

SUMMARY OF DATA FOR CHEMICAL SELECTION

***n*-Butyl Bromide**

109-65-9

BASIS OF NOMINATION TO THE CSWG:

n-Butyl bromide is brought to the attention of the CSWG as an alkylating agent widely utilized in organic synthesis. It is also a product of a classical nucleophilic substitution reaction, which is carried out in numerous student organic chemistry laboratories. Its structural analogs, *n*-propyl bromide and isopropyl bromide, have recently been nominated by the Occupational Safety and Health Administration (OSHA) for testing by the National Toxicology Program (NTP). Lack of carcinogenicity data on these and other alkyl bromides, combined with their reported mutagenicity, warrants an investigation into the carcinogenic potential of this class of chemicals. *n*-Butyl bromide was originally considered by the CSWG in 1995, and the decision was deferred until additional human exposure data could be obtained. It is being resubmitted based on the information update.

Annual production of *n*-butyl bromide was previously estimated by the Environmental Protection Agency (EPA) to be in the range of 218 – 700 thousand pounds. Based on the 1998 Toxic Substances Control Act (TSCA) Chemical Inventory Update Rule (IUR) data, the EPA has expressed intent to include this compound in its High Production Volume (HPV) Challenge program. The US International Trade Commission (USITC) estimated the annual sales quantities of *n*-butyl bromide at 500 – 800 thousand pounds. This compound has also been identified as a drinking water pollutant. Human exposure to *n*-butyl bromide can occur via any of the three major routes: inhalation, ingestion, or dermal contact.

Suspicion of carcinogenicity of *n*-butyl bromide and other alkyl bromides is based on their alkylating ability and is reinforced by the mutagenicity data. The presence of this compound in drinking water and its wide-spread use in student laboratory experiments further contribute to the need for the evaluation of its toxicity.

INPUT FROM GOVERNMENT AGENCIES/INDUSTRY:

Dr. John Walker, Executive Director of the TSCA Interagency Testing Committee, provided the information on the annual production level of *n*-butyl bromide.

Mr. James Darr of the Office of Pollution Prevention and Toxics, EPA, provided a copy of the draft report, *Use and Exposure Profile*, for *n*-butyl bromide.

SELECTION STATUS

ACTION BY CSWG: 12/12/00

Studies requested:

- Subchronic (90-day) toxicity test
- Reproductive effects

Priority: High

Rationale/Remarks:

Mutagenic alkylating agent, suggesting strong likelihood of carcinogenic activity

Increasing usage, now reaching high production volume (>1 million lb/yr) status

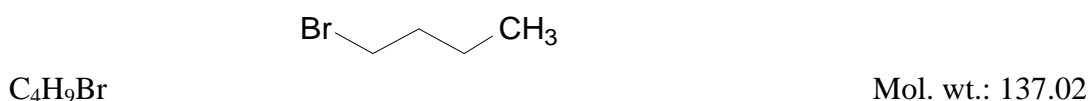
Additional usage/exposure potential in student organic chemistry laboratories that is not accounted for in EPA/ITC production figures

Consider with *n*-propyl bromide and isopropyl bromide to develop an overall testing strategy, including carcinogenicity testing, that will be applicable to alkyl bromides as a class

CHEMICAL IDENTIFICATION

<u>CAS Registry No.:</u>	109-65-9
<u>CAS Name:</u>	Butane, 1-bromo- (8CI, 9CI)
<u>Synonyms:</u>	<i>n</i> -Butyl bromide; butyl bromide; 1-bromobutane
<u>Structural Class:</u>	Alkyl bromide

Structure: Molecular Formula and Molecular Weight:



Chemical and Physical Properties:

<u>Description:</u>	Colorless liquid (Merck, 2000)
<u>Boiling Point:</u>	101.6°C (Lewis, 1993)
<u>Melting Point:</u>	-112.4°C (Lewis, 1993)
<u>Flash Point:</u>	23.9°C (Lewis, 1993)
<u>Density:</u>	1.2686 (Merck, 2000)
<u>Solubility:</u>	Insoluble in water; soluble in alcohol and ether (Lewis, 1993)
<u>Reactivity:</u>	Stable under normal temperatures and pressures; incompatible with oxidizing agents, strong bases, magnesium, sodium, potassium; extremely flammable (Fisher Scientific, 1999)
<u>Octanol/Water Partition Coefficient:</u>	Log $K_{O/W}$ = 2.75 (Hansch <i>et al.</i> , 1995)
<u>Vapor Pressure:</u>	40 mm Hg at 25°C

