sec-Butanol

(CAS No. 78-92-2)

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CONTENTS

EXECUTIVE SUMMARY

This report has been produced as part of the Joint Assessment of Commodity Chemicals (JACC) programme. It presents a critical evaluation of the physico-chemical, ecotoxicity and toxicity data of sec butanol (sBA). Since the last comprehensive review of sBA published by IPCS[a] in 1987, new data have become available. A hazard/risk assessment will be required under current OECD/EC schemes[bc].

Almost all sBA, produced world-wide is used for the synthesis of methyl ethyl ketone (MEK). To a lesser extent, sBA is used as a solvent, and in the manufacture of other materials.

When released to the environment, sBA partitions entirely into water and air. sBA contributes to the formation of tropospheric ozone, but has a low ozone creation potential. sBA is readily biodegradable and is not expected to accumulate. sBA has a low order of toxicity at all trophic levels.

In laboratory animals, sBA is rapidly absorbed and partly excreted as sBA or in conjugated form; the major part is metabolised to MEK. For this reason, the toxicities of sBA and MEK in animals are considered to be closely similar. Accordingly, data from studies conducted with MEK were also reviewed to provide a more complete evaluation of the toxicity of sBA.

sBA has a low order of acute toxicity to laboratory animals when administered in single doses, by inhalation or otherwise. sBA is non-irritant to rabbit skin, but is severely irritant to the eye. It is not a skin sensitiser in guinea pigs.

The few repeated-dose toxicity studies on sBA are limited. However, studies with MEK suggest that sBA should be of low subchronic toxicity by the inhalation and oral routes of exposure. MEK produced minimal or no systemic effects in laboratory animals following repeated exposures to high doses.

sBA is not genotoxic and there is no concern for a carcinogenic potential.

sBA showed some foetotoxicity in laboratory animals at high concentrations toxic to the mother, but is devoid of selective developmental toxicity.

No adverse systemic effects associated with acute or repeated exposure to sBA have been reported in humans. As sBA is volatile, high exposure levels may result in acute central nervous system effects, including headache and dizziness. sBA, after transformation to MEK, may potentiate neurotoxicity of certain neurotoxic ketones; such effects, however, have not been reported so far in humans.

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[a] IPCS Environmental Health Criteria Documents [http://www.who.int/pcs/ra_site/ehc.html]

[b] OECD Existing Chemicals Programme [http://www1.oecd.org/ehs/hazard.htm]

[c] EU Existing Chemicals Work Area [http://ecb.ei.jrc.it/existing-chemicals/]

THE ECETOC SCHEME FOR THE JOINT ASSESSMENT OF COMMODITY CHEMICALS

This report has been produced by an ECETOC Task Force as part of the Joint Assessment of Commodity Chemicals (JACC) programme for preparing critical reviews of the toxicology and ecotoxicology of selected existing industrial chemicals. In the programme, commodity chemicals (i.e. those produced in large tonnage by several companies and having widespread and multiple uses) are jointly reviewed by experts from a number of companies with knowledge of the chemical. It should be noted that in a JACC review only the chemical itself is considered; products in which it appears as an impurity are not normally taken into account.

This report presents a critical evaluation of the ecotoxicology, toxicology and physico-chemical properties of *sec*-butanol (sBA; CAS No. 78-92-2). This information is supplemented by toxicological data on methyl ethyl ketone (MEK)[a], which is the metabolic oxidation product of sBA.

Where relevant, the Task Force has assigned a Code of Reliability (CoR) to (eco)toxicological studies to reflect the degree of confidence that can be placed on the reported results. The criteria used to assess and categorise reliability are included in Appendix B.

[a] A list of abbreviations used throughout this report is at Appendix A

1. SUMMARY AND CONCLUSIONS

sec-Butanol (sBA) is a colourless, flammable liquid with a pleasant odour. It is soluble in water and miscible with a large number of organic solvents. Greater than 95% of all sBA produced worldwide (approximately 900 kt/y) are dehydrogenated for the synthesis of methyl ethyl ketone (MEK). sBA is also used as a solvent, and in the manufacture of plasticisers, paints and varnishes, inks, wetting agents, and other materials.

sBA enters the environment during its production and use, and from natural sources. When released to the environment, it partitions into water and air, but does not absorb significantly to soil or sediment. sBA contributes to the formation of tropospheric ozone, but has a relatively low ozone creation potential compared to other volatile organic compounds (VOCs).

sBA is readily biodegradable and does not appear to bioaccumulate in aquatic organisms. It poses a minimal hazard to aquatic organisms, LC_{50} values are generally falling in the range of 3,000 to 4,000 mg/l in fish and daphnia, and with an EC_{50} of approximately 8,900 mg/l in algae.

