

## SCREENING-LEVEL HAZARD CHARACTERIZATION

### **Sponsored Chemical Chloroacetyl chloride (CASRN 79-04-9)**

### **Supporting Chemical Chloroacetic acid (CASRN 79-11-8)**

The High Production Volume (HPV) Challenge Program<sup>1</sup> was conceived as a voluntary initiative aimed at developing and making publicly available screening-level health and environmental effects information on chemicals manufactured in or imported into the United States in quantities greater than one million pounds per year. In the Challenge Program, producers and importers of HPV chemicals voluntarily sponsored chemicals; sponsorship entailed the identification and initial assessment of the adequacy of existing toxicity data/information, conducting new testing if adequate data did not exist, and making both new and existing data and information available to the public. Each complete data submission contains data on 18 internationally agreed to “SIDS” (Screening Information Data Set<sup>1,2</sup>) endpoints that are screening-level indicators of potential hazards (toxicity) for humans or the environment.

The Environmental Protection Agency’s Office of Pollution Prevention and Toxics (OPPT) is evaluating the data submitted in the HPV Challenge Program on approximately 1400 sponsored chemicals by developing hazard characterizations (HCs). These HCs consist of an evaluation of the quality and completeness of the data set provided in the Challenge Program submissions. They are not intended to be definitive statements regarding the possibility of unreasonable risk of injury to health or the environment.

The evaluation is performed according to established EPA guidance<sup>2,3</sup> and is based primarily on hazard data provided by sponsors; however, in preparing the hazard characterization, EPA considered its own comments and public comments on the original submission as well as the sponsor’s responses to comments and revisions made to the submission. In order to determine whether any new hazard information was developed since the time of the HPV submission, a search of the following databases was made from one year prior to the date of the HPV Challenge submission to the present: (ChemID to locate available data sources including Medline/PubMed, Toxline, HSDB, IRIS, NTP, ATSDR, IARC, EXTTOXNET, EPA SRS, etc.), STN/CAS online databases (Registry file for locators, ChemAbs for toxicology data, RTECS, Merck, etc.) and Science Direct. OPPT’s focus on these specific sources is based on their being of high quality, highly relevant to hazard characterization, and publicly available.

OPPT does not develop HCs for those HPV chemicals which have already been assessed internationally through the HPV program of the Organization for Economic Cooperation and

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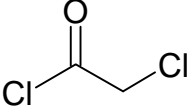
<sup>1</sup> U.S. EPA. High Production Volume (HPV) Challenge Program; <http://www.epa.gov/chemrtk/index.htm>.

<sup>2</sup> U.S. EPA. HPV Challenge Program – Information Sources; <http://www.epa.gov/chemrtk/pubs/general/guidocs.htm>.

<sup>3</sup> U.S. EPA. Risk Assessment Guidelines; <http://cfpub.epa.gov/ncea/raf/rafguid.cfm>.

Development (OECD) and for which Screening Initial Data Set (SIDS) Initial Assessment Reports (SIAR) and SIDS Initial Assessment Profiles (SIAP) are available. These documents are presented in an international forum that involves review and endorsement by governmental authorities around the world. OPPT is an active participant in these meetings and accepts these documents as reliable screening-level hazard assessments.

These hazard characterizations are technical documents intended to inform subsequent decisions and actions by OPPT. Accordingly, the documents are not written with the goal of informing the general public. However, they do provide a vehicle for public access to a concise assessment of the raw technical data on HPV chemicals and provide information previously not readily available to the public.

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|--|--|
| <p><b>Chemical Abstract Service Registry Number (CASRN)</b></p>  | <p><b>79-04-9</b></p>  |
| <p><b>Chemical Abstract Index Name</b></p>   | <p><b>Acetyl chloride, 2-chloro-</b></p>   |
| <p><b>Structural Formula</b></p>   |  |
| <p style="text-align: center;"><b>Summary</b></p> <p>This chemical is a liquid at room temperature with high vapor pressure and its water solubility cannot be measured due to its rapid hydrolysis in water. However, the major hydrolysis products, chloroacetic acid (CASRN 79-11-8) and hydrogen chloride, exhibit high solubility in water. This chemical and its aqueous hydrolysis products are expected to be highly mobile in soil. Its rate of hydrolysis is considered rapid under environmental conditions (pH 5–9). The rate of biodegradation for the organic hydrolysis product (CASRN 79-11-8) was rapid based on the results of a ready biodegradation test. Volatilization is not an important fate property since hydrolysis occurs rapidly and the organic hydrolysis product exists as an anion in the environment. The hydrogen chloride hydrolysis product exists mainly as hydrochloric acid in the aqueous phase. The rate of vapor-phase photooxidation in the ambient atmosphere is negligible. CASRN 79-04-9 is expected to have low persistence potential (P1) and low bioaccumulation potential (B1).</p> <p>The acute oral, inhalation and dermal toxicity of this chemical (CASRN 79-04-9) is moderate. Acute oral and dermal toxicity of the hydrolysis product (CASRN 79-11-8) is also moderate. CASRN 79-04-9 is corrosive to rabbit eyes and skin. Systemic toxicity in inhalation repeated-dose studies with CASRN 79-04-9 in rats and mice showed mortality at low doses (LOAEL of 0.011 mg/L) and local effects (inflammation/cellular abnormalities in the nasal mucosa) at the lowest tested dose (LOAEL of 0.002 mg/L). In oral repeated-dose studies with CASRN 79-11-8, effects on the liver and heart (rats - LOAEL of 60 mg/kg-bw/day; NOAEL of 30 mg/kg-bw/day) and mortality (mice - LOAEL of 200 mg/kg-bw/day; NOAEL of 150 mg/kg-bw/day) were observed. Although there were no reproductive toxicity studies with either CASRN 79-04-9 or CASRN 79-11-8, there were no effects in reproductive organs in oral repeated-dose studies with CASRN 79-11-8 at doses up to 200 mg/kg-bw/day in rats and 150 mg/kg-bw/day in mice. A developmental toxicity study with CASRN 79-11-8 in rats showed maternal toxicity (reduction in both body weight and weight gain) and developmental toxicity (increased cardiovascular malformations in fetuses) at the same dose (LOAEL of 140 mg/kg-bw/day; NOAEL of 70 mg/kg-bw/day). CASRN 79-04-9 did not induce gene mutations in bacteria. In <i>in vitro</i> studies with mammalian cell cultures, CASRN 79-11-8 did not induce chromosomal aberrations, but did induce sister chromatid exchanges. Oral exposure to CASRN 79-11-8 for 104 weeks did not result in increase in tumor incidence in rats or mice compared to controls.</p> <p>Because CASRN 79-04-9 undergoes rapid hydrolysis to CASRN 79-11-8 in water, data on aquatic organisms are available for the hydrolysis product. For CASRN 79-11-8, the measured 96-hour LC<sub>50</sub> for fish is 369 mg/L, the measured 48-hour EC<sub>50</sub> for aquatic invertebrates is 77 mg/L and the measured 72-hour EC<sub>50</sub> for aquatic plants is 0.025 mg/L (biomass) and 0.033 mg/L</p> |  |

