  |
| USA California Prop 65 | Present | Since 5/1/96 |

## V. PRODUCTION/IMPORT INFORMATION:

EPA Inventory Update Reporting (IUR), IUR reporting years:

| **1986 Range** | **1990 Range** | **1994 Range** | **1998 Range** | **2002 Range** |
| --- | --- | --- | --- | --- |
| 10-500 K | No report | 10-500 K | 10-500 K | 10-500 K |

## VI. ORGANIZATIONAL SOURCES AND RECOMMENDATIONS:

1. **TLV (ACGIH 2005):** Basis is Testicular germinal cell epithelial degeneration, upper respiratory tract irritation, developmental toxicity and cancer
2. LOAEL 12.5 mg/kg/day (sodium salt) in dogs 90 day study showed degeneration of testicular germinal cell epithelium and syncytial giant cell formation.
	* + - * Adjusting for 70 kg body weight and 10 M3/day inhalation, gives 87.5 mg/M3 LOAEL, TLV of 2.6 mg/M3 (Cicmanec JL 1991) (*Note: The TLV documentation is not clear on the basis for the uncertainty factors applied, however one can extrapolate that a factor of about 34 was used to derive the TLV value.)*
				* TLV documentation indicated (Bhat HK 1991) and (Katz R 1981) also found testicular effects respectively at 50 mg/kg/day (lowest dose administered) in rats for 6 months, and at 50 mg/kg/day (lowest dose administered), with these effects also seen at the higher dose levels.
3. TLV Skin notation based on lethality in rabbit skin painting study of 510 mg/kg (Smyth HF 1951)
4. A3 Carcinogen: TLV recommendation said 40 mg/kg/day was the lowest tumorigenic dose but which study is unclear. States also that DCA is only carcinogenic at relatively high hepatotoxic doses in mice and rats.
	* + - * TLV document also noted liver cancer associated with hepatotoxic doses in a number of animal studies.
5. **(EPA 2003): Reference dose calculation** (Non-cancer) 0.004 mg/kg/day
	* 1. Based on the LOAEL of 12.5 mg/kg/day found by (Cicmanec JL 1991).
		2. Critical effects: lesions in testes, cerebrum, cerebellum and liver
		3. Used uncertainty factor of 3000 based on:
* 10 for inter-human variability in susceptibility
* 3 for animal to human extrapolation
* 10 for LOAEL for nervous system effects seen in patients exposed to 25 to 50 mg/kg/day during treatment with DCA for lactic acidosis and other disorders
* 3 for subchronic to chronic
* 3 for deficiencies in the database (lack of multi-generation study for reproductive and developmental effects)
* 1 for Modifying Factor
1. **CHEMINFO**: Corrosive to eyes, skin and respiratory tract; Inhalation of high concentrations can cause pulmonary edema
2. **Cancer:**
	* 1. **((IARC) 1995)**: 2B, possibly carcinogenic to humans. Inadequate evidence in humans for carcinogenicity. Sufficient evidence in experimental animals for carcinogenicity. Based on eight studies, neutralized dichloroacetic acid administered in the drinking-water to male and/or female mice increased the incidences of hepatocellular adenomas and/or carcinomas. Dichloroacetic acid is genotoxic *in vivo* and *in vitro*. It also causes DNA hypomethylation *in vivo*. Thus, a genotoxic effect, possibly involving an indirect, epigenetic mechanism, may contribute to the carcinogenic mode of action of dichloroacetic acid. Insufficient data were found to extrapolate human risk to DCA.
		2. **US EPA IRIS (EPA 2004) - Cancer** potency 700 ug/L in water for 1/1000 risk level.
			+ - Classification: EPA believes that DCA is likely to be a carcinogen in humans; oral slope factor = 0.05 per mg/kg/day where tumor types were hepatoadenoma and hepatocarcinoma; test animals = male B6C3F1 mice; route = drinking water; last reviewed 9/11/2003
				- Assumes linear extrapolation (ie. 70 ug/L for 1/10,000 risk level) and is based on (DeAngelo 1999) exposed male B6C3F1 mice to 0, 0.05, 0.5, 1, 2, or 3.5 g/L of DCA in drinking water for 90-100 weeks. This corresponded to mean daily doses of 0, 8, 84, 168, 315, or 429 mg/kg-day, respectively.
		3. **(NTP 2007)** Drinking water studies in mice, with low doses in range of 40 to 50 mg/kg, 41 weeks.
			+ - Concluded: DCA did not cause cancer in the genetically modified p53 haploinsufficient mice and gave only weakly positive responses when given to Tg.AC mice (all at high doses). Stated that mice may not have been as sensitive since results are at odds with other studies. Found squamous cell papillomas with skin painting on Tg.AC mice.
		4. **Proposition 65 :** On list for cancer as of May 1, 1996
		5. **Determination of the cancer risk**:(HEAC 2007)
			+ - OEHHA Method: One method for how to use the slope factor to estimate the cancer risk associated with the ACGIH TLV for DCA of 0.5 ppm.

