

Fact Sheet Date: April 2000

**NEW YORK STATE
- HUMAN HEALTH FACT SHEET -**

**Ambient Water Quality Value for
Protection of Sources of Potable Water**

SUBSTANCE: n-Butanol

CAS REGISTRY NUMBER: 71-36-3

AMBIENT WATER QUALITY VALUE: 50 ug/L

BASIS: General organic guidance value

INTRODUCTION

The ambient water quality value applies to the water column and is designed to protect humans from the effects of contaminants in sources of drinking water; it is referred to as a Health (Water Source) or H(W S) value.

Regulations (6 NYCRR 702.15) require that a water quality guidance value be based on the procedures in sections 702.3 through 702.7, or a "general organic guidance value" of 50 ug/L. Potential water quality values for n-butanol (1-butanol) are derived below, and the general organic guidance value of 50 ug/L was selected as described under "Selection of Value."

PRINCIPAL ORGANIC CONTAMINANT CLASSES AND SPECIFIC MCL (702.3)

A. Discussion

n-Butanol does not have a Specific MCL for New York State as defined in 700.1. It is not in a principal organic contaminant class as defined in 700.1.

For information, US EPA does not regulate n-butanol under the federal Safe Drinking Water Act. Also for information, the New York State Department of Health has a maximum contaminant level (MCL) of 50 ug/L for drinking water for n-butanol based on its categorization as an unspecified organic contaminant (UOC). Under the State Sanitary Code (10 NYCRR Part 5), this UOC MCL applies to any organic chemical that does not have a specific MCL and is not a principal organic contaminant.

B. Derivation of Water Quality Value

Because n-butanol does not have a Specific MCL and is not in a principal organic contaminant class, a water quality value cannot be derived based on 702.3.

ONCOGENIC EFFECTS (702.4)

US EPA (1998) places n-butanol in Class D (not classifiable as to human carcinogenicity), because of inadequate human and animal data (See Exhibit 1). Thus, the potential for n-butanol to cause cancer is not known and n-butanol cannot be classified as an oncogen under New York State regulations (700.1). Therefore, a value based on oncogenic effects cannot be derived.

NON-ONCOGENIC EFFECTS (702.5)

A. Data

US EPA (1998) evaluated the non-oncogenic effects of n-butanol for their derivation of an oral Reference Dose (RfD), placed on their on-line integrated Risk Information System (IRIS) in 1990. The Department believes this to be an adequate review and assessment of the literature through the late 1980s. A search of more recent literature, conducted for the Department by the New York State Library, found a few additional studies, which are described below.

US EPA's (1998) oral RfD of 0.1 mg/kg/day (Exhibit 1) is comparable to an acceptable daily intake, or ADI, under 702.5. The RfD is based on a no-observed-adverse-effect level (NOAEL) of 125 mg/kg/day, for hypoactivity and ataxia in rats exposed by gavage for 13 weeks (US EPA, 1986). The study consistently demonstrated these effects at 500 mg/kg/day and the lack thereof at 125 mg/kg/day.

In a separate, 13-week drinking water study, on male Wistar rats, Wakabayashi et al. (1984) found adverse effects on liver mitochondrial structure and function at the only dose-level tested (6.9%). US EPA (1989) calculated a dosage of 6,990 mg/kg/day for this, which would represent a lowest-observed-adverse-effect level (LOAEL) for this study.

Nelson et al. (1989 a,b,c) evaluated the developmental toxicity of inhalation exposure to n-butanol in rats. In one report (Nelson et al., 1989a), 15 pregnant female Sprague-Dawley rats were exposed to 3,000 to 6,000 ppm 7hr/day throughout gestation. Eighteen males were similarly exposed for 6 weeks and mated to unexposed females. The authors reported “few” neurochemical or behavioral alterations in the offspring. Although results from the photoelectric activity monitor in female offspring from males exposed at the low dose were significantly lower than controls, it is unclear whether this demonstrates a LOAEL. However the higher concentration exposure to males did result in elevations in brain serotonin and dopamine in offspring ($p < 0.05$).

Nelson et al. (1989b), from a study in which male and female Sprague-Dawley rats were exposed to unspecified concentrations in a similar protocol to that above, reported that defects in offsprings were noted from n-butanol but only at concentrations above 5,000 ppm, which also produced maternal toxicity.

