

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY  
WASHINGTON, D.C. 20460

OFFICE OF  
SOLID WASTE AND EMERGENCY  
RESPONSE

Ms. Elizabeth B. Knauss  
Hazardous Waste Program  
Southwest District  
Florida Department of Environmental Protection  
3804 Coconut Palm Drive  
Tampa, FL 33619

Dear Ms. Knauss:

I am writing in response to your inquiry concerning the regulation of the commercial chemical product chloral as Hazardous Waste No. U034.

Chloral is a hygroscopic substance and readily hydrates to chloral hydrate (CAS# 302-17-0) on exposure to moisture. In EPA's Integrated Risk Information System (IRIS) under section: I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD). EPA states that "Sanders *et al.* (1982) dissolved chloral in water to form chloral hydrate" in order to study the toxic effects of chloral. Clearly the toxicity studies for chloral include the results of the toxic effects of the hydrated form, chloral hydrate. In any contact with the internal organs of the human body, chloral would necessarily come in contact with water and form chloral hydrate. See also the attached IRIS Profile for Chloral.

As you are aware, 40 CFR 261.33(f) assigns hazardous waste number U034 to chloral (CAS# 75-87-6). Chloral also is listed as a hazardous constituent in 40 CFR 261 APPENDIX VIII. Chemical Abstract Numbers (CAS) were added "as an identification aid" to the tables in 40 CFR 261.33 (51 FR 28296). The hazardous waste codes of '261.33(e) and (f) apply to all commercial chemical products or manufacturing chemical intermediates having the generic name listed (§261.33(a)).

In the case of chloral, separate CAS numbers are assigned to "anhydrous" chloral (CAS# 75-87-6) and chloral hydrate (CAS# 302-17-0) by the abstract service. However, both the anhydrous chloral and chloral hydrate are referenced generically simply as "chloral" and are regulated as Hazardous Waste No. U034.

This is consistent with our interpretative letter dated August 24, 1992 for the commercial chemical product cyclophosphamide as Hazardous Waste No. U058, which you referenced in your letter. In that letter, EPA clarified that the hydrated form, cyclophosphamide monohydrate, was also regulated as Hazardous Waste No. U058.

RO 14175

With regards to possible clarifications of 40 CFR 261.33, EPA currently is investigating other commercial chemical products that have similar problems with hydrated forms and those that have mixed isomers that also are not specified in 40 CFR 261.33. At this time, EPA has not decided on the best way to present these clarifications, but understands that such clarifications would assist hospitals, pharmacies and drug distributors as well as other generators of these U and P Wastes.

If we can be of further assistance, please call Wanda Levine of my staff at 703-308-0338.

Sincerely,

William F. Brandes, Chief  
Waste Identification Branch

Enclosure

Department of Environmental Protection

Lawton Chiles  
Governor

Southwest District  
3804 Coconut Palm Drive  
Tampa, Florida 33619

Virginia B. Wetherell  
Secretary

February 20, 1998

United States Environmental Protection Agency  
Office of Solid Waste and Emergency Response  
401 M Street S. E.  
Washington, D. C. 20460

Dear sirs:

re: Listing of Chloral, EPA Waste Number U034

I am writing to request request clarification as to whether the listing of chloral in 40 CFR 261.33(f) includes chloral hydrate. Chloral and chloral hydrate have different CAS number. Last year, the RCRA Hotline stated in a phone conversation that the U035 listing does not include chloral hydrate, although that compound is formed by mixing chloral with 20% water.

However, I have since located the attached letter from Edwin F. Abrams dated August 24, 1992 which discusses the listing of cyclophosphamide and cyclophosphamide monohydrate. Mr. Abrams stated that the U058 listing included both compounds, although only one CAS number was listed in the EPA waste identification table. As a follow up, I called the RCRA Hotline again, and requested that they check the chloral background Ming document. This document uses chloral and chloral hydrate interchangeably.

The State of Florida has two DEA licensed reverse pharmaceutical distributors who arrange for the destruction of waste drugs. Based on the original Hotline guidance, I told one of them that they could manage chloral as non-hazardous. If this is interpretation is incorrect, please respond in writing as soon as possible confirming that the U034 listing includes chloral hydrate. In addition, I suggest that you clarify the EPA waste table to prevent confusion, as many hospitals, pharmacies and drug distributors

generate choral hydrate.

Sincerely,

Elizabeth B. Knauss  
Hazardous Waste Program  
Southwest District

cc:

My linda Cross, S. A. I. Transport, Inc.

