

***n*-BUTYL ACETATE**
CAS # 123-86-4
ORAL RISK ASSESSMENT DOCUMENT



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EXECUTIVE SUMMARY

n-Butyl Acetate – Oral Risk Assessment CAS # 123-86-4			
PARAMETER	LEVEL	UNITS	CALCULATED
NOAEL (no observed-adverse-effect level)	600	mg/kg-day	From a 13-week gavage study in rats
Oral RfD (oral reference dose)	0.2	mg/kg-day	From a 13-week gavage study in rats
TAC (total allowable concentration)	1	mg/L	For a 70 kg adult drinking 2 L/day with a 20% Relative Source Contribution for drinking water.
SPAC (single product allowable concentration)	0.1	mg/L	For a 70 kg adult drinking 2 L/day.
STEL (short term exposure level)	20	mg/L	From a 13-week gavage study in rats, for a 10 kg child drinking 1 L/day.
KEY STUDY	General Foods Corporation. 1978. Butyl Acetate. Ninety-Day Oral Toxicity Study in Rats. Report Number 377-004. Prepared by General Food Corporation. October 2.		
CRITICAL EFFECT(S)	In both sexes, dose-related stomach lesions and reduced motor activity.		
UNCERTAINTY FACTORS	Factors applied in calculating the oral RfD: • 10x for interspecies extrapolation • 10x for intraspecies extrapolation • 10x for subchronic to chronic extrapolation • 1x for extrapolation from a LOAEL to a NOAEL • 3x for database deficiencies The total uncertainty factor is therefore 3,000x.		
TOXICITY SUMMARY	The critical study chosen to derive the oral RfD was a 13-week gavage study in which rats were administered 0, 600, 2,000, or 6,000 mg/kg-day of n-butyl acetate in corn oil. The low dose was considered the NOAEL. At the mid dose, which was considered the LOAEL, histopathological examination revealed slight to moderate stomach lesions, described as inflammatory infiltrates, edema, degeneration, and/or necrosis of the non-glandular and/or glandular mucosa and submucosa, and/or epithelial hyperkeratosis and acanthosis. The stomach lesions were observed in 3/20 male rats and 3/20 female rats. Reduced motor activity was also observed, but quantitative data were not provided. At the high dose, the incidence of stomach lesions and reduced motor activity increased, such that the stomach lesions were observed in 11/20 males and 10/20 females. Quantitative data for reduced motor activity were again not provided. Sedation and hypoactivity were also observed in a subchronic gavage study in mice and two subchronic inhalation studies in rats. The gavage study was chosen as the key study, since an oral study is more appropriate for calculation of the RfD. In developmental studies in rabbits and rats, statistically significant increases in retinal folds, misaligned sternalbrae, and clear gallbladders were observed in the offspring of rabbit dams inhaling human equivalent doses of 2,030 mg/kg n-butyl acetate for seven hours/day during GD 1-19. In rats, a statistically significant reduction in fetal size and increased incidences of hydroureters, rib dysmorphology, and reduced pelvic ossification were observed in offspring from dams inhaling human equivalent doses of 2,030 mg/kg n-butyl acetate for seven hours/day during various gestational and non-gestational exposure paradigms. Reduced food consumption and body and/or organ weight changes were observed in both rabbit and rat dams. The mode of action of the stomach lesions is unknown. Since n-butyl acetate is rapidly metabolized to n-butanol in the blood and brain, the likely mediator of the sedation and hypoactivity caused by n-butyl acetate is n-butanol. n-Butyl acetate was not genotoxic in <i>Salmonella</i>, <i>E. coli</i>, <i>S. cerevisiae</i>, or Chinese hamster ovary cell assays.		
CONCLUSIONS	The critical effects of oral exposures to n-butyl acetate in rats are stomach lesions and reduced motor activity. Due to the lack of chronic data in humans and laboratory animals, the carcinogenic potential of n-butyl acetate <i>cannot be determined</i>. The weight of genotoxicity evidence suggests that n-butyl acetate is not genotoxic. The uncertainty factors used to account for the database deficiencies, such as the lack of adequate oral studies, and two-generation reproduction or immunological data, should ensure that the drinking water action levels are protective of human health.		