Metabolism and pharmacokinetics data indicate that sBA is rapidly absorbed, partly excreted in the form of conjugates, but mostly metabolised to MEK. MEK is subsequently converted to metabolites that are exhaled, excreted in the urine, or incorporated into endogenous metabolic processes. Based on this metabolic relationship, and because no fundamental species differences are known in terms of oxidation of secondary alcohols, the toxicities of sBA and MEK in animals are considered to be closely similar. Accordingly, to provide a more complete evaluation of the toxicity of sBA, it was considered important also to review data from studies conducted with MEK.

sBA has a low order of acute toxicity with LD_{50} values of 2.2 to 6.5 g/kgbw and > 2 g/kgbw in rats for the oral and dermal routes, respectively. The LC_{50} value in rats is between 8,000 and 16,000 ppm (25,000 - 49,000 mg/m^3) for a 4-hour inhalation exposure. The data on MEK provide additional support for the low order of acute toxicity of sBA. sBA is non-irritant to rabbit skin, but is severely irritant to the eye. It was found not to be active when tested for skin sensitisation in several Magnusson-Kligman maximisation tests in guinea pigs.

There are few repeated-dose toxicity studies on sBA itself, and most of these are limited by brevity of exposure duration and the assessment of only few toxicological endpoints. Additional information from studies with MEK suggests that sBA possesses a low order of subchronic toxicity by the inhalation and oral routes of exposure. MEK produced minimal or no systemic effects in laboratory animals following repeated exposures to high doses. The only effects seen following subchronic inhalation of MEK vapour concentrations as high as 2,500 ppm (7,500 mg/m^3) were an increase in liver weight, and

a decreased body weight at 5,000 ppm (15,000 mg/m^3). Data on respiratory irritation and facilitation of bronchiopneumonia development at such levels are contradictory.

sBA showed no mutagenic activity *in vitro* when tested in a number of bacterial gene mutation assays with *Salmonella typhimurium* and in a gene conversion assay in the yeast *Saccharomyces cerevisiae*. sBA had no clastogenic activity in a chromosomal aberration assay with Chinese hamster ovary cells. Since tests with MEK failed to produce a mutagenic effect *in vivo*, it may also be concluded that sBA has no genotoxic potential. No studies have been conducted to evaluate the chronic toxicity or carcinogenic potential of sBA or MEK.

Rats were exposed to 0.3, 1 and 3% (2% in second generation) sBA in drinking water in a 2 generation reproductive toxicity study which also incorporated a developmental toxicity study. In the main study, 3% sBA caused reductions in body weight gain during pre-mating, in the number of pups born, and pup body weight, but fertility was not affected. There were no statistically significant effects reported in the second generation exposed to the reduced concentration of 2%. In the developmental toxicity study, 2% sBA caused a depression in foetal weight, and there was evidence of retarded skeletal maturation, but no skeletal or visceral malformations. The authors considered these changes as mild toxicity and reminiscent of stress lesions. The no-observed adverse effect level (NOAEL) for reproductive parameters and developmental toxicity was 1%, estimated to be between 1,500 to 1,770 mg/kgbw/d.

In a later study of developmental toxicity, rats were exposed by inhalation to 3,500, 5,000 or 7,000 ppm sBA (10,900, 15,000 or 22,000 mg/m^3) on days 1 to 19 of gestation. Maternal weight gain and food consumption were significantly reduced at all dose levels, and narcosis was observed in dams at the two high dose levels. The number of live foetuses was significantly reduced and resorptions were increased at 7,000 ppm; foetal body weights were significantly reduced at 5,000 ppm and greater. The NOAELs were 3,500 ppm sBA for developmental toxicity and less than 3,500 ppm for maternal toxicity.

In a study with MEK, a low level of developmental toxicity was reported at 3,000 ppm (9,000 mg/m^3), but the significance of the findings was considered to be questionable.