(growth rate).

There were no data gaps identified under the HPV Challenge Program.

The sponsor, Dow Chemical Company, submitted a Test Plan and Robust Summaries to EPA for chloroacetyl chloride (CASRN 79-04-9; CA index name: acetyl chloride, 2-chloro-) on December 18, 2001. EPA posted the submission on the ChemRTK HPV Challenge website on January 23, 2002 (<http://www.epa.gov/oppt/chemrtk/pubs/summaries/chloroa/c13405tc.htm>). EPA comments on the original submission were posted to the website on August 22, 2002. Public comments were also received and posted to the website. The sponsor submitted updated/revised documents on November 10, 2006, which were posted to the ChemRTK website on December 22, 2006.

The sponsor proposed reduced health effects testing, claiming that chloroacetyl chloride is a closed-system intermediate (CSI) under the HPV Challenge Program. EPA's evaluation of the original and revised/updated information indicates that the chemical does not meet the criteria to fully support the CSI status for this chemical and that the chemical does not qualify for reduced testing. Therefore data for repeated-dose and reproductive toxicity endpoints are needed for the purposes of the HPV Challenge Program.

### **Justification for Supporting Chemical**

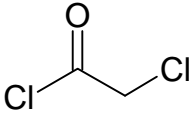
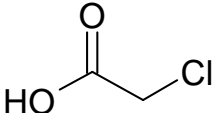
Chloroacetyl chloride undergoes rapid hydrolysis (half life less than 30 minutes) to form chloroacetic acid. Therefore, the sponsor has provided data for chloroacetic acid (CASRN 79-11-8) as a hydrolysis product. EPA agrees that data for chloroacetic acid can be used to address the SIDS endpoints for chloroacetyl chloride for environmental fate, ecological and human health endpoints for the purposes of the HPV Challenge Program. Chloroacetic acid has been reviewed in the OECD HPV program and the data can be found at the following website: <http://cs3-hq.oecd.org/scripts/hpv/>

## **1 Chemical Identity**

### **1.1 Identification and Purity**

The HPV Challenge submission reports that the organic liquid CASRN 79-04-9 has a purity of 99.4%.

The structures of the supporting chemical and the sponsored chemical are shown in Table 1.

| <b>Table 1. Structures of Sponsored and Supporting Chemicals</b> |   |   |
|--|---|---|
|  | <b>SPONSORED CHEMICAL<br/>Chloroacetyl chloride<br/>(CASRN 79-04-9)</b>             | <b>SUPPORTING CHEMICAL<br/>Chloroacetic acid<br/>(CASRN 79-11-8)</b>                  |
| <b>Structure</b>   |  |  |

## 1.2 Physical-Chemical Properties

The physical-chemical properties of CASRN 79-04-9 and its major organic hydrolysis product, CASRN 79-11-8, are summarized in Table 2. CASRN 79-04-9 is a liquid at room temperature. It has high vapor pressure and reacts rapidly with water.

| Property                                 | Chloroacetyl Chloride                                      | Chloroacetic Acid  |
|--|--|--|
| CASRN                                    | 79-04-9  | 79-11-8  |
| Molecular Weight                         | 112.9  | 94.50  |
| Physical State                           | Colorless to light yellow liquid                           | White solid  |
| Melting Point                            | <b>-22°C (measured)</b>                                    | <b>63°C (measured)</b>                                     |
| Boiling Point                            | <b>106°C (measured)</b>                                    | <b>189°C (measured)</b>                                    |
| Vapor Pressure                           | <b>25.0 mm Hg at 25°C (measured)</b>                       | <b>0.065 mm Hg (measured)</b>                              |
| Water Solubility                         | Decomposes   | <b>1.95×10<sup>-5</sup> (measured)</b>                     |
| Dissociation Constant (pK <sub>a</sub> ) | Not applicable   | 2.87 <sup>2</sup>  |
| Henry's Law Constant                     | 2.63×10 <sup>-5</sup> atm-m <sup>3</sup> /mole (estimated) | 1.57×10 <sup>-7</sup> atm-m <sup>3</sup> /mole (estimated) |
| Log K <sub>ow</sub>                      | -0.22 (estimated), decomposes in water                     | <b>0.22 (measured)</b>                                     |

<sup>1</sup> Eastman Chemical Company. 2003. Robust Summary for 3,4-Dichlorotrifluorotoluene.

<http://www.epa.gov/chemrtk/pubs/summaries/eth3meth/c14884tc.htm>.