1.0 INTRODUCTION

This document has been prepared to allow toxicological evaluation of the unregulated contaminant **n-butyl acetate** in drinking water, as an extractant from one or more drinking water system components evaluated under NSF/ANSI 61 (2002), or as a contaminant in a drinking water treatment chemical evaluated under NSF/ANSI 60 (2002). Both non-cancer and cancer endpoints have been considered, and risk assessment methodology developed by the U.S. Environmental Protection Agency (U.S. EPA) has been used.

Non-cancer endpoints are evaluated using the reference dose (RfD) approach (Barnes and Dourson, 1988; Dourson, 1994; U.S. EPA, 1993), which assumes that there is a threshold for these endpoints that will not be exceeded if appropriate uncertainty factors (Dourson et al., 1996) are applied to the highest dose showing no significant effects. This highest dose is derived from human exposure data when available, but more often is derived from studies in laboratory animals. Either the no-observed-adverse-effect level (NOAEL) taken directly from the dose-response data, or the calculated lower 95% confidence limit on the dose resulting in an estimated 10% increase in response (the LED₁₀ or BMDL from benchmark dose programs) can be used (U.S. EPA, 2001). The lowest-observed-adverse-effect level (LOAEL) can also be used, with an additional uncertainty factor, although the benchmark dose approach is preferred in this case. The RfD is expressed in mg/kg-day. It is defined by the U.S. EPA as “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” (Barnes and Dourson, 1988; U.S. EPA, 1993; U.S. EPA, 1999a).

NSF uses the RfD to derive three product evaluation criteria for non-cancer endpoints. The total allowable concentration (TAC), generally used to evaluate the results of extraction testing normalized to static at-the-tap conditions, is defined as the RfD multiplied by the 70 kg weight of an average adult assumed to drink two liters of water per day. A relative source contribution (RSC), to ensure that the RfD is not exceeded when food and other non-water sources of exposure to the chemical are considered, is also applied in calculating the TAC. The relative source contribution should be data derived, if possible. Alternately, a 20% default contribution for water can be used (U.S. EPA, 1991a). The TAC calculation is then as follows:

$$\text{TAC (mg/L)} = \frac{[\text{RfD (mg/kg-day)} \times 70 \text{ kg}] - [\text{total contribution of other sources (mg/day)}]}{2\text{L/day}}$$

or

$$\text{TAC (mg/L)} = \frac{\text{RfD (mg/kg-day)} \times 70 \text{ kg}}{2\text{L/day}} \times 0.2 \text{ (RSC)}$$

The single product allowable concentration (SPAC), used for water treatment chemicals and for water contact materials normalized to flowing at-the-tap conditions, is the TAC divided by the estimated total number of sources of the substance in the drinking water treatment and distribution system. In the absence of source data, a default multiple source factor of 10 is used.

This accounts for the possibility that more than one product in the water and/or its distribution system could contribute the contaminant in question to drinking water.

Finally, a short-term exposure level (STEL), at a higher level than the TAC, may be calculated for contaminants such as solvents expected to extract at higher levels from new product, but also expected to decay rapidly over time. The STEL is calculated from the NOAEL or the LED₁₀ of an animal study of 14- to 90-days duration, with uncertainty factors appropriate to the duration of the study. The contaminant level must decay to the TAC or below under static conditions, or to the SPAC or below under flowing conditions within 90 days, based on the contaminant decay curve generated from over-time laboratory extraction data.

Endpoints related to cancer are evaluated using modeling to fit a curve to the appropriate dose-response data (U.S. EPA, 1996a; U.S. EPA, 1999b). If there is sufficient evidence to use a non-linear model, the LED₁₀ or BMDL, divided by the anticipated exposure, is calculated to give a margin of exposure. If there is insufficient evidence to document non-linearity, a linear model drawing a straight line from the LED₁₀ or BMDL to zero, is used as a default. If a linear model (generally reflecting a genotoxic carcinogen) is used, a target risk range of 10^{-6} to 10^{-4} is considered by the U.S. EPA to be safe and protective of public health (U.S. EPA, 1991a). For the purposes of NSF/ANSI 60 (2002) and 61 (2002), the TAC is set at the 10^{-5} risk level, and the SPAC is set at the 10^{-6} risk level. Use of a higher risk level is not ruled out but would generally require documentation of a benefit to counteract the additional risk.