Technical Products and Impurities: *n*-Butyl bromide is available from Sigma-Aldrich at 99+% purity (Sigma-Aldrich, 2000). *n*-Butanol is listed as a common contaminant (0.5% w/w) of *n*-butyl bromide (Albemarle Corporation, 2000).

EXPOSURE INFORMATION

Production and Producers:

Manufacturing Process. *n*-Butyl bromide is prepared from *n*-butyl alcohol and hydrogen bromide (EPA, 1998; Especial Gas, 1998; Merck, 2000). The reaction is shown in Fig. 1.

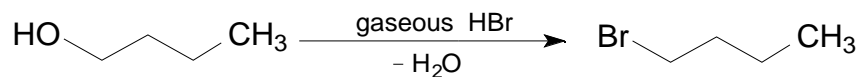


Figure 1. *n*-Butyl bromide synthesis from *n*-butanol

The compound is manufactured in a series of batch operations. *n*-Butyl alcohol is charged to a reactor where it is treated with hydrogen bromide. The gas flow is stopped when the solution reaches the designated specific gravity. The reaction product solution is transferred to the wash tank for treatment with soda ash, while the reaction product vapors are sent to condensers and then a separator. From the separator, liquid hydrobromic acid is sent to the hydrobromic acid storage tank and recycled reactants are sent to the reactor. The wash tank supernatant is sent to storage prior to packaging for shipment (EPA, 1998).

Production/Import Level. *n*-Butyl bromide is listed in the EPA's Toxic Substances Control Act (TSCA) Inventory (NLM, 1999). The annual US production of *n*-butyl bromide was reported to be in the range of 218 to 700 thousand pounds according to the non-confidential information received by the EPA for 1989 (Walker, 1995). According to the 1998 TSCA IUR data, *n*-butyl bromide production has since shown significant increase, and the EPA is planning to include this compound in its HPV Challenge program (Walker, 2000).

The draft of the EPA's 1998 Use and Exposure Profile report estimates import levels of *n*-butyl bromide at 79,000 lb/yr (EPA, 1998).

n-Butyl bromide is listed in the USITC publication *Synthetic Organic Chemicals, US Production and Sales* (USITC, 1990; USITC, 1993; USITC, 1994) (Table 1).

Although no specific production data are reported, the USITC reporting guidelines specify that each company's report of a chemical represents manufacture of a quantity of at least 4,500 kg (approx. 10,000 lb) or sales of \$10,000.

n-Butyl bromide is manufactured in the US by one known facility, whose manufacturing volume constitutes confidential business information and is not available (EPA, 1998).

**Table 1. Production/sales of *n*-butyl bromide
(USITC, 1993; USITC, 1994)**

Year	Production (kg)	Sales Quantity (lb)
1992	*	554,400
1991	*	811,800

*Reported data are accepted in confidence and may not be published, or no data were reported.

Producers and Importers: *n*-Butyl bromide is manufactured in the US by Great Lakes Chemical Corporation and is imported by D&O Chemicals, Inc. (EPA, 1998). It is distributed by 45 companies world-wide, 23 of them in the US (Chemical Sources International, 2000). The US distributors include Aceto Corporation; Albemarle Corporation; Alfa Aesar; Allied Signal, Inc., Specialty Chemicals; AmeriBrom, Inc.; Austin Chemical Company, Inc.; CBC (America) Corporation; Contract Chemicals, Inc.; Diaz Chemical Corporation; Elf Atochem; Great Lakes Chemical Corporation; Honeywell, Inc., Performance Polymers and Chemicals; J.T. Baker; Morre-Tec Industries, Inc.; Spectrum Bulk Chemicals; Storchem, Inc.; and www.fobchemicals.com (Chemyclopedia, 2000; Hunter, 2000; Tilton, 2000).