<sup>2</sup> Estimated by Sparc, May 2008 release w4.21405-s4.21408 (<http://ibmlc2.chem.uga.edu/sparc>).

## 2 General Information on Exposure

### 2.1 Production Volume and Use Pattern

This HPV chemical had an aggregated production and/or import volume in the U.S. in the range of 50 to 100 million pounds in 2005.

Non-confidential information in the IUR indicated that the industrial processing and uses of this chemical includes processing as a reactant in pesticide and other agricultural chemical manufacturing. Non-confidential information in the IUR indicated that commercial and consumer products are listed as "other." Information from the HSDB and the HPV Challenge Program submission indicates that this chemical is primarily used as an intermediate in the manufacture of tear gas, pharmaceutical compounds, herbicides and surfactants.

### 2.2 Environmental Exposure and Fate

No quantitative information is available on releases of this chemical to the environment.

The environmental fate properties of both the sponsored and supporting chemicals are shown in Table 3. CASRN 79-04-9 and its hydrolysis product are expected to be highly mobile in soil. Its

rate of hydrolysis is considered rapid under environmental conditions (pH 5–9). The rate of biodegradation for its organic hydrolysis product (CASRN 79-11-8) was rapid based on the results of a ready biodegradation test. Volatilization is not an important fate property since hydrolysis occurs rapidly; the organic hydrolysis product, CASRN 79-11-8, exists as an anion in the environment and the hydrogen chloride exits as hydrochloric acid in the aqueous phase. The rate of vapor-phase photooxidation in the ambient atmosphere is negligible. CASRN 79-04-9 is expected to have low persistence potential (P1) and low bioaccumulation potential (B1).

| <b>Property</b>            | <b>Chloroacetyl Chloride</b>  | <b>Chloroacetic Acid</b>  |
|----------------------------|---|---|
| Photodegradation Half-life | 450 days (estimated; assumes 12-hour day and $1.5 \times 10^6$ hydroxyl radicals/cm <sup>3</sup> ) <sup>2</sup> | 13.65 days (estimated; assumes 12-hour day and $1.5 \times 10^6$ hydroxyl radicals/cm <sup>3</sup> ) <sup>2</sup> |
| Hydrolysis Half-life       | <30 minutes at 25°C (measured)  | Dissociates in water  |
| Biodegradation             | 100% after 28 days (readily biodegradable)  | 100% after 28 days (readily biodegradable)  |
| Bioconcentration           | BCF = 3.162 (estimated) <sup>2</sup>  | BCF = 3.162 (estimated) <sup>2</sup>  |
| Log K <sub>oc</sub>        | 0.6 (estimated)   | 0.08 (estimated)  |
| Fugacity (Level III Model) | Air = 16%<br>Water = 84%<br>Soil = 0%<br>Sediment = 0%  | Air = 0.2%<br>Water = 38.3%<br>Soil = 61.4%<br>Sediment = 0.1%  |
| Persistence                | P1 (low) <sup>3</sup>   | P1 (low) <sup>3</sup>   |
| Bioaccumulation            | B1 (low) <sup>3</sup>   | B1 (low) <sup>3</sup>   |

<sup>1</sup>Dow AgroSciences LLC. 2006. Revised Robust Summary for the Chloroacetyl Chloride.

<http://www.epa.gov/chemrtk/pubs/summaries/chloroa/c13405tc.htm>.

<sup>2</sup>U.S. EPA. 2008. Estimation Programs Interface Suite™ for Microsoft® Windows, v 3.20. U.S. Environmental Protection Agency, Washington, DC, USA. <http://www.epa.gov/opptintr/exposure/pubs/episuite.htm>.

<sup>3</sup>Federal Register. 1999. Category for Persistent, Bioaccumulative, and Toxic New Chemical Substances. *Federal Register* 64, Number 213 (November 4, 1999) pp. 60194–60204.

### **3. Human Health Hazard**

#### ***Acute Oral Toxicity***

##### ***Chloroacetyl chloride (CASRN79-04-9)***

(1) Rats (2/sex; strain not provided) were administered chloroacetyl chloride as a 10% solution in corn oil at 1260 (male) or 2500 (female) mg/kg-bw and observed for 14 days. Mortality (100%) occurred in males at 1260 mg/kg-bw, and there were no mortalities in females at 2500 mg/kg-bw.

**LD<sub>50</sub> (males) < 1260 mg/kg-bw**

**LD<sub>50</sub> (females) > 2500 mg/kg-bw**

(2) Sprague-Dawley rats (2/sex/dose) were administered chloroacetyl chloride as a 50% solution in corn oil at 126, 158, 200 or 251 mg/kg-bw and observed for 9 days. Survival time was several hours to 2 days with most deaths occurring within 1 day. Toxic signs included increasing weakness, collapse and death. Survivors at higher (unspecified) doses showed only a slight weight gain. Necropsy of animals not surviving the observation period revealed hemorrhagic lungs and inflammation of liver and gastrointestinal tract. Necropsy findings of those surviving until terminal sacrifice revealed lung congestion, slight liver discoloration and gastrointestinal inflammation.

**LD<sub>50</sub> = 207 mg/kg-bw**

***Chloroacetic acid (CASRN 79-11-8, Supporting Chemical)***

(1) Female rats (strain and number per dose not provided) were dosed with unspecified concentrations of chloroacetic acid. No details on the number of deaths or clinical signs of toxicity were provided.

**LD<sub>50</sub> = 90.4 mg/kg-bw**

(2) Mice (strain, number and gender not provided) were dosed with unspecified concentrations of chloroacetic acid in two studies. No details on deaths or clinical signs of toxicity were provided.