The RfD, TAC, SPAC, and STEL values derived in this document are based on available health effects data and are intended for use in determining compliance of products with the requirements of NSF/ANSI 60 (2002) and 61 (2002). Application of these values to other exposure scenarios should be done with care, and with a full understanding of the derivation of the values and of the comparative magnitude and duration of the exposures. These values do not have the rigor of regulatory values, as data gaps are generally filled by industry or government studies prior to regulation. Data gaps introduce uncertainty into an evaluation and require the use of additional uncertainty factors to protect public health.

The general guidelines for this risk assessment include those from the National Research Council (1983) and from The Presidential/Congressional Commission on Risk Assessment and Risk Management (1997a, 1997b). Other guidelines used in the development of this assessment may include the following: Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986a), Proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996a), draft revised Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1999b), Guidelines for Developmental Toxicity Risk Assessment (U.S. EPA, 1991b), Guidelines for Reproductive Toxicity Risk Assessment (U.S. EPA, 1996b), Guidelines for Neurotoxicity Risk Assessment (U.S. EPA, 1998), Recommendations for and Documentation of Biological Values for Use in Risk Assessment (U.S. EPA, 1988), and Health Effects Testing Guidelines (U.S. EPA 1996c, OPPTS series 870; U.S. EPA, 2002a, 40 CFR Part 798).

The literature search strategy employed for this compound was based on the Chemical Abstract Service Registry Number (CASRN) and at least one common name. As a minimum, the following data banks were searched:

- CHEMID Plus
- Registry of Toxic Effects of Chemical Substances (RTECS)
- Hazardous Substances Data Bank (HSDB)
- GENE-TOX
- Environmental Mutagen Information Center (EMIC)
- Environmental Mutagen Information Center Backfile (EMICBACK)
- Developmental and Reproductive Toxicology (DART)
- Environmental Teratology Information Center Backfile (ETICBACK)
- TOXLINE
- CANCERLINE
- Chemical Carcinogenesis Research Information System (CCRIS)
- Integrated Risk Information System (IRIS)
- Syracuse Research Corporation Online Toxic Substance Control Act Database (TSCATS)

2.0 PHYSICAL AND CHEMICAL PROPERTIES

n-Butyl acetate is an aliphatic ester of butyl alcohol and acetic acid, and has the following structure:



It has synonyms of acetic acid, butyl ester; acetic acid n-butyl ester; butyl acetate; 1-butyl acetate; and butyl ethanoate.

The physical and chemical properties of n-butyl acetate are listed in Table 1.

Table 1. Physical and chemical properties of n-butyl acetate

Property	Data	Reference
Empirical Formula	C ₆ H ₁₂ O ₂	HSDB, 2001
CAS#	123-86-4	HSDB, 2001
Molecular Weight	116.1596	Lide, 1996
Physical State and Color	Colorless liquid	NIOSH, 1997
Melting Point	-78 °C	Lide, 1996
Boiling Point	126.1 °C	Lide, 1996
Density	0.8826 g/mL @ 20 °C	Budavari, 1996
Vapor Pressure	11.5 mm Hg @ 25 °C	Daubert and Danner, 1989
Water Solubility	14 g/L @ 20 °C 5 g/L @ 25 °C	Verschuren, 1983
Dissociation Constant (pK _a)	Not located	
n-Octanol/Water Partition Coefficient (log K _{ow})	1.85 (estimated)	SRC, 2001 http://esc.syrres.com
Henry's Law Constant (air/water partition)	2.8X10 ⁻⁴ atm-m ³ /mole	Staudinger and Roberts, 1996

2.1 Organoleptic Properties

It has been reported that n-butyl acetate has a strong, fruity odor (Lewis, 1993; Ruth, 1986), a pleasant, banana-like odor (Furia, 1980), or a sweet odor (Verschueren, 1983). n-Butyl acetate has been reported to have a “burning then sweet taste reminiscent of pineapple” (Furia and Bellanca, 1975), or a pleasant, banana-like taste (Furia, 1980). Odor thresholds have been reported as 0.066 mg/L in water (Verschueren, 1983) and 33.13 mg/m³ (odor low) and 94.66 mg/m³ (odor high) in air (Ruth, 1986).