The U.S. EPA oral slope factor is 0.05 (mg/kg-day)-1. To derive a unit risk factor from an oral slope factor, a default approach that is often applied is:

Oral slope factor = 0.05 per mg/kg/day

Inhaled volume per day = 20 m3

Weight of male = 70 kg

Time = 24 hours

**0.05 (mg/kg-day)-1 x 20 m3/day x 1/70 kg = 0.014 (mg/m3)-1**

To estimate the cancer risk associated with the TLV of 0.5 ppm (which was reported by ACGIH to be equal to 2.6 mg/m3), the following approach which accounts for a worker exposure scenario can be taken where:

Unit risk exposure = 0.014 mg/m3-1

TLV – 0.5 ppm = 2.6 mg/m3

Oral slope factor = 0.05 per mg/kg/day

Inhaled volume per day = 20 m3

Weight of male = 70 kg

Time = 8 hours

Days = 5 days

Weeks = 50 weeks

Working Lifetime = 40 years

**2.6 mg/m3 x 0.014 (mg/m3)-1x 8 hr/24 hr x 5 d/7 d x 50 wk/52 wk x 40 yr/70 yr**

The above approach produces a cancer risk of 0.00485, or approximately 5 excess cancer cases in 1,000 exposed workers when exposed to 0.5 ppm 8-hour TWA.

If the worker is assumed to have a heavier breathing rate, the calculation would be as follows:

2.6 mg/m3 x 0.014 (mg/m3)-1x 10 m3/20 m3 x 5 d/7 d x 50 wk/52 wk x 40 yr/70 yr

With the heavier breathing rate, the cancer risk increases to 0.00729, or approximately 7 excess cancer cases in 1,000 exposed workers.

So, if a TLV of 0.5 ppm yields a cancer risk of 5 in 1,000 or 7 in 1,000 then a PEL associated with a cancer risk of 1 in 1,000 would be either 0.1 ppm or 0.07 ppm, depending on whether the heavier breathing rate for workers is used.

Stated otherwise: 0.001 = 0.05 x LADD

LADD = 0.02 mg/kg/day  x 79 kg and divided by 10 m3/day = 0.14 mg/m3  adjustments of 70/40 and 52/50 and 7/5 and units conversion  0.07 ppm or ~0.1 ppm, similar to that for non-cancer.

Pharmacokinetic/Metabolism Issues: Considering potential pharmacokinetic differences: a simple pharmacokinetic difference that could be considered is the absorption rate by each route. If the absorption rate by the oral route was 100% for DCA, but the absorption rate for the inhalation route was only 50%, the risks reported above would be lowered by 50%. In rats, 24% to 30% of the total dose was excreted as CO2; whereas in mice only about 2% of the dose was excreted as CO2. Elimination half times for DCA were about 1.5 and 0.9 hours in mice and rats, respectively.(Larson 1992) There is no clear evidence of a difference in oral uptake, metabolism, and excretion compared to the absorption and metabolism of DCA by inhalation route of exposure, therefore no conclusions can be drawn.

Regarding half-life

Pharmacokinetics of DCA in humans was reviewed by (Stacpoole 1989) and more recently by (Fox 1996). DCA is as rapidly absorbed and eliminated in humans as it is in rodents. DCA is detected in plasma within 15 minutes after single oral dose of 50 mg/kg and has a half-life in human plasma of between 0.5 and 2 hours. Peak plasma levels following a single oral or intravenous dose of 50 mg/kg have been reported to range from about 150 to 250 g/L, and areas under the concentration-time curve were equivalent following either oral or intravenous administration indicating equal bioavailability. (Curry 1991) Detailed investigation of the pharmacokinetics of DCA performed during clinical trials of DCA for use in correcting lactic acidosis and diabetes confirms elimination half-lives of about 2 hours in healthy volunteers following an initial intravenous dose of 50 mg/kg, and has also demonstrated a significant increase in plasma elimination half-times following additional dose(s) of DCA, supporting the notion that DCA inhibits its own metabolism. (Curry 1985; Henderson 1997)