**LD<sub>50</sub> = 165 – 260 mg/kg-bw**

***Acute Inhalation Toxicity***

***Chloroacetyl chloride (CASRN79-04-9)***

(1) Fischer 344 rats (6/sex/concentration) were exposed to chloroacetyl chloride vapors at measured concentrations of 32, 208, 522 or 747 ppm (~ 0.15, 0.96, 2.41 or 3.45 mg/L, respectively) for 1 hour and observed for 14 days. The 1-hour exposures were universally marked by signs of ocular irritation, including squinting and tearing, and by signs of respiratory distress from exposures to 208 ppm and above, including gasping and labored breathing. During the 2-week post-exposure observation, treated animals showed persisting eye squint (208 ppm and above), tearing (522 ppm and above), labored breathing (522 ppm and above) and progressive irritative or stress-related clinical signs, including urine stained perineums (32 ppm and above), lethargy (208 ppm and above), reddish periocular stains (208 ppm and above), and salivation with reddish muzzle stains (522 ppm and above). Generally, weight loss during week 1 post-exposure was regained during week 2. Mortality consisted of 5/6 males and 1/6 females and was consistent with a 1-hour LC<sub>50</sub> of 660 ppm for males and greater than 747 ppm for female rats. Necropsy of study lethalties revealed lung and nasal tissue congestion or general circulatory collapse (shock). One male lethality and 5/6 female survivors also had bilaterally enlarged adrenals which, with facial and perineal soiling, the study authors attributed to stress. (Note: Some of the above study details were not in the submitted robust summary but were obtained from a literature search.)

**LC<sub>50</sub> = ~ 3.05 mg/L**

(2) Mice (10/concentration, sex and strain not provided) were exposed to chloroacetyl chloride at a range of concentrations between 0.5 and 30 mg/L for 2 hours or to concentrations ranging from 10 to 65 mg/L for 5 minutes. The animals were observed for 5 days. Clinical signs, necropsy results and mortalities were not provided.

**LC<sub>50</sub> = ~ 11.09 mg/L**

### ***Acute Dermal Toxicity***

#### ***Chloroacetyl chloride (CASRN79-04-9)***

New Zealand White rabbits (2/sex/dose) were administered chloroacetyl chloride at 126, 200, 316, 501, 794, 1260, 2000, 5010 or 10,000 mg/kg to clipped, intact skin under occluded conditions for 24 hours and observed for 14 days. Chloroacetyl chloride was corrosive, extending into the dermis. Mortalities occurred within 3 hours to 2 days. Clinical signs included reduced appetite for 2 – 5 days in survivors, increasing weakness, dyspnea and collapse. Enlarged gall bladders and hemorrhagic lungs and livers were seen in animals dying prior to the end of the observation period.

**LD<sub>50</sub> = 316 – 501 mg/kg**

#### ***Chloroacetic acid (CASRN 79-11-8, Supporting Chemical)***

(1) Female rats (strain and number not provided) were exposed to chloroacetic acid at unspecified concentrations. No details on the method, number of deaths or signs of toxicity were provided.

**LD<sub>50</sub> = 305 mg/kg-bw**

(2) Rabbits (gender, strain and number per concentration not provided) were exposed to chloroacetic acid at unspecified concentrations. No details on the method, number of deaths or signs of toxicity were provided.

**LD<sub>50</sub> = 250 mg/kg-bw**

### ***Repeated-Dose Toxicity***

#### ***Chloroacetyl chloride (CASRN79-04-9)***

Fischer 344 rats, CD-1 mice and Golden Syrian hamsters (10/sex/concentration) were exposed to chloroacetyl chloride vapors at 0, 0.5, 1, 2.5 or 5 ppm (0, 0.002, 0.005, 0.011 or 0.023 mg/L, respectively) for 6 hours/day 5 days/week for 4 weeks. Mortality in rats was 17/20 and 19/20 at 0.011 and 0.023 mg/L respectively during the first two weeks of exposure. Mortality in mice at 0.011 and 0.023 mg/L was 20 and 30% respectively. All rats and mice in the other exposure groups and all the hamsters survived. Other signs of toxicity observed in rats (0.011 and 0.023 mg/L) and mice (0.023mg/L) included rough and discolored fur, irritability, sneezing, lethargy, nasal exudates, rales and eye irritation. The signs of clinical toxicity in hamsters included dose related sneezing and eye closure. Dose related decreases in body weight occurred in mice and rats exposed at 0.005 mg/L and above. Body weight decrease was observed in female hamsters at 0.011 and 0.023 mg/L and at 0.023 mg/L in male hamsters. Gross and microscopic changes were observed in the respiratory tract in rats and mice at 0.011 and 0.023 mg/L. Changes were most severe in the lungs (darkened, hemorrhagic, failure to collapse on puncture) and nasal regions (rhinitis). Histological examination revealed inflammation, hypertrophy and hyperplasia

with occasional squamous metaplasia in the mucosa of the rat respiratory epithelium and intracytoplasmic eosinophilic inclusions in mice. These changes were slight to moderate at 0.002 mg/L in rats and mice. Numbers of macrophages surrounding the large bronchi, with red indistinct cytoplasmic masses increased in mice. Additional cellular changes observed in the mice include accentuated hepatic lobules, depletion of mesenteric adipose tissue, and ovarian, uterine and cervical epithelial atrophy at 0.011 and 0.023 mg/L, and microvesicular changes in periportal hepatocytes of male mice at 0.002 and 0.005 mg/L. Hamsters showed no gross pathological respiratory effects and were not assessed histopathologically. (Note: Some of the above study details were not in the submitted robust summary but were obtained from a literature search.)