3.0 PRODUCTION AND USE

3.1 Production

In 1993, the U.S. production of n-butyl acetate was reported to be 1.3×10^8 kilograms (approximately 286 million pounds) (U.S. ITC, 1994). In 1990, n-butyl acetate was listed on the U.S. EPA High Production Volume (HPV) chemical list, indicating that it was produced in or imported to the U.S. in amounts over one million pounds per year (U.S. EPA, 2002b).

3.2 Use

The U.S. Food and Drug Administration (U.S. FDA, 2002), in 21 CFR 172.515, permits the use of n-butyl acetate as a food additive for direct addition to food for human consumption as a synthetic flavoring substance and adjuvant. n-Butyl acetate is also listed under 21 CFR 175.320 as an adjuvant for the food contact surface of resinous and polymeric coatings for polyolefin films, and under 21 CFR 177.1200, at up to 0.1% in cellophane and water-insoluble hydroxyethyl cellulose films. According to the Priority-Based Assessment of Food Additives database, the consumption of n-butyl acetate in the United States is approximately 3,400 pounds per year (U.S. FDA, 2000), but it was not specified how this figure was determined.

n-Butyl acetate is also used as a solvent for inks, adhesives, nitrocellulose-based lacquers, and automotive coatings (SRC, 2001). The cosmetic uses of n-butyl acetate are as a solvent in nail polish, nail polish removers, basecoats, and other manicuring preparations (CIREPS, 1989). In 1987, 566 cosmetic products were reported to contain n-butyl acetate, with the majority of the uses in the > 10-25% range (CIREPS, 1989).

4.0 ANALYTICAL METHODS

4.1 Analysis in Water

In water, NSF International uses a modified U.S. EPA Method 625 gas chromatography/mass spectrometry (GC/MS) method to detect n-butyl acetate with a detection limit of 0.004 mg/L.

4.2 Analysis in Biological Matrices

Gas chromatography/mass spectrometry was used to identify and quantitate n-butyl acetate in heparinized whole blood samples isolated from adult humans exposed to a mixture of volatile organic compounds, which included n-butyl acetate (Ashley and Prah, 1997). Although a detection limit was not specified, concentrations of n-butyl acetate as low as 0.00033 ± 0.00008 ppm were reported. Gas chromatography/mass spectrometry was also used to identify n-butyl acetate in the stomach, blood, and urine of an adult human poisoned with an unknown dose of furniture varnish containing n-butyl acetate (Tkachenko and Tishchenko, 1976). The sample preparation procedures, concentrations of n-butyl acetate, or the detection limit were not specified.

Reverse phase high performance liquid chromatography (HPLC) with flow-through radiochemical detection was used to determine the concentration of ^{14}C -n-butyl acetate in heparinized whole blood and brain homogenates isolated from Sprague-Dawley rats intravenously administered ^{14}C -n-butyl acetate (Deisinger and English, 1997). The heparinized whole blood and brain samples were deproteinized with sodium tungstate and cupric sulfate. The column effluent was mixed with scintillant before radiochemical detection. Although a detection limit was not specified, mean normalized concentrations as low as $0.29 \mu\text{g}$ equivalents/gram of n-butyl acetate were reported. In the same study, liquid scintillation spectrometry was used to quantitate the total radiochemical concentration of ^{14}C -n-butyl acetate in heparinized whole blood and brain homogenates, which were solubilized in Flourosol before counting. Although a detection limit was not specified, mean normalized concentrations as low as $3 \mu\text{g}$ equivalents/gram of n-butyl acetate were reported.

5.0 SOURCES OF HUMAN AND ENVIRONMENTAL EXPOSURE

5.1 Sources of Human Exposure

In the National Occupational Exposure Survey conducted from 1981-1983, NIOSH statistically estimated that 720,812 workers, of which 123,854 were female, were potentially exposed to n-butyl acetate in the U.S. (NIOSH, 1983). Occupational exposure to n-butyl acetate may be through inhalation or dermal contact at workplaces where n-butyl acetate is produced or used (SRC, 2001).