Nelson et al. (1989c) exposed about 15 pregnant Sprague-Dawley rats to 0, 3,500, 6,000, or 8,000 ppm n-butanol 7hr/day over gestation days 1-19. Fetal weight was reduced at 6,000 but not 3,500 ppm ($p < 0.05$). By those authors’ calculation, 3,500 ppm equals a daily absorbed dose of 350 mg/kg/day, which represents a NOAEL for this study.

B. Derivation of Value

The study by US EPA (1986), as used by US EPA to derive the oral RfD, is selected as the most appropriate basis to derive a potential ambient water quality value because of the oral route of exposure and that it showed effects at a lower dose than Nelson et al. (1989c). A total uncertainty factor (UF) of 1,000 is applied to the NOAEL of 125 mg/kg/day, consistent with the procedures in 702.5 for an animal study of less than chronic duration. The total UF of 1,000 consists of factors of 10 each to account for intraspecies (human) variability in sensitivity, interspecies differences and for the use of a study of less than chronic duration. An ADI is calculated as follows:

$$\text{ADI} = \frac{\text{NOAEL}}{\text{UF}} = \frac{125 \text{ mg/kg/day}}{1,000} = 0.125 \text{ mg/kg/day}$$

From this ADI, an ambient water quality value is calculated, using a human body weight of 70 kg, a daily water consumption rate of 2 L/day, and apportioning 20% of the ADI to drinking water:

$$\begin{aligned} \text{Water Quality Value} &= \frac{(0.125 \text{ mg/kg/day}) (1000 \text{ ug/mg}) (70 \text{ kg}) (0.2)}{(2 \text{ L/day})} \\ &= 875 \text{ ug/L, rounded to } 900 \text{ ug/L} \end{aligned}$$

CHEMICAL CORRELATION (702.7)

A potential water quality value for n-butanol using chemical correlation was not derived because relevant information upon which to base such a value was not found.

SELECTION OF VALUE

The regulations in 702.15 require that a guidance value be the more stringent of the values derived by applying the procedures from 702.3 through 702.7, or the “general organic guidance value” of 50 ug/L. The latter may be applied only where there are insufficient data to justify values greater than 50 ug/L for at least one of sections 702.4 or 702.5. There are data gaps for n-butanol for both oncogenic and non-oncogenic effects. The lack of cancer study data and lack of lifetime studies for non-oncogenic effects both preclude the use of the value of 900 ug/L based on the 13-week rat study described above. Because of these significant data gaps, the ambient water quality guidance value for n-butanol is derived by applying the general organic guidance value of 50 ug/L.

REFERENCES

Nelson, B.K., W.S. Brightwell, S.K. Robertson, A. Khan, E.F. Krieg, Jr. and V.J. Massari. 1989a. Behavioral teratology investigation of 1-butanol in rats. *Neurotoxicology and Teratology* 11:313-315.

Nelson, B.K., W.S. Brightwell and E.F. Krieg. 1989b. Developmental toxicology of industrial alcohols: a summary of 13 alcohols administered by inhalation to rats. *Teratology* 39(5): 471.

Nelson, B.K., W.S. Brightwell, A. Khan, J.R. Burg and P.T. Goad. 1989c. Lack of selective developmental toxicity of three butanol isomers administered by inhalation to rats. *Fundamental and Applied Toxicology* 12:469-479.

6 NYCRR (New York State Codes, Rules and Regulations). Water Quality Regulations, Surface Water and Groundwater Classifications and Standards: Title 6, Chapter X, Parts 700 - 706. Albany, NY: New York State Department of Environmental Conservation.

10 NYCRR (New York State Codes, Rules and Regulations). Public Water Systems: Title 10 NYCRR, Chapter 1, State Sanitary Code, Subpart 5-1. Albany, NY: New York State Department of Health, Bureau of Public Water Supply Protection.

USEPA (U.S. Environmental Protection Agency). 1986. Butanol: Rat oral subchronic toxicity study. Office of Solid Waste, Washington D.C. [As cited by U.S. EPA, 1998]

US EPA (U.S. Environmental Protection Agency). 1989. Health and Environmental Effects Document for 1-Butanol. EPA/600/8-90/031. PB91-216465. Cincinnati, OH: Environmental Criteria and Assessment Office.