Use Pattern: *n*-Butyl bromide, which is an alkylating agent, is used as an organic laboratory reagent, an intermediate in the synthesis of other chemicals and pharmaceuticals, and a solvent (Anon, 1996; Lewis, 1993). Distillers Co., Ltd., of Great Britain was assigned a patent, which describes utilization of this compound

in production of butanol (Sherman, 1978). *n*-Butyl bromide can also be used as a chain-transfer agent for styrene polymerization (Platt & Wallace, 1983).

Human Exposure: Human exposure to *n*-butyl bromide can occur through dermal contact, inhalation, or ingestion (NLM, 2000b).

Occupational Exposure. The National Occupational Exposure Survey (NOES), which was conducted by the National Occupational Safety and Health (NIOSH) between 1981 and 1983, estimated that 1,822 workers, including 272 female employees, were potentially exposed to *n*-butyl bromide in the workplace (NLM, 1999).

Based on the data supplied voluntarily by one *n*-butyl bromide manufacturer, the EPA reports that five workers are exposed to the compound for 1 – 8 hr/d, 10 – 100 d/yr (EPA, 1998). The estimated airborne concentrations of *n*-butyl bromide are presented in Table 2 (EPA, 1998).

Of particular significance is the utilization of *n*-butyl bromide in organic chemistry teaching laboratories. It is a product of a classical nucleophilic substitution reaction carried out in student organic chemistry experiments, thus resulting in a high level of exposure among college students (Hunt, 2000; Majeti, 2000; Muzyka & Workman, 1999).

Dermal exposure could occur for workers engaged in product sampling, product drumming, and equipment maintenance (EPA, 1998). Dermal exposure is also likely in student organic chemistry laboratories. No monitoring data are available to characterize dermal exposure.

Table 2. Estimated occupational inhalation exposures associated with *n*-butyl bromide manufacturing

Worker Activity	Typical Case		Worst Case	
	Airborne concentration (mg/m ³)	Potential inhalation dose rate (mg/person/d)	Airborne concentration (mg/m ³)	Potential inhalation dose rate (mg/person/d)
Product sampling	14	140	760	7,600
Product drumming	240	2,400	22,000	220,000
Equipment maintenance	670	1,700	20,000	50,000

Environmental Occurrence: The manufacturer estimates the annual on-site land release of *n*-butyl bromide by underground injection at 31,000 lb (EPA, 1998). The manufacturer-estimated annual air releases of *n*-butyl bromide are presented in Table 3 (EPA, 1998).

Table 3. Estimated annual air releases of *n*-butyl bromide from manufacturing facilities

Facility	Fugitive Release		Stack	
	lb/yr	d/yr	lb/yr	d/yr
Great Lakes Chemical Corp.	< 0.1	38*	300	6*

*The production unit operated for 38 days in 1996. Stack releases only occurred during packaging which occurred for six days in 1996.

Regulatory Status: No standards or guidelines have been set by NIOSH or OSHA for occupational exposure to or workplace allowable levels of *n*-butyl bromide. *n*-Butyl bromide is not on the American Conference of Governmental Industrial Hygienists (ACGIH) list of compounds for which recommendations for a threshold limit value (TLV) or biological exposure index (BEI) have been made.

n-Butyl bromide is regulated as a flammable liquid by the US Department of Transportation (DOT) (University of California, 1996; NLM, 2000b).

EVIDENCE FOR POSSIBLE CARCINOGENIC ACTIVITY

Human Data: No epidemiological studies or case reports investigating the association of exposure to *n*-butyl bromide and cancer risk in humans were identified in the available literature.

Animal Data:

Carcinogenesis Studies. No two-year carcinogenicity studies of *n*-butyl bromide were found in the available literature.

Acute Studies. *n*-Butyl bromide was absorbed through the skin and found to be a skin irritant in mice and an eye irritant in rabbits (Kosenko, 1972a; Kosenko, 1973). In another study, however, topical application of *n*-butyl bromide to the dorsal surface of the ear of CBA/Ca mice did not result in skin sensitization, as determined by the local lymph node assay (Basketter *et al.*, 1992). The acute toxicity values reported for *n*-butyl bromide are presented in Table 4.