The general population may be exposed to n-butyl acetate through the inhalation of ambient air and the ingestion of drinking water (SRC, 2001). N-butyl acetate occurs naturally in many fruits and plants (SRC, 2001). Dermal contact can occur through the use of nail polish, since n-butyl acetate is a common solvent in nail polish (Hausen et al., 1995; CIREPS, 1989).

The general population may also be exposed to n-butyl acetate through the ingestion of food sources that contain n-butyl acetate, as n-butyl acetate is a food additive permitted for direct addition to food for human consumption, and an adjuvant for the food contact surface of coatings for polyolefin films, cellophane, and hydroxyethylcellulose films. n-Butyl acetate also occurs naturally in bananas and related fruits (ACGIH, 1996). According to the Priority-based Assessment of Food Additives database, the per capita human consumption of n-butyl acetate is

approximately 0.003 mg/kg-day (U.S. FDA, 2000). The concentration in foodstuffs such as baked goods, dairy products, chewing gum, and candy ranges from 3-450 ppm. The concentration in fruits, such as guava, passion fruit and grapes, ranges from 0-0.2 ppm, and the concentration in beverages (unspecified non alcoholic and alcoholic, such as rum and wine) ranges from 0.01-20 ppm (RIFM, 2001).

n-Butyl acetate has been detected in the extractant water from drinking water system components tested to NSF/ANSI 61 requirements at normalized concentrations up to 1.5 mg/L in epoxy coatings, 0.001 mg/L in CPVC fittings, and 0.02 mg/L in tank liners.

5.2 Sources of Environmental Exposure

The production and use of n-butyl acetate as a solvent for inks, adhesives, nitrocellulose-based lacquers and automotive coatings may lead to its release to the environment through various waste streams (SRC, 2001). n-Butyl acetate occurs naturally in plants and may be released into the environment as a plant volatile (Guenther et al., 1994).

6.0 COMPARATIVE KINETICS AND METABOLISM IN HUMANS AND LABORATORY ANIMALS

The available data demonstrate that n-butyl acetate is absorbed into the bloodstream after oral and inhalation exposure in humans. In animals, n-butyl acetate is rapidly metabolized to n-butanol in the blood and brain after intravenous administration. No comparative human or animal kinetic or metabolic data were located.

6.1 Absorption

6.1.1 Humans

6.1.1.1 Oral Exposure

n-Butyl acetate was detected by GC/MS analysis in the stomach, blood and urine of an adult (sex unspecified) fatally poisoned with an unknown quantity of furniture varnish containing n-butyl acetate among four other unspecified chemicals (Tkachenko and Tishchenko, 1976). The time course of the analysis and the concentrations of n-butyl acetate detected were not specified.

6.1.1.2 Inhalation Exposure

Five adult volunteers (four men and one woman) were exposed to a mixture of 21 volatile organic compounds, including n-butyl acetate, at either 3.2 ppm or 6.4 ppm for either four or six hours. Based on a default human inhalation rate of 20 m³/day and body weight of 70 kg, the 3.2 ppm dose is equivalent to 0.7 mg/kg-day for a four-hour exposure and 1.1 mg/kg-day for a six-hour exposure, and the 6.4 ppm dose is equivalent to human oral doses of approximately 1 mg/kg-day for a four-hour exposure and 2 mg/kg-day for a 6-hour exposure. Plateau blood concentrations 50-240 minutes after the four-hour exposure were 0.00033 ± 0.00008 ppm after exposure to 3.2 ppm of the mixture, and 0.00048 ± 0.00021 ppm after exposure to 6.4 ppm of the

mixture. The authors stated that the pattern after the six-hour exposure was similar, although data were not reported (Ashley and Prah, 1997).

6.1.2 Laboratory Animals

No studies reporting the absorption of n-butyl acetate in laboratory animals were located.

6.2 Distribution

6.2.1 Humans

n-Butyl acetate was detected in the stomach, blood, and urine of an adult fatally poisoned with furniture varnish containing n-butyl acetate (Tkachenko and Tishchenko, 1976).

6.2.2 Laboratory Animals

No studies reporting the distribution of n-butyl acetate in laboratory animals were located.

6.3 Metabolism

The available data demonstrate that rapid hydrolysis of n-butyl acetate to its corresponding acid and alcohol occurs *in vivo* in the blood and brain and *in vitro* in the intestines and liver of rats, but no human data are available.