US EPA (U.S. Environmental Protection Agency). 1998. n-Butanol. On-Line as of September 24. Integrated Risk Information System (IRIS).

Wakabayashi, T., M. Horiuchi, M. Sakaguchi, H. Onda and M. Iijima. 1984. Induction of megamitochondria in the rat liver by N-propyl alcohol and N-butyl alcohol. Acta. Pathol. Jap. 34 (3) : 471-480. [As cited in US EPA, 1989].

New York State Department of Environmental Conservation
Division of Water
SJS
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Exhibit 1 for n-Butanol (Excerpted from U.S. EPA's on-line Integrated Risk Information System (IRIS). Sept. 24, 1998).

0140

n-Butanol; CASRN 71-36-3 (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 n-Butanol

File On-Line 03/31/87

<u>Category (section)</u>	<u>Status</u>	<u>Last Revised</u>
Oral RfD Assessment (I A)	on-line	09/01/90
Inhalation RfC Assessment (I B)	no data	
Carcinogenicity Assessment (II)	on-line	03/01/91

I. CHRONIC HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

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

Substance Name -- n-Butanol

CASRN -- 71-36-3

Last Revised -- 09/01/90

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

<u>Critical Effect</u>	<u>Experimental Doses*</u>	<u>UF</u>	<u>MF</u>	<u>RfD</u>
Hypoactivity and ataxia	NOAEL: 125 mg/kg/day LOAEL: 500 mg/kg/day	1000	1	1E-1 mg/kg/day

Rat Oral Subchronic Study

U.S. EPA, 1996

*Conversion Factors: none

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

U.S. EPA. 1986. Butanol: Rat oral subchronic toxicity study. Office of Solid Waste, Washington, DC.

Four groups of male and female rats (30/sex/group) were dosed daily by gavage with 0, 30, 125 and 500 mg/kg/day of butanol for 13 weeks. Six weeks after the initiation of dosing, an interim sacrifice of 10 rats/sex was performed to evaluate clinical, biochemical and gross morphological changes. The remaining animals continued in the experiment until the day of the final sacrifice (day 92 or 93). Data generated from this study on body and organ weight changes, food consumption, moribundity, mortality, and ophthalmological, gross, and histopathologic examinations did not show any dose-related differences between control and treated animals. Slight but significant reductions in some hematologic parameters were observed in the mid- and high-dosed females at the interim, but not at final sacrifice. This effect was considered to be transitory rather than adverse. Ataxia and hypoactivity were consistently observed in high-dosed (500 mg/kg/day) males and females during the final 6 weeks of the dosing period. Thus, the 125 mg/kg/day dose of butanol is considered a NOAEL for central nervous system effects in rats. By application of an uncertainty factor of 1000, an RfD of 0.1 mg/kg/day or 9 mg/day for a 70 kg-person is derived.

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

UF -- An uncertainty factor of 1000 was applied: 10 for intraspecies variability, 10 for interspecies extrapolation, and 10 for expanding subchronic to long-term exposure.

MF -- None

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

Sterner et al. (1949) reported that occupational exposure to 100 ppm (300 mg/cu.m) butanol had no impact on workers' health. This 10-year study included hematological evaluations, test of liver function, urine analysis, chest X-rays, ophthalmological examinations, and comparison of absenteeism among butanol-exposed men vs. all men in the plant. Details of the experimental protocol of this study were not available for risk analysis. Several other human inhalation studies have reported irritations to eyes, nose, and throat, and mild headaches, at concentrations of 50 ppm (150 mg/cu.m) or higher; however, these effects were transitory in nature. An abstract of a rat inhalation study (4-month exposure) suggested a NOAEL of 0.8 mg/cu.m for reversible blood cholinesterase activity and increased thyroid activity.

I.A.5. CONFIDENCE IN THE ORAL RfD

Study -- High
Data Base -- Low
RfD -- Low

The oral subchronic study provided more than adequate toxicologic endpoints based on a very well-designed experimental protocol; therefore, a high confidence is recommended. The data base does not provide pertinent information on oral chronic or reproductive studies; therefore, a low confidence is recommended. A low to medium confidence is recommended for the RfD.