Kathryn D. Lynnes  
Director of Environmental Compliance  
BHL Consultants, Ltd.  
2 Fountain Place  
Suite 350  
Grand Rapids, MI 49503

Dear Ms. Lynnes:

I am writing in response to your inquiry concerning the regulation of the commercial chemical product cyclophosphamide as Hazardous Waste No. U058.

cyclophosphamide is a hygroscopic substance and readily hydrates to cyclophosphamide monohydrate (CAS# 6055-19-2) on exposure to moisture. Storage in air tight containers is recommended. IARC cancer review indicates sufficient evidence of human carcinogenicity for both forms of the chemical. The carcinogenicity of cyclophosphamide was the basis for hazardous waste regulation.

As you are aware, 40 CFR 261.33(f) assigns hazardous waste number U058 to cyclophosphamide (CAS/ 50-18-0). Cyclophosphamide is also listed as a hazardous constituent in 40 CFR 261 APPENDIX VIII. Chemical Abstract Numbers (CAS) were added "as an identification aid " to the tables in §261.33 ( 51 FR 28296). The hazardous waste codes of §261.33(e) and (f) apply to all commercial chemical products or manufacturing chemical intermediates having the generic name listed (§261.33(a)).

In the case of cyclophosphamide, separate CAS numbers are assigned to anhydrous cyclophosphamide (CAS# 50-18-0) and cyclophosphamide monohydrate (CAS# 6055-19-2) by the abstract service. However, both the anhydrous cyclophosphamide and cyclophosphamide monohydrate are generically referenced as simply "cyclophosphamide" and are regulated as Hazardous Waste No. U058.

Sincerely,

Edwin F. Abrams, Chief

EPA Form 1320-1 (12-70)  
OFFICIAL FILE COPY

RO 14175

## ENCLOSURE -- IRIS PROFILE FOR CHLORAL

0304

Chloral; CASRN 75-87-6 (03/01/97)

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

### STATUS OF DATA FOR Chloral

File On-Line 08/22/88

Category (section)	Status	Last Revised
--------------------	--------	--------------

Oral RfD Assessment (I.A.)	on-line	02/01/96
----------------------------	---------	----------

Inhalation RfC Assessment (I.B.)		
----------------------------------	--	--

no data

Carcinogenicity Assessment (II.)		
----------------------------------	--	--

no data

## I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR WONCARCINOGENIC EFFECTS

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

Substance Name -- Chloral

CASRN -- 75-87-6

Last Revised -- 02/01/96

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units

of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this 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.

#### I.A.1. ORAL RfD SUMMARY

Critical Effect	Experimental Doses*	UF	MF	RfD
-----------------	---------------------	----	----	-----

Hepatotoxicity	NOAEL: none	10,000	1	2E-3 mg/kg-day
----------------	-------------	--------	---	-------------------

Mouse Oral LOAEL: 15.7 mg/kg-day  
Subchronic Study

Sanders et al., 1982

\*Conversion Factors: Drinking water concentrations converted to dosages by investigators based on water consumption and body weight data.

#### I.A.2. PRINCIPAL AND SUPPORTING STUDIES (ORAL RfD)

Sanders, V.M., B.M. Kauffman, K.L. White, Jr., et al. 1982. Toxicology of chloral hydrate in the mouse. *Environ. Health Perspect.* 44: 137-146.

Sanders et al. (1982) dissolved chloral in water to form chloral hydrate. Groups of 140 male and 140 female CD-1 mice were maintained on the water solution at concentrations of 0.07 or 0.7 mg/mL as chloral for 90 days starting at 1 week of age; 260 mice/sex received deionized water and served as controls. Low and high TWA dosages based on measured water intake were reported to be 15.7 and 159.8 mg/kg/day for the males and 18.2 and 173.4 mg/kg/day for females, respectively. Growth, hematology and serum chemistry parameters, liver enzyme activities and microsomal parameters. organ (liver, lungs, spleen, thymus, kidneys, testes and brain) weights and gross pathology were evaluated. Significant effects included dose-related increased final body weights in males, increased final body weights in high-dose females.

dose-related increased relative liver weights in males, increased serum LDH and SGOT in high-dose males and increased microsomal cytochrome b5 content and aminopyrine N-demethylase and aniline hydroxylase activities in high- and low-dose males. The liver therefore appears to be a target organ for chloral toxicity. and the dose of 15.7 mg/kg/day in males is the LOAEL. Since this was the lowest dose tested, this study does not define a NOAEL or NOEL. Dividing the LOAEL of 15.7 mg/kg/day by an uncertainty factor of 10,000 yields an RfD of 0.002 mg/kg/day, or 0.1 mg/day for a 70 kg person.