**LOAEL (systemic toxicity) = 0.011 mg/L** (based on mortality in rats and mice)

**NOAEL (systemic toxicity) = 0.005 mg/L**

**LOAEL (local effects) = 0.002 mg/L** (based on inflammation, hypertrophy, hyperplasia and occasionally squamous metaplasia in the respiratory epithelium of the nasal mucosa in rats and mice)

**NOAEL (local effects) = Not established**

***Chloroacetic acid (CASRN 79-11-8, Supporting Chemical)***

1) In an NTP study, F344/N rats (20/sex/dose) were administered monochloroacetic acid via gavage at 0, 30, 60, 90, 120 or 150 mg/kg-bw/day 5 days/week for 13 weeks. All animals administered 120 and 150 mg/kg-bw/day and 9/10 of the males and all females administered 90 mg/kg-bw/day doses died. For the remaining doses (30 and 60 mg/kg-bw/day), surviving animals exhibited dose-dependant increases in blood urea nitrogen (BUN), alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels, and decreases in cholinesterase. Elevated relative kidney and liver weights (without any histopathology), and increases in absolute and relative heart weights with associated histological effects (myocardial degeneration with an associated inflammatory response) were observed at 60 mg/kg-bw/day. According to the NTP study report and evaluation, increased serum levels of AST is consistent with this finding of heart effects; however, the study report further states that a tissue source for this enzyme other than the heart cannot be ruled out. Elevated ALT and decreased cholinesterase levels, in conjunction with the increased liver weight, may suggest, according to the NTP report, that the liver is also affected. The report finally concluded the elevation in BUN was a secondary effect, not related to kidney toxicity. No other effects were reported. No treatment related effects were seen in the reproductive organs (right testis, ovaries, prostate gland and uterus) evaluated. (Note: The full NTP report can be obtained at <http://ntp.niehs.nih.gov/?objectid=03F26044-E181-8E01-4D2D72F43E351DB4>)

**LOAEL = 60 mg/kg-bw/day** (based on signs of liver toxicity and heart lesions with corresponding changes in blood chemistry parameters)

**NOAEL = 30 mg/kg-bw/day**

(2) In a NTP study, B6C3F1 mice (20/sex/dose) were administered monochloroacetic acid via gavage at 0, 25, 50, 100, 150 or 200 mg/kg-bw/day 5 days/week for 13 weeks. All males and 2/10 females at 200 mg/kg-bw/day died and exhibited cytoplasmic vacuolation of the liver. Of the surviving females in the 200 mg/kg-bw/day dose group, significantly reduced body weight gains were observed. This effect was not observed at any other dose level, and did not show dose-trend. Absolute and relative liver weights were significantly increased in female mice at

the 200 mg/kg-bw/day dose group, along with decreases in cholinesterase levels in females at the 150 and 200 mg/kg-bw/day dose levels. The study authors concluded that decreases in cholinesterase levels could be an indicator of liver toxicity in females. No other treatment-related serum chemistry or histopathological changes were reported. No treatment related effects were seen in the reproductive organs (right testis, ovaries, prostate gland and uterus) evaluated. (Note: The full NTP report can be obtained at <http://ntp.niehs.nih.gov/?objectid=03F26044-E181-8E01-4D2D72F43E351DB4>)

**LOAEL = 200 mg/kg-bw/day** (based on mortality in males and females)

**NOAEL = 150 mg/kg-bw/day**

(3) There were three other repeated-dose toxicity studies performed with chloroacetic acid. These studies used a lower number of animals/dose than required by the guidelines, only one sex (males) of animals and only one dose in 2 of the 3 studies. These studies lend limited information to the overall weight of evidence and therefore, are not used in this hazard characterization.

### ***Reproductive Toxicity***

There were no studies specifically designed to assess the reproductive toxicity of either chloroacetyl chloride or chloroacetic acid. Available data from a 28-day study with chloroacetyl chloride in mice showed effects on the uterus following inhalation exposure (but no such effects were observed in rats and hamsters under similar exposure conditions). There were no effects on reproductive organs in either mice or rats exposed via gavage to chloroacetic acid in the 13-week NTP studies described above. In the chloroacetic acid NTP cancer studies described below under carcinogenicity, there were no effects on reproductive organs in rats or male mice, but female mice had uterine stromal polyps (2/60, 7/57, and 10/60 for the control, low and high dose groups, respectively). The only tumor, however, was in the control group. The NTP dismissed the polyp findings as all being within historical controls (range of 10-38%) and the concurrent control group having a lower incidence (3%) than normal (mean of 21%). (Note: The full NTP report can be obtained at [http://ntp-apps.niehs.nih.gov/ntp\\_tox/index.cfm?fuseaction=ntpsearch.searchresults&searchterm=79-11-8](http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=ntpsearch.searchresults&searchterm=79-11-8))

### ***Developmental Toxicity***

#### ***Chloroacetic acid (CASRN 79-11-8, Supporting Chemical)***

Pregnant Long-Evans rats (number unspecified) were administered chloroacetic acid in distilled water via oral gavage at 0, 17, 35, 70 or 140 mg/kg-bw/day during gestation days 6-15. Maternal animals were observed for clinical signs, body weights, gross evaluation of organ weights and uterine contents at necropsy. Live fetuses were examined for external, skeletal and soft tissue malformations. At 140 mg/kg-bw/day, a significant decrease in maternal body weight gain was observed (p-level not stated) and a significantly elevated number of fetal cardiovascular malformations were observed (p-level not stated). The malformations consisted primarily of levocardia (abnormal positioning of abdominal and thoracic organs other than the heart). No fetal skeletal malformations or toxicity were observed at any dose. No differences were seen in mean percent resorptions per litter or live fetal weights when comparing treated groups with controls. The study (Smith et al. 1990) was available as an abstract and limited information was provided. Developmental studies (Smith et al., 1989, 1992) with dichloroacetic acid and

trichloroacetic acid showed similar signs of toxicity that included reduced fetal crown rump length, decreased fetal body weight and increased cardiovascular soft tissue anomalies.