Subacute Studies. Histopathological investigation of Sprague-Dawley rats, treated with *n*-butyl bromide by gavage (50, 200, or 500 mg/kg bw) for 28 days, showed vacuolar liver cell degeneration (Eriksson *et al.*, 1993).

Subchronic Studies. Poirier and coworkers conducted a 24-week study in which groups of 10 male and 10 female strain A mice were injected intraperitoneally (ip) three times per week for a total dose of 1.2, 0.6, and 0.24 mmol/kg bw of *n*-butyl bromide. Histopathological examination showed no significant increase in lung tumor frequency. However, due to its high toxicity, fewer injections and lower doses of *n*-butyl bromide were administered, as compared to some other alkyl halides tested (Poirier *et al.*, 1975).

Table 4. Acute toxicity values for n-butyl bromide

Route	Species	Toxicity Value	Reference
Oral	Rat (Sprague-Dawley), male Rat (Sprague-Dawley), female	LD ₅₀ = 2761 mg/kg LD ₅₀ = 3161 mg/kg	Albright & Wilson, Inc., 1992 Albright & Wilson, Inc., 1992
Inhalation	Mammal (species not specified)	LC ₅₀ = 25,800 mg/m ³	Lyublina & Rabotnikova, 1974
Intraperitoneal	Rat (strain not specified) Mouse (strain not specified) Mouse (albino, outbred)	LD ₅₀ = 4450 mg/kg LD ₅₀ = 6680 mg/kg LD ₅₀ = 1424 mg/kg	Kosenko, 1972b Kosenko, 1972b Rabotnikova & Rabotnikov, 1976

Short-Term Tests: n-Butyl bromide has shown mutagenic activity in *Salmonella typhimurium* but not in *Escherichia coli*. The results of n-butyl bromide genotoxicity studies are summarized in Table 5.

Table 5. Genotoxicity studies of n-butyl bromide

Test system	Strain	Metabolic activation	Results	Reference
Ames <i>S. typhimurium</i>	TA100, TA1535	None/S-9	Positive	NLM, 2000a
<i>E. coli</i> polA Rec-assay	W3119 vs. P3478	None	Inconclusive	NLM, 1999; NLM, 2000c
Chinese hamster DNA precipitation assay	V79	None	Positive	Eriksson <i>et al.</i> , 1991

Metabolism: In a study of n-butyl bromide metabolism, female rats and rabbits were gavaged with 50 and 625 mg of n-butyl bromide, respectively, and the urine was screened for metabolites. The results are summarized in Table 6. S-Butylglutathione, S-butylcysteinylglycine, and S-butylcysteine were excreted by rats in the bile. Based on these data and the results of assays of rat and rabbit liver slices, the authors suggested a model for n-butyl bromide metabolism, which is presented in Figure 1 (James *et al.*, 1968).