6.3.1 Humans

No studies reporting the metabolism of n-butyl acetate in humans were located.

6.3.2 Laboratory Animals

6.3.2.1 *In vivo*

An intravenous administration study in rats was conducted by Eastman Kodak to determine the rate of hydrolysis of n-butyl acetate in the blood and brain (Deisinger and English, 1997). ^{14}C -n-butyl acetate (99.9% as a 5.5 mg/mL solution in 0.9% sodium chloride) was administered through the tail vein of 32 male Sprague-Dawley rats at a mean concentration of 30.2 ± 0.1 mg/kg (16.8 ± 0.6 $\mu\text{Ci}/\text{rat}$), followed by liquid scintillation analysis of whole blood and brain tissue. Four animals at each of eight time points ranging from approximately two minutes to one hour after dosing were studied. High performance liquid chromatography with flow-through radiochemical detection was used to quantitate n-butyl acetate, the hydrolysis product, n-butanol, and the corresponding n-butanol oxidative and conjugative metabolites (refer to section 4.2 for sample preparation and procedure). The authors calculated the total ^{14}C values using the total radiochemical concentration of the whole blood or brain homogenate before deproteinization divided by the specific activity of the ^{14}C -n-butyl acetate dose solution. The concentrations of the individual metabolites were calculated from the area percent of each high-performance liquid chromatography peak multiplied by the radiochemical concentration of the deproteinized sample

divided by the specific activity of the ^{14}C -n-butyl acetate dose solution. The resulting values were represented as mean μg equivalents/gram $\pm$ the standard deviation. According to the authors, the difference between the total radioactivity concentrations and the sum of each of the metabolites reflected the ^{14}C recovery efficiency of the deproteinization procedure. The results from the analysis of whole blood and brain are summarized in Table 2.

Table 2. Mean concentrations of n-butyl acetate and metabolites in whole blood and brain following intravenous administration of $30.2 \pm 0.1 \text{ mg/kg } ^{14}\text{C}$ -n-butyl acetate [μg equivalents/gram ($\pm$ standard deviation), modified from Deisinger and English, 1997]

Sampling Time in Minutes	n-Butyl Acetate	n-Butanol	n-Butyric Acid	Polar Metabolites	Total Radioactivity
Whole Blood					
1.88	7.84 (4.75)	45.40 (3.91)	3.85 (2.49)	4.61 (2.30)	78.96 (10.12)
2.61	3.71 (1.01)	51.49 (14.3)	5.42 (2.02)	9.15 (3.18)	84.51 (8.59)
4.24	0.37 (0.09) ^a	20.74 (3.89)	4.83 (2.13)	12.19 (1.40)	49.04 (2.35)
7.41	ND ^b	10.02 (1.14)	5.66 (0.49)	5.92 (0.81)	33.93 (1.42)
10.19	ND	5.35 (1.86)	4.41 (0.81)	4.48 (0.92)	25.37 (2.86)
15.27	ND	1.76 (0.36)	3.90 (0.42)	2.64 (0.14)	18.75 (0.93)
20.44	ND	1.00 ^c (0.17) ^c	3.81 (0.44)	2.31 (0.63)	15.45 (1.08)
60.17	ND	ND	1.91 ^a (0.65) ^a	0.78 ^d (NA) ^c	6.27 (0.74)
Brain					
1.88	3.77 (3.84)	71.03 (10.61)	ND	ND	82.95 (17.94)
2.61	2.13 (1.11)	69.57 (10.19)	ND	0.29 ^d (NA) ^c	82.94 (12.94)
4.24	ND	27.73 (2.58)	0.48 ^d (NA) ^c	1.05 ^d (NA) ^c	37.21 (4.03)
7.41	ND	15.87 (1.53)	ND	1.61 ^d (NA) ^c	22.12 (1.64)
10.19	ND	9.95 (2.26)	ND	ND	16.15 (1.60)
15.27	ND	4.40 (0.65)	ND	ND	10.55 (0.67)
20.44	ND	3.31 ^a (0.35) ^a	ND	ND	9.02 (0.94)
60.17	ND	ND	ND	ND	4.23 (0.66)
^a metabolite detected in 3 of 4 samples ^b ND not detected (detection limit not specified) ^c metabolite detected in 2 of 4 samples ^d metabolite detected in 1 of 4 samples ^e NA not applicable					

No mortality was reported. In blood during the first four minutes following dosing, a maximum of $7.84 \pm 4.75 \mu\text{g}$ equivalents/gram of n-butyl acetate was detected, but the parent compound was not detected thereafter. n-Butanol was found at higher concentrations, but was also rapidly eliminated, since it was not detected after the 20 minute sampling time. n-Butyric acid and the early eluting polar metabolites were detected at all time points and were found to decline slowly.