**LOAEL (maternal/developmental toxicity) = 140 mg/kg-bw/day** (based on reduced body weight and weight gain in dams and increased cardiovascular malformations in fetuses)

**NOAEL (maternal/developmental toxicity) = 70 mg/kg-bw/day**

### *Genetic Toxicity – Gene Mutations*

#### *In vitro*

##### ***Chloroacetyl chloride (CASRN79-04-9)***

(1) *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 and TA1538 were exposed to chloroacetyl chloride at 0.5 – 500 µg/plate, in the presence and absence of metabolic activation. Information on positive and negative controls or cytotoxicity was not provided.

**Chloroacetyl chloride was not mutagenic in this assay.**

##### ***Chloroacetic acid (CASRN 79-11-8, Supporting Chemical)***

(1) *Salmonella typhimurium* strains TA97, TA98, TA100, TA1535 and TA1537 were exposed to chloroacetic acid at 0.8 – 3333 µg/plate and TA1530 was exposed to 10,206 µg/plate, in the presence and absence of metabolic activation. Cytotoxicity was seen within the range of concentrations tested. Two to four replicates per concentration were tested. Information on positive and negative controls was not provided.

**Chloroacetic acid was not mutagenic in this assay.**

(2) Mouse lymphoma cells (L5178Y TK +/-) were exposed to chloroacetic acid at concentrations of 139.4 – 1048.2 µg/mL in one assay in the presence of metabolic activation and 50 – 800 µg/mL in another assay in the absence of metabolic activation. Positive results were obtained in both assays at cytotoxic concentrations (above 400 µg/mL). The test substance was negative at noncytotoxic concentrations. Information on positive and negative controls was not provided.

**Chloroacetic acid was not mutagenic in these assays.**

(3) In an HGPRT assay, V79 cells were exposed to  $\leq 198.45$  µg/mL of chloroacetic acid in the absence of metabolic activation. No information on positive and negative controls, number of replicates, cytotoxicity or methodology was provided.

**Chloroacetic acid was not mutagenic in this assay.**

### *Genetic Toxicity – Chromosomal Aberrations*

#### *In vitro*

##### ***Chloroacetic acid (CASRN 79-11-8, Supporting Chemical)***

(1) Chinese hamster ovary cells (CHO-W-B1) were exposed to chloroacetic acid at concentrations ranging from 50 to 500 µg/mL in the absence of metabolic activation. No information on positive and negative controls, number of replicates, cytotoxicity or methodology was provided. Sister chromatid exchanges were observed at concentrations above 160 µg/mL.

**Chloroacetic acid induced sister chromatid exchanges in this assay.**

(2) Chinese hamster ovary cells (CHO-W-B1) were exposed to chloroacetic acid at concentrations ranging from 50 to 1600 µg/mL in the presence of metabolic activation. No information on positive and negative controls, number of replicates, cytotoxicity or methodology was provided.

**Chloroacetic acid did not induce chromosomal aberrations in this assay.**

(3) Chinese hamster lung fibroblasts (CHL) were exposed to chloroacetic acid at 0.06 – 0.25 mg/mL in the absence of metabolic activation. No information on positive and negative controls, number of replicates, cytotoxicity or methodology was provided.

**Chloroacetic acid did not induce chromosomal aberrations in this assay.**

### *Genetic Toxicity – Other*

#### *In vitro*

##### *Chloroacetic acid (CASRN 79-11-8, Supporting Chemical)*

Rat bone marrow cells were exposed to chloroacetic acid at 1.5 – 151.2 µg/mL and examined for inhibition of DNA synthesis. No information on positive and negative controls, number of replicates, cytotoxicity or methodology was provided.

**Chloroacetic acid was negative for inhibiting DNA synthesis in rat bone marrow in this assay.**

### *Additional Information*

#### *Skin Irritation*

##### *Chloroacetyl chloride (CASRN 79-04-9)*

(1) Chloroacetyl chloride was applied dermally to intact sites on the shaved abdomens of rabbits (1 male/dose) under semi-occlusive conditions for 0.5, 1 or 3 minutes. Redness, swelling and necrosis were observed at the application sites with time-related increasing severity. Exposure for 3 minutes caused slight redness and moderate necrosis, which, upon healing, left a scar.

**Chloroacetyl chloride was corrosive to rabbit skin in this study.**

(2) Undiluted chloroacetyl chloride was applied dermally to the clipped backs of 3 male and 3 female rabbits under occlusive conditions for 24 hours. The rabbits were observed for several days following application. The maximum Draize score was 8 out of 8 within 2 hours and there was no change within 168 hours except that the edema and erythema gradually disappeared.

**Chloroacetyl chloride was corrosive to rabbit skin in this study.**

##### *Chloroacetic acid (CASRN 79-11-8, Supporting Chemical)*

Rabbits were exposed to chloroacetic acid dermally under occlusive patches for 24 hours. No information concerning site preparation was provided.

**Chloroacetic acid was corrosive to rabbit skin in this study.**

### *Eye Irritation*

#### ***Chloroacetyl chloride (CASRN 79-04-9)***

(1) Two drops of the undiluted chloroacetyl chloride were instilled into the right eye of a male New Zealand white rabbit. The eye was washed within 30 seconds for 2 minutes with a stream of tepid water. Two drops of the material were instilled into the left eye, which was left unwashed. The eyes were examined at 2 – 3 minutes, 1, 24 and 48 hours and 6 – 8 days post-treatment. Both washed and unwashed eyes had similar reactions: slight pain and very severe conjunctival and corneal irritation, which had not healed within one week.

**Chloroacetyl chloride was corrosive to rabbit eyes in this assay.**

(2) Chloroacetyl chloride (0.1 mL) was instilled into the right eyes of 1 male and 1 female rabbit. In one rabbit, the eye was washed within 30 seconds with warm isotonic saline. In the other rabbit, the eye was washed with warm isotonic saline within 5 seconds. The eyes were examined immediately following instillation and for several days after. The Draize score in each eye was 110 out of 110. Immediately after instillation, the rabbits exhibited signs of severe discomfort. Within 10 minutes, the eyes had moderate erythema, edema and discharge. Corneal opacity and severe iritis were seen.