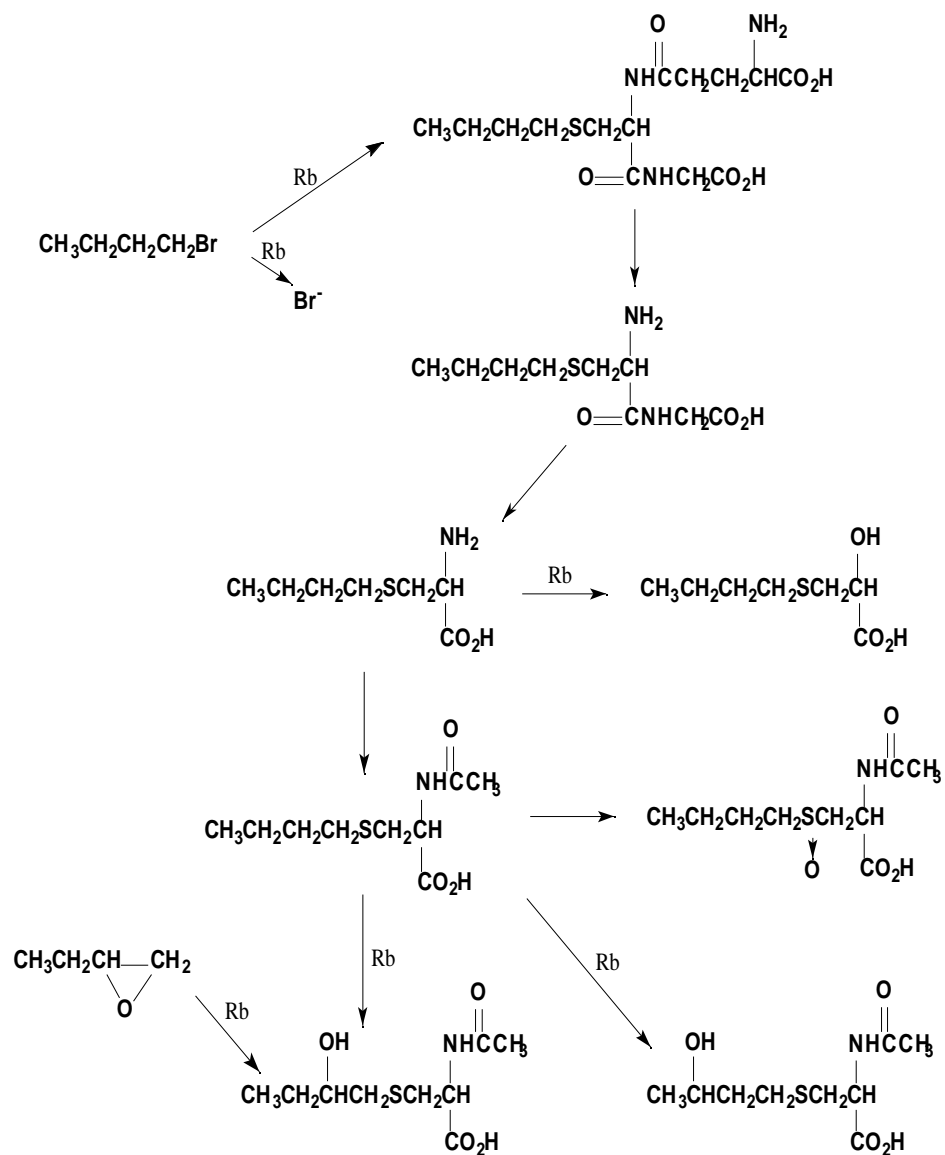


Figure 1. A schematic representation of *n*-butyl bromide metabolic pathway

All reactions occurred in the rat while those marked with Rb also occurred in the rabbit (James *et al.*, 1968).

Table 6. Metabolites of *n*-butyl bromide detected in rat and rabbit urine

Metabolite	Presence in Urine	
	Rat	Rabbit
Butylmercapturic acid	+	+
(2-Hydroxybutyl)mercapturic acid	+	Traces
(3-Hydroxybutyl)mercapturic acid	+	+*
3-(Butylthio)lactic acid	Traces	+

* Isolated as dicyclohexylammonium salt

Another study in rats demonstrated that *n*-butyl bromide administered orally (at the LD₅₀) was deposited mainly in the brain, liver, and perirenal cellular system, and excreted primarily by the lungs (Kosenko & Salyaev, 1975).

n-Butyl bromide was shown to accumulate in mouse tissues after repeated ip administration. While ethyl bromide and *n*-propyl bromide were rapidly (within minutes) detoxified in the mouse organism, detoxification of *n*-butyl bromide required approximately one day (Kosenko, 1972b). These data suggest that the detoxification rate of alkyl bromides may be a function of the length of the hydrocarbon chain.

Aberu and Emerson conducted a study, in which mice were exposed to brominated hydrocarbons, including *n*-butyl bromide, by inhalation (0.75 – 25 mmol/ml for up to 60 min). Concentrations of inorganic bromide in the liver were higher in the animals exposed to the saturated brominated hydrocarbons (including *n*-butyl bromide) than in those exposed to the unsaturated compounds. The saturated compounds also exhibited a higher degree of hydrolysis than the unsaturated compounds. It was concluded that liver tissue damage was probably caused directly by the brominated hydrocarbons rather than by hydrobromic acid which was released very slowly during hydrolysis (Aberu & Emerson, 1940).