**Additional Peer-Reviewed Journal Articles and Other Studies with endpoints for Consideration:**

| **Citation (author/ journal/date)**  | **Study type**  | **Results/Conclusions**  | **Discussion and Assessment**  |
| --- | --- | --- | --- |
| (Cicmanec JL 1991) | 90-day oral chronic dosing dogs |  | 1. CEREBELLAR SYNDROMEa. Cicmanec reported significant pathological changes in the cerebrum and cerebellum in DCA treated dogs in a 90 day DCA toxicity study. Doses ranged from 12.5 mg/kg/day to 72 mg/kg/day.Vacuolization of white myelinated tracts was observed in all dogs, with changes present in both the cerebrum and cerebellum in some dogs. Clinical findings included bilateral posterior paresis in some of the dogs during the study.b. DCA administered chronically to dogs (up to 100 mg/kg/day for 3 months) produced dose-dependent effects of hind limb weakness and/or paralysis (Katz et al, 1981).HEPATITISa. In a 90-day toxicity study of DCA in dogs, hepatic vacuolar changes and chronic hepatitis were present in 4 high-dose animals (72 mg/kg/day) and one mid-dose (39.5 mg/kg/day) animal as seen on microscopy at necropsy. Hepatic lesions were considered primary lesions. Significant elevations in serum liver enzymes (ALT, AST, LDH) were apparent by trend analyses |
| (Cicmanec JL 1991) | 90-day oral chronic dosing dogs |  | ANEMIAReduced total erythrocyte counts and hemoglobin levels were noted by day 30 of the study in both high-dose (72 mg/kg/day) males and females. Hemoglobin levels dropped in mid-dose (39.5 mg/kg/day) dogs at days 45, 60, 75 and 90, and were found to be significant by trend analyses. |
| (Stacpoole 1979) | 90-day oral chronic dosing rats |  | TESTIS DISORDERStacpoole et al (1979) reported germinal epithelial degeneration of the testes in rats given 125 to 2000 mg/kg/day of DCA for 90 days. |
| (Moser 1999) | 2-yr Neurotox in Long-Evans and Fisher-344 rats:Oral gavage or Drinking Water | NEUROBEHAVIORAL TOXICITY was progressive and more persistent with gavage and drinking water routes of continuous exposures as low as 16 mg/kg/day [lowest dose tested] (in drinking water) (LOAEL) compared to bolus dosages given by oral gavage. In all studies, the data show a reliable dose–response relationship, with thelowest dose (intake approximately 16 mg/kg/day) producing significant gait changes. Note that this lowest dose produced no other neuromuscular changes, indicating that gait abnormalities constitute the “critical effect” for DCA. | NEUROBEHAVIORAL TOXICITY was manifested by limb weakness, effects on gait and righting reflex, mild tremors, ocular abnormalities, and a unique chest-grasping response.  |
| (Toth GP 1992) | Male rats |  | TESTIS DISORDERMale rats with subchronic exposures to sodium DCA demonstrated adverse effects of the reproductive system. The lower doses (31.25 and 62.5 mg/kg) affected the accessory organs and sperm. Higher doses (125 mg/kg) affected the testis (retention of step 19 spermatids into stage 10 seminiferous tubules). |
| (Smith MK 1992)((IARC) 1995) | Female rats - Repro |  | DEVELOPMENTAL1. Altered development of the heart and major vessels, and less frequently, the kidneys and the orbits of the eyes was reported in fetuses of female rats following DCA doses of 140 to 2400 mg/kg/day on days 6 to 15 of gestation (Smith et al, 1992; IARC, 1995). Within the cardiovascular system, defects between the ascending aorta and the right ventricle were predominant. Skeletal malformations were not reported.2. The no observed adverse effect level (NOAEL) for developmental DCA toxicity in the rat is 14 mg/kg/day (Smith et al, 1992).  |
| (Stacpoole 1989) | Healthy male & female subjects – oral therapeutic doses |  | Healthy male and female subjects have received oral doses of 25 milligrams/ kilogram, and 250, 25, and 2.5 micrograms/kilogram/day sequentially in pharmacokinetic studiesA young adult received oral daily doses of 50 milligrams /kilogram for 4 months for treatment of familial hypercholesterolemiaDCA has been shown to readily cross the blood-brain barrier in humans. DCA concentrations can be measured in the cerebrospinal fluid of patients receiving DCA |

| **Citation (author/ journal/date)**  | **Study type**  | **Results/Conclusions**  | **Discussion and Assessment**  |
| --- | --- | --- | --- |
| (Stacpoole 1978) | Adult male diabetics |  | Adults with diabetes mellitus and/or hyperlipoproteinemia have been treated with 3 to 4 grams per day of sodium dichloroacetate for 6 to 7 days |
| (Shangraw 1996) | Humans |  | DCA is metabolized exclusively in the liver in humans (Shangraw & Fisher, 1996). |