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 -- U.S. EPA, 1986 Agency Work Group Review -- 05/14/86
Verification Date -- 05/14/86

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).

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name -- n-Butanol
CASRN -- 71-36-3
Last Revised -- 03/01/91

Section II 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 exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

II.A. EVIDENCE FOR CLASSIFICATION AS TO HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CLASSIFICATION

Classification -- D; not classifiable as to human carcinogenicity

Basis -- Based on no human and no animal cancer data.

II.A.2. HUMAN CARCINOGENICITY DATA

None.

II.A.3. ANIMAL CARCINOGENICITY DATA

None.

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

1-Butanol was negative in reverse mutation and DNA damage tests in *Salmonella typhimurium* (McCann et al., 1975; Connor et al., 1985; Nakamura et al., 1987), but weakly positive for inhibition of DNA synthesis in *Escherichia coli* (Yoshiyama et al., 1973). Negative results were reported for sister chromatid exchanges in chick embryo and Chinese hamster cells and for micronucleus formation in Chinese hamster cells (Bloom, 1982; Obe and Ristowe, 1977; Lasne et al., 1984). 1-Butanol induced spindle disturbances in Chinese hamster V79 lung cells (Onfelt, 1987).

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

None.

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

None.

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

II.D.1. EPA DOCUMENTATION

Source Document -- U.S. EPA, 1989

The 1989 Health and Environmental Effects Document for 1-Butanol has received Agency and external peer review.

II.D.2. REVIEW (CARCINOGENICITY ASSESSMENT)

Agency Work Group Review -- 12/06/90

Verification Date -- 12/06/90

II.D.3. U.S. EPA CONTACTS (CARCINOGENICITY ASSESSMENT)

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).

VI. BIBLIOGRAPHY

Substance Name -- n-Butanol

CASRN -- 71-36-3

Last Revised -- 03/01/91

VI.A. ORAL RfD REFERENCES

Sterner, J.H., H.C. Crouch, H.F. Brockmyre and M. Cusak. 1949. A ten-year study of butyl alcohol exposure. Am. Ind. Hyg. Assoc. 10(3): 53-59.

U.S. EPA. 1986. Butanol: Rat oral subchronic toxicity study. Office of Solid Waste, Washington, DC.

VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Bloom, S.E. 1982. 6. Detection of sister chromatid exchanges in vivo using avian embryos. In: Cytogen. Assays Environ. Mutagens. p. 137-159.

Connor, T.H., J.C. Theiss, H.A. Hanna et al. 1985. Genotoxicity of organic chemicals frequently found in the air of mobile homes. Toxicol. Lett. 25(1): 33-40.

Lasne, C., Z.W. Gu, W. Venegas and I. Chouroulinkov. 1984. The in vitro micronucleus assay for detection of cytogenetic effects induced by mutagen-carcinogens: Comparison with the in vitro sister-chromatid exchange assay. Mutat. Res. 130(4): 273-282.

McCann, J., E. Choi, E. Yamasaki and B.N. Ames. 1975. Detection of carcinogens as mutagens in the Salmonella/microsome test: Assay of 300 chemicals. Proc. Natl. Acad. Sci. USA. 72(12): 5135-5139.

Nakamura, S., Y. Oda, T. Shimada et al. 1987. SOS-inducing activity of chemical carcinogens and mutagens in Salmonella typhimurium TA1535/pSK1002: Examination with 151 chemicals. Mutat. Res. 192(4): 239-246.

Obe, G. and H. Ristow. 1977. Acetaldehyde, but not ethanol, induces sister chromatid exchanges in Chinese hamster cells in vitro. Mutat. Res. 56(2): 211-213.

Onfelt, A. 1987. Spindle disturbances in mammalian cells. III. Toxicity, c- mitosis and aneuploidy with 22 different compounds. Specific and unspecific mechanisms. Mutat. Res. 182(3): 135-154.

U.S. EPA. 1989. Health and Environmental Effects Document for 1-Butanol. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC.

Yoshiyama, Y., K. Nagai, H. Some and G. Tamura. 1973. Selective inhibition by pantoyl lactone and butyl alcohol of the initiation of DNA replication in E. coli. Agric. Biol. Chem. 37(6): 1317-1320.