**Chloroacetyl chloride was corrosive to rabbit eyes in this assay.**

### *Chronic Toxicity/Carcinogenicity*

#### ***Chloroacetic acid (CASRN 79-11-8, Supporting Chemical)***

(1) In an NTP study, F344/N rats (70/sex/dose) were administered chloroacetic acid via gavage at 0, 15 or 30 mg /kg-bw/day for 5 days/week for 104 weeks. Complete necropsy and histological examinations were performed on all animals. Ten animals/sex/dose and control group were selected for an interim sacrifice after 6 months and seven animals/sex/dose were selected for a second interim sacrifice after 15 months. Mortality was elevated in high-dose males and treated females compared to controls. After 30 weeks of exposure, the mean body weights of high-dose males were 8 – 10% less than controls. No increase in tumor incidence was noted compared to controls.

**No increase in tumor incidence was noted in this study.**

(2) In an NTP study, B6C3F1 mice (60/sex/dose) were administered chloroacetic acid via gavage at 0, 50 or 100 mg/kg-bw/day 5 days/week for 104 weeks. Mortality was increased in high-dose males compared to controls. Mean body weights of male mice were similar to those of controls. Mean body weights in females of both treatment groups were decreased by 6 – 10% compared to controls after 52 weeks. An increase in the incidence of nasal mucous membrane inflammations, epithelial metaplasia of the olfactory epithelium and squamous cell hyperplasia in the forestomach was noted in treated mice. No increase in the incidence of tumors was noted.

**No increase in tumor incidence was noted in this study.**

### *Neurotoxicity*

#### ***Chloroacetic acid (CASRN 79-11-8, Supporting Chemical)***

Swiss-Webster mice (males, number not stated) were administered monochloroacetic acid via gavage at 260 or 380 mg/kg-bw. No information was provided on method, duration, controls or GLP. Surviving animals exhibited limb rigidity, occasionally bent back and had severe convulsions followed by death. Animals surviving up to 6 months showed no improvement in symptoms. Histological examination revealed damage to the Purkinje cells primarily in the cerebellum, but also in the hippocampus and cortex. Because the doses used were near the oral LD50, the study was not considered suitable for this hazard characterization.

**Conclusion:** The acute oral, inhalation and dermal toxicity of this chemical (CASRN 79-04-9) is moderate. Acute oral and dermal toxicity of its hydrolysis product (CASRN 79-11-8) is also moderate. CASRN 79-04-9 is corrosive to rabbit eyes and skin. Systemic toxicity in inhalation repeated-dose studies of CASRN 79-04-9 in rats and mice showed mortality at low doses (LOAEL of 0.011 mg/L) and local effects (inflammation/cellular abnormalities in the nasal mucosa) at the lowest tested dose (LOAEL of 0.002 mg/L). In oral repeated-dose studies of CASRN 79-11-8, effects on the liver and heart (rats - LOAEL of 60 mg/kg-bw/day; NOAEL of 30 mg/kg-bw/day) and mortality (mice - LOAEL of 200 mg/kg-bw/day; NOAEL of 150 mg/kg-bw/day) were observed. Although there were no reproductive toxicity studies with either CASRN 79-04-9 or CASRN 79-11-8, there were no effects in reproductive organs in oral repeated-dose studies in rats or mice exposed to CASRN 79-11-8 at doses up to 200 mg/kg-bw/day in mice. A developmental toxicity study with CASRN 79-11-8 in rats showed maternal toxicity (reduction in both body weight and weight gain) and developmental toxicity (increased cardiovascular malformations in fetuses) at the same dose (LOAEL of 140 mg/kg-bw/day; NOAEL of 70 mg/kg-bw/day). CASRN 79-04-9 did not induce gene mutations in bacteria. In *in vitro* studies with mammalian cell cultures, CASRN 79-11-8 did not induce chromosomal aberrations, but did induce sister chromatid exchanges. Oral exposure to CASRN 79-11-8 for 104 weeks did not result in increase in tumor incidence in rats or mice compared to controls.

## **4 Hazards to the Environment**

### ***Acute Toxicity to Fish***

#### ***Chloroacetic acid (CASRN 79-11-8, Supporting Chemical)***

(1) Golden orfes (*Leuciscus idus melanotus*) were exposed to chloroacetic acid at nominal concentrations of 1 – 500 mg/L under static conditions for 96 hours. No mortalities, changes in behavior or gross physical changes were seen at the 1 – 100 mg/L concentrations (pH 8.3 - 8.7). At 500 mg/L (pH 3.8) 100 % of the fish died 78 - 173 min after addition of the preparation, likely due to the low pH.

**96-h LC<sub>50</sub> > 100 mg/L**

(2) Guppies (*Poecilia reticulata*) were exposed to chloroacetic acid at unspecified concentrations under static conditions for 96 hours (pH 8.0 – 8.3 at 24 - 26°C). No further details were provided.

**96-h LC<sub>50</sub> = 369 mg/L**

### *Acute Toxicity to Aquatic Invertebrates*

#### ***Chloroacetic acid (CASRN 79-11-8, Supporting Chemical)***

Water fleas (*D. magna*) were exposed to chloroacetic acid at unspecified concentrations for 48 hours in two separate assays. Information was not provided for the conditions of assay, analytical monitoring methods or water chemistry, except that the pH was  $\geq 7$  (at 20 °C).

**48-h EC<sub>50</sub> = 77 – 88 mg/L**

### *Toxicity to Aquatic Plants*

#### ***Chloroacetic acid (CASRN 79-11-8, Supporting Chemical)***

(1) Green algae (*Scenedesmus subspicatus*) were exposed to chloroacetic acid at unspecified nominal concentrations for 72 hours. Information was not provided for the conditions of assay, photoperiod or water chemistry, except that the pH was 7.7 – 8.1.