Cicmanec (1991) is preferred over the Moser (1999) study or over the other non-cancer studies because the study has the lowest LOAEL available (12 mg/kg/day) and is in the juvenile dog, a more appropriate species for comparison. Moser, although comparing routes of exposure, concentrations, age time/day of exposure, was only in rats. It is an excellent study, but Cicmanec is the lowest NOAEL or LOAEL we have for a non-cancer endpoint. However, Cicmanec’s histology and pathology confirmed the neurotoxicity on the very same endpoints of concern in the rats.

### HEAC Health-based assessment and recommendation

The proposed HEAC 5155 PEL for Dichloroacetic Acid is 0.1 ppm TWA to protect against all endpoints studied and is based on the lowest LOAEL for reproductive effects and neurotoxicity, calculating the unit risk factor of 0.014 mg/m3, calculating the worker exposure risks at the 1 in 1000 risk of cancer level. (Cicmanec JL 1991; EPA 2004; HEAC 2007) So, if a TLV of 0.5 ppm yields a cancer risk of 5 in 1,000 or 7 in 1,000 then a PEL associated with a cancer risk of 1 in 1,000 would be either 0.1 ppm or 0.07 ppm, depending on whether the heavier breathing rate for workers is used.

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There is additional support that the non-cancer endpoints are supportive of 0.1 ppm as well. Non-cancer endpoint calculations may be done using the LOAEL from (Moser 1999; HEAC 2007) Neurotoxicity study where applying a safety factor of 10 for inter-human variability, a factor of 7 for animal (rat) to human extrapolation, and a factor of 3 for LOAEL-to-NOAEL extrapolation [cumulative factor of 210], thus supporting the OEL for non-cancer endpoint of approximately 0.1 ppm:

(16 mg/kg/day x 70 kg) / (210 x 10 m3/day) = 0.53 mg/m3  0.107 ppm

A Skin notation is appropriate based on the ability of DCA to be absorbed readily through the skin and contribute to overall exposure. (Smyth HF 1951)

The lowest LOAEL in animal studies is in the 90-day dog study where neurotoxicity and testicular degeneration occurred at 12.5 mg/kg/day.

The neurotoxic and testicular effects were observed at relatively low dosages in dogs (lowest-observed adverse- effect level [LOAEL] = 12.5 mg/kg/day) —equivalent to an inhalation dose of 87.5 mg/m3.

**Non-cancer Endpoints**: DCA is not acutely toxic orally. It is systemically toxic through dermal exposure, and is severely irritating and corrosive to the eyes and skin and is expected to be irritating to the respiratory tract. In repeat-dose studies in animals, histopathological changes in the lenses, gall bladder, liver, kidneys, brain, and testes were reported.

**Developmental:** Cardiac malformations were observed in rats at higher dosages (140 mg/kg/day). Genotoxicity studies indicated that DCA is weakly mutagenic. The compound produced liver tumors in mice and rats at dosages and modes of action that may not be relevant at workplace exposures. Human data are limited; however neurotoxicity has been reported in humans (receiving the sodium salt of DCA for 16 weeks at a dosage of 50 mg/kg/day for treatment of diabetes).

### Measurement information

OSHA has sampling and analytical method for trichloroacetic acid (TCA) PV2017

Summary: Samples are collected by drawing a known volume of air through a silica gel tube. Samples are desorbed with 1 mL deionized water and analyzed by high pressure liquid chromatography with an ultraviolet detector (HPLC-UV).

LOD TCA: 1 ug/sample = 0.1 mg/M3 for recommended 10 L (0.01 M3) sample

OSHA Salt Lake City Laboratory personnel suggest that with dichloroacetic acid being more volatile than trichloroacetic acid, sampling volume may need to be reduced (eg. to 5 M3 which would double LOD to 0.2 mg/M3)

No NIOSH analytical method located

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