#### I.A.3. UNCERTAINTY AND MODIFYING FACTORS (ORAL RfD)

UF -- 10 for extrapolation from a LOAEL to a NOAEL, 10 for use of a subchronic assay, 10 for extrapolation from animals to humans. and 10 for protection of sensitive human subpopulations.

MF -- None

#### I.A.4. ADDITIONAL COMMENTS (ORAL RfD)

In female mice it appears that the immune system, particularly the ability to produce IgM antibody to a T-dependent antigen is the most sensitive indicator (Kauffmann et al.. 1982). In male mice the liver is the most sensitive organ. Both effects occurred at the lowest concentration tested. 0.07 mg/mL or 15.7 mg/kg (Sanders et al.. 1982). The adverse effects on the immune system observed at the 15.7 mg dosage level support the LOAEL used to derive the RfD.

Offspring from mice that were exposed throughout pregnancy to 204 mg/kg/day but not 21.3 mg/kg/day chloral in the drinking water had a behavioral impairment (impaired learning retention of a passive avoidance task) (Kallman et al., 1984). Gross malformations or effects on maternal reproductive parameters were not noted.

Intratesticular injection of 300 mg/kg chloral hydrate produced decreased spermatogenesis in mice (Borzelleca and Carchman, 1981).

Chloral has not been adequately tested for teratogenicity, reproductive effects or chronic toxicity.

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

Study -- Low

Data Base -- Low

RfD -- Low



Although large groups of animals were exposed to chloral in drinking water, a low level of confidence is assigned because a NOEL or NOAEL was not identified and because histological evaluations were not conducted. Confidence in the data base is low because corroborating or additional subchronic or chronic toxicity data are not available. The low level of confidence in the RfD reflects the low level of confidence in the study and data base.

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

Source Document -- This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation -- None

Agency Work Group Review -- 10/15/87, 03/24/88

Verification Date -- 03/24/88

#### I.A.7. EPA CONTACTS (ORAL RfD)

Please contact the Risk Information Hotline for all questions concerning this assessment or IRIS, in general, at (513)569-7254 (phone), (513)569-7159 (FAX) or RIH.IRIS@EPAMAIL.EPA.GOV (internet address).

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

Substance Name -- Chloral

CASRN -- 75-87-6

Not available at this time.

#### II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- Chloral

CASRN -- 75-87-6

This substance/agent has not been evaluated by the U.S. EPA for evidence of human carcinogenic potential.

#### VI. BIBLIOGRAPHY

Substance Name -- Chloral

CASRN -- 75-87-6

Last Revised -- 01/01/90

#### \_VI.A. ORAL RfD REFERENCES

Borzelleca, J.F. and R.A. Carchman. 1982. Effects of selected organic drinking water contaminants on male reproduction. EPA 600/1-81-009. NTIS PB 82-259847.

Kallman, M.J., G.L. Kaempf and R.L. Balster. 1984. Behavioral toxicity of chloral in mice: An approach to evaluation. Neurobehav. Toxicol. Teratol. 6: 137-146.

Kauffmann, B.M., K.L. White, Jr., V.M. Sanders, et al. 1982. Humoral and cell-mediated immune status in mice exposed to chloral hydrate. Environ. Health Perspect. 44: 147-151.

Sanders, V.M., B.M. Kauffmann, K.L. White, Jr., et al. 1982. Toxicology of chloral hydrate in the mouse. Environ. Health Perspect. 44: 137-146.

#### \_VI.B. INHALATION RfD REFERENCES

None

#### \_VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

None

#### \_VII. REVISION HISTORY

Substance Name -- Chloral  
CASRN -- 75-87-6

Date Section Description

08/22/88 I.A. Oral RfD summary on-line  
01/01/90 VI. Bibliography on-line  
01/01/92 I.A.7. Secondary contact changed  
01/01/92 IV. Regulatory Action section on-line  
02/01/96 I.A.1. Minor text change

SYNONYMS

Substance Name -- Chloral  
CASRN -- 75-87-6  
Last Revised -- 08/22/88

75-87-6  
acetaldehyde, trichloro-  
anhydrous chloral  
Chloral  
cloralio  
grasex  
RCRA waste number U034  
trichloroacetaldehyde  
2,2,2-trichloroacetidehyde  
trichloroethanal  
UN 2075