Other Biological Effects: Treatment of freshly isolated rat hepatocytes with *n*-butyl bromide (100 μM/10⁶ cells for 1 – 60 min), depleted intracellular glutathione (GSH) levels in a time-dependent manner. Cytotoxicity of *n*-butyl bromide (5

mM) was measured by trypan blue uptake. The data are presented in Table 7 (Khan & O'Brien, 1991).

Table 7. Trypan blue uptake by *n*-butyl bromide-treated rat hepatocytes

Treatment time (hr)	0.5	1.0	2.0	3.0
Trypan blue uptake (%)	29 ± 3	45 ± 4	54 ± 5	63 ± 8

Results are expressed as an average of three experiments ± standard deviation.

Matsumoto and coworkers found that primary alkyl halides, including *n*-butyl bromide, showed second order kinetics in their reaction with the superoxide ion (rate constant for *n*-butyl bromide was 0.79×10^3 L/mol/sec); produced peroxy radicals as the major product; and were dimerized or reduced by a second superoxide ion. The dimerization or reduction occurred so rapidly (within 3 sec) that no reactivity with the radical trapping agent, 1,4-cyclohexadiene, was detected. The authors concluded the rapid formation of dimerized peroxy species and their ability to dioxygenate highly conjugated aromatic systems pose a serious biological hazard (Matsumoto *et al.*, 1988).

In pregnant rats, *n*-butyl bromide decreased the survival rate among developing embryos, impaired normal development in the postnatal period, and "increased the number of offspring with serious mutation" (Oktyabr'skii, 1977).

Structure/Activity Relationships: A structural analog of *n*-butyl bromide, *n*-propyl bromide, has been selected for carcinogenicity/toxicity testing by NTP (OSHA, 1999). Isomers of *n*-butyl bromide, iso-, *sec*-, and *tert*-butyl bromide, showed positive results in strain A mouse lung adenoma study (Poirier *et al.*, 1975). Isopropyl bromide, *sec*- and *tert*-butyl bromide, and ethyl bromide proved mutagenic in *S. typhimurium* (NLM, 2000a). The carcinogenicity and mutagenicity data on the alkyl bromides, most closely related to *n*-butyl bromide, are presented in Table 8.

Table 8. Carcinogenicity and mutagenicity studies of *n*-butyl bromide and related compounds

Compound	Carcinogenicity Data	Mutagenicity Data
<i>n</i> -Butyl bromide [109-65-9]	No effect on lung tumor frequency in strain A mice. Too toxic to test at high dose (Poirier <i>et al.</i> , 1975).	Positive in Ames test w/wo S-9 (NLM, 2000a).
Isobutyl bromide [78-77-3]	Increased lung tumor frequency in strain A mice (Poirier <i>et al.</i> , 1975).	No data found in the available literature.
<i>sec</i> -Butyl bromide [78-76-2]	Increased lung tumor frequency in strain A mice (Poirier <i>et al.</i> , 1975).	Positive in Ames test w/wo S-9 (NLM, 2000a).
<i>tert</i> -Butyl bromide [507-19-7]	Increased lung tumor frequency in strain A mice (Poirier <i>et al.</i> , 1975).	Positive in Ames test w/wo S-9 (NLM, 2000a).
<i>n</i> -Propyl bromide [106-94-5]	No data found in the available literature.	No data found in the available literature.
Isopropyl bromide [75-26-3]	No data found in the available literature.	Positive in <i>S. typhimurium</i> TA100 and TA1535 w S-9; negative in <i>S. typhimurium</i> TA98 and TA1537 w/wo S-9; negative in <i>E. coli</i> WP2 <i>uvrA</i> (NLM, 2000a).
Ethyl bromide [74-96-4]	Induced adrenal medulla tumors in male F344 rats and uterine tumors in B6C3F1 mice (NLM, 2000a).	Positive in Ames test w/wo S-9 (NLM, 2000a).

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