In the brain, a maximum of $3.77 \pm 3.84 \mu\text{g}$ equivalents/gram of n-butyl acetate was detected, and this maximum was detected at the initial time point, approximately 1.5 minutes after dosing. The individual concentrations detected in each animal at 1.88 minutes were 2.02, 2.43, 1.15, and 9.47 $\mu\text{g/g}$. n-Butyl acetate was not detected four minutes after dosing and thereafter. n-Butanol was found at higher initial concentrations, but was also rapidly eliminated, since it was not detected after the 20-minute sampling time. n-Butyric acid and early eluting polar metabolites were either not detected or detected at only trace concentrations in one animal. The polar metabolites were

presumed by the authors to represent Krebs cycle intermediates of ^{14}C -n-butanol and/or glucuronide and sulfate conjugates of ^{14}C -n-butanol.

Estimates of various pharmacokinetic parameters in the brain and blood were determined using Minsq (1992) software, a nonlinear least squares data fitting program. The elimination half-lives for total radioactivity detected in blood and brain were determined to be 3.2 and 1.6 minutes, respectively. The elimination half-life for n-butyl acetate in blood was 0.41 minutes. Due to an insufficient number of data points, the half-life for n-butyl acetate in brain could not be determined. The volume of distribution of n-butyl acetate in blood was determined to be 155 mL/kg. The elimination half-lives for n-butanol in blood and brain were 1.0 and 1.2 minutes, respectively.

The authors estimated that hydrolysis of n-butyl acetate in blood and brain by non-specific esterases at the tested dose was 99% complete by 2.7 minutes.

6.3.2.2 *In vitro*

An *in vitro* assay showed that hydrolysis of n-butyl acetate (unspecified purity in ethanol) to butanol and acetic acid readily occurred in male F344/N rat liver (unspecified fraction) and intestinal (mucosal) homogenates, while artificial gastrointestinal juices showed relatively limited hydrolysis. The assay employed high-performance liquid chromatography with diisopropyl ether as the extractant and eucalyptol as the internal standard (Longland et al., 1977). The half-lives for n-butyl acetate hydrolysis at 37 °C in artificial gastric and pancreatic juice were 318 and 66 minutes, respectively. The half-lives for n-butyl acetate hydrolysis in rat liver and small intestinal homogenates were eight and two minutes, respectively. The authors concluded that the hydrolysis rates for n-butyl acetate were consistent with first-order kinetics.

Another *in vitro* study examined the hydrolysis rates of n-butyl acetate (purity unspecified) in male F344/N rat liver S-9 homogenates, and reported that among straight chain aliphatic alcohol acetates, n-butyl acetate had the fastest hydrolysis rate among the butyl acetate isomers. The hydrolysis rates for n-, iso-, sec-, and t-butyl acetate were 77 ± 3 , 67 ± 3 , 62 ± 3 , and 42 ± 2 nmol/mg S-9 protein/minute, respectively (Dahl et al., 1987).

6.4 Excretion

6.4.1 Humans

n-Butyl acetate was detected in the urine of an adult (sex unspecified) fatally poisoned with an unknown quantity of furniture varnish containing n-butyl acetate (Tkachenko and Tischenko, 1976). For additional study details, refer to Section 6.1.1.1.

6.4.2 Laboratory Animals

No studies reporting the elimination of n-butyl acetate in laboratory animals were located.

7.0 EFFECTS ON HUMANS

Ocular and upper respiratory tract irritation has been noted after inhalation of n-butyl acetate. After topical dermal exposure to n-butyl acetate, there was no evidence of skin irritation. Sensitization effects were not noted after dermal exposure to n-butyl acetate. No repeated-dose oral data were available.