**72-h EC<sub>50</sub> (biomass) = 0.025 mg/L**

(2) Green algae (*S. subspicatus*) were exposed to chloroacetic acid at unspecified nominal concentrations for 72 hours. Information was not provided for the conditions of assay, photoperiod or water chemistry, except that the pH was 7.7 – 8.1.

**72-h EC<sub>50</sub> (growth rate) = 0.033 mg/L**

### *Chronic Toxicity to Daphnia*

#### ***Chloroacetic acid (CASRN 79-11-8, Supporting Chemical)***

Water fleas (*D. magna*) were exposed to chloroacetic acid at unspecified nominal concentrations for 21 days. Test conditions, method of analytical monitoring and water chemistry were not provided, except that the pH was not  $< 7$  and the deviation between the concentration measured and the nominal concentration was  $< 20\%$ . The evaluated endpoints were reproduction rate, mortality and first appearance of offspring.

**21-d NOEC = 32 mg/L**

**Conclusion:** Because CASRN 79-04-9 undergoes rapid hydrolysis to CASRN 79-11-8 in water, data on aquatic organisms are available for the hydrolysis product. For CASRN 79-11-8, the measured 96-hour LC<sub>50</sub> for fish is 369 mg/L, the measured 48-hour EC<sub>50</sub> for aquatic invertebrates is 77 mg/L, and the measured 72-hour EC<sub>50</sub> for aquatic plants is 0.025 mg/L (biomass) and 0.033 mg/L (growth rate).

| <b>Table 4: Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program</b> |   |  |
|---|---|--|
| <b>Endpoints</b>  | <b>SPONSORED CHEMICAL<br/>Chloroacetyl chloride<br/>(CASRN 79-04-9)</b> | <b>SUPPORTING CHEMICAL<br/>Chloroacetic acid<br/>(CASRN 79-11-8)</b>   |
| <b>Summary of Human Health Data</b>   |   |  |
| <b>Acute Oral Toxicity<br/>LD<sub>50</sub> (mg/kg)</b>  | <b>207</b>  | <b>90.4</b>  |
| <b>Acute Inhalation Toxicity<br/>LC<sub>50</sub> (mg/L)</b>   | <b>~3.05</b>  | <b>–</b>   |
| <b>Acute Dermal Toxicity<br/>LD<sub>50</sub> (mg/kg)</b>  | <b>316</b>  | <b>250</b>   |
| <b>Repeated-Dose Toxicity<br/>NOAEL/LOAEL<br/>Oral (mg/kg-bw/day)</b>   | <b>–*</b>   | <b>NOAEL = 30<br/>LOAEL = 60</b>   |
| <b>Repeated-Dose Toxicity<br/>NOAEL/LOAEL<br/>Inhalation (mg/L/day)</b>   | <b>NOAEL = Not established<br/>(4-wk)<br/>LOAEL ~0.002 (4-wk)</b>       | <b>–</b>   |
| <b>Reproductive Toxicity<br/>NOAEL/LOAEL</b>  | <b>–*</b>   | No effects were seen following evaluation of reproductive organs in rats and mice in 13-week and two-year oral gavage repeated-dose studies. |
| <b>Developmental Toxicity<br/>NOAEL/LOAEL<br/>Oral (mg/kg-bw/day)</b>   | <b>–*</b>   |  |
| <b>Maternal</b>   |   | <b>NOAEL = 70<br/>LOAEL = 140</b>  |
| <b>Developmental</b>  |   | <b>NOAEL = 70<br/>LOAEL = 140</b>  |
| <b>Genetic Toxicity – Gene Mutations<br/><i>In vitro</i></b>  | <b>Negative</b>   | <b>Negative</b>  |
| <b>Genetic Toxicity – Chromosomal Aberrations<br/><i>In vitro</i></b>   | <b>–*</b>   | <b>Positive</b>  |
| <b>Genetic Toxicity – Other<br/><i>In vitro</i><br/>Unscheduled DNA Synthesis</b>                                     | <b>–*</b>   | <b>Negative</b>  |

| <b>Table 4: Summary Table of the Screening Information Data Set as Submitted under the U.S. HPV Challenge Program</b>       |   |  |
|---|---|--|
| <b>Endpoints</b>  | <b>SPONSORED CHEMICAL<br/>Chloroacetyl chloride<br/>(CASRN 79-04-9)</b> | <b>SUPPORTING CHEMICAL<br/>Chloroacetic acid<br/>(CASRN 79-11-8)</b> |
| <b>Additional Information</b><br><b>Skin Irritation</b><br><b>Eye Irritation</b><br><b>Chronic Toxicity/Carcinogenicity</b> | <b>Corrosive</b><br><b>Corrosive</b><br><b>—*</b>                       | <b>Corrosive</b><br><b>—</b><br><b>Negative</b>                      |
| <b>Summary of Environmental Effects – Aquatic Toxicity Data</b>   |   |  |
| <b>Fish</b><br><b>96-h LC<sub>50</sub> (mg/L)</b>   | <b>—*</b>   | <b>&gt; 100</b>  |
| <b>Aquatic Invertebrates</b><br><b>48-h EC<sub>50</sub> (mg/L)</b>  | <b>—*</b>   | <b>77 – 88</b>   |
| <b>Aquatic Plants</b><br><b>72-h EC<sub>50</sub> (mg/L)</b><br><b>(growth rate)</b><br><b>(biomass)</b>                     | <b>—*</b>   | <b>0.033</b><br><b>0.025</b>   |
| <b>Chronic Aquatic Toxicity</b><br><b>(mg/L)</b>  | <b>—*</b>   | <b>21-d NOEC = 32</b>  |

— indicates that endpoint was not addressed for this chemical; \* Chloroacetyl chloride rapidly hydrolyzes to chloroacetic acid.