7.1 Case Reports

An oral exposure showed detection of n-butyl acetate in the stomach, blood, and urine of an adult (sex unspecified) fatally poisoned with furniture varnish (Tkachenko and Tischenko, 1976). For additional study details, refer to Section 6.1.1.1.

7.2 Epidemiological Studies

No reports of epidemiological studies investigating exposure to n-butyl acetate alone were located.

7.3 Irritation and Sensitization Studies

7.3.1 Irritation

Several studies have reported that adult humans exposed to n-butyl acetate vapors at concentrations ranging from 2-3,300 ppm (9.5-15,700 mg/m³) for various durations, experienced eye, nose, respiratory and/or throat irritation (RIFM, 2001; HSDB, 2001). The irritant effects of inhalation exposure to n-butyl acetate were examined in 24 male and female adult humans without previous history of occupational solvent exposure. In three different experiments, after exposure to n-butyl acetate for either 20 minutes at concentrations from 70-1,400 mg/m³ or four hours at concentrations from 70-700 mg/m³, measurements of eye irritation and pulmonary function were taken. The authors concluded that there was a very slight irritation potential for airborne n-butyl acetate (Iregren et al., 1993).

The irritant effects of inhalation exposure to n-butyl acetate for three to five minutes were examined in approximately 10 (specific number not noted) male and female humans. At 200 ppm (950 mg/m³), n-butyl acetate inhalation was reported as being irritating to the throat. At 300 ppm (1,425 mg/m³), n-butyl acetate inhalation was reported as being severely irritating to the throat, and irritating to the eyes and nose of all subjects (Nelson et al., 1943).

7.3.2 Sensitization

Dermal studies showed no sensitization in adult human subjects exposed to n-butyl acetate test patches at concentrations from 4% (40,000 mg/L) to 10% (100,000 mg/L) using petrolatum as the vehicle (RIFM, 2001). Closed patch tests with 10% n-butyl acetate in white petrolatum were conducted on 12 adult females with known or suspected nail polish hypersensitivity, since n-butyl acetate is a common solvent in nail polish. The patches were applied for a one-day

duration, and reactions were assessed after both one hour and three days. No effects were noted (Hausen et al., 1995).

8.0 EFFECTS ON LABORATORY ANIMALS AND *IN VITRO* TEST SYSTEMS

8.1 Limited-Exposure Effects

8.1.1 Irritation and Sensitization Studies

Numerous reports of nose and throat irritation after inhalation exposure to n-butyl acetate vapors at concentrations ranging from 1 to 735 ppm (~50 to 35,000 mg/m³) for various time durations have been reported in rats, mice, rabbits, and cats (HSDB, 2001; RIFM, 2001). Dermal sensitization with topical 50% (500,000 mg/L) and 100% (1,000,000 mg/L) n-butyl acetate concentrations was not demonstrated in mouse ear swelling or guinea pig maximization assays, respectively (RIFM, 2001).

8.1.2 Ocular Exposure Studies

In three Draize studies, 0.1 mL of n-butyl acetate (purity unspecified) instilled in a single application into the eyes in New Zealand white rabbits had mild to moderate irritant effects, characterized by iritis and/or conjunctivitis (RIFM, 2001).

8.2 Single-Exposure Studies

Numerous acute toxicity studies have determined LD₅₀ or LC₅₀ values in rats, mice, rabbits, and guinea pigs via the dermal, oral, inhalation, and intraperitoneal routes of exposure (HSDB, 2001; RIFM, 2001). These results indicate that there are route- and species-specific differences in the acute toxicity of n-butyl acetate. Overall, the results indicate that n-butyl acetate has a low order of acute toxicity via the oral route and a moderate order of acute toxicity via the inhalation route (Table 3).

Several single-dose studies examining systemic toxicity were located in the published literature and are summarized in Table 4. The inhalation studies ranged from 20 minutes to 16 hours duration, and many demonstrated the lungs as the target organ. Systemic effects were also noted in the liver, kidney, and brain. Considerable variation occurred in inhalation results, attributed to chemical purity, head only versus whole-body exposure, and/or vapor versus aerosol exposure (Norris et al., 1997). Signs of intoxication noted after n-butyl acetate inhalation exposure have been reported as decreased activity, respiratory rate, and disturbances in locomotor activity and pain perception.