No adverse systemic effects associated with acute or repeated exposure to sBA have been reported in humans. As sBA is volatile, exposure to higher levels may result in acute effects on the central nervous system, including headache and dizziness. Though MEK, on its own does not exert neurotoxicity, it has been shown to potentiate the neurotoxicity of *n*-hexane, 2,5-hexanedione and related compounds. Therefore, sBA may also potentiate the neurotoxic effects of certain chemicals; however, so far such effects have not been reported.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Name: *sec*-Butanol (sBA)

IUPAC name: Butan-2-ol

Synonyms: *s*-Butanol
sec-Butyl alcohol
2-Butyl alcohol
Butylene hydrate
Ethyl methyl carbinol
2-Hydroxybutane
1-Methyl propanol
1-Methyl-1-propanol
1-Methylpropyl alcohol
Methylethylcarbinol
Secondary butyl alcohol

CAS name: 2-Butanol

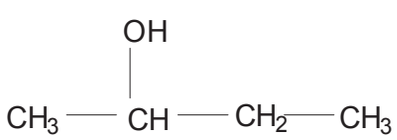
CAS registry No: 78-92-2

UN number: 1120

Molecular mass: 74.12

Formula: $C_4H_{10}O$

Structural formula:



2.2 EC classification and labelling

EC (EINECS) No:	201-158-5	
EEC No.	603-004-6	
EEC classification:	Flammable, irritant	
EEC labelling, symbol:	Xi	Irritant
R-Phrases:	R 10	Flammable
	R 36/37	Irritating to eyes and respiratory system
	R 67	Vapours may cause drowsiness and dizziness
	S-Phrases:	(S 2 Keep out of reach of children) [a]
	S 7/9	Keep container tightly closed and in a well-ventilatedplace
	S 13	Keep away from food, drink and animal feedstuff
	S 24/25	Avoid contact with skin and eyes
	S 26	In case of contact with eyes, rinse immediately with plenty of water and seek medical advice
	S 46	If swallowed, seek medical advice immediately and show this container or label

2.3 Physical and chemical properties

sec-Butanol (sBA) is a colourless, flammable liquid with a pleasant odour. It is soluble in water and miscible with a large number of organic solvents. Data on physical and chemical properties are listed in Table 1.

[a] Only for consumer products

Table 1: Physical and chemical properties

Property	Value, unit	Reference
Melting point	-114 - -115°C	Company data sheets [a]
	-114.7°C	Hahn *et al*, 1986
Boiling point at 1,013 hPa	89 - 103°C	Company data sheets [a]
	99.5°C	Hahn *et al*, 1986; Weast et al, 1989
Relative density D_4^{20} (density of water at 4°C is 1,000 kg/m^3)	806	Shell, 1999
	806.5	Hahn *et al*, 1986
	806.3 [b]	Weast *et al*, 1989
Viscosity at 20°C	3.08 mPa·s	ExxonMobil, 1998
	3.54 mPa·s	Elf Atochem, 1996
	4.2 mPa·s	Shell, 1999
Refractive index nD at 20°C	1.395	Shell, 1999
	1.39719	Hahn *et al*, 1986
Vapour pressure, hPa at 20°C	15.2 [c] - 15.3 hPa	Shell, 1994, 1999
	16	Elf Atochem, 1996
	17	ExxonMobil, 1998
Vapour density at 20°C (air = 1)	2.6	Shell, 1994
Threshold odour concentration	8.0 mg/m^3 [d]	Amoore and Hautala, 1983
Surface tension at 20°C	23.3 mN/m	Shell, 1999
	23.5 mN/m	Hahn *et al*, 1986
Solubility in water at 20°C	125 g/kg [e]	Hahn *et al*, 1986; Elf Atochem, 1996; Shell, 1999
	180 g/kg	Matsuda *et al*, 1993 cited in Beilstein, 2002
	200 g/kg	ExxonMobil, 1998
Solubility of water in sBA, g/kg at 20°C	450	Shell, 1999
Miscible with alcohol, ether, acetone and benzene (most organic solvents)	Yes	Weast *et al*, 1989; Elf Atochem, 1996
Partition coefficient, log K_{ow} (octanol/water) at 20°C	0.61 [f]	Elf Atochem, 1996
Partition coefficient, log K_{oc} (organic carbon/water) at 20°C	0.75 [g]	This report
Henry's Law constant at 25°C	0.90 Pa·m^3/mol [h]	This report
	1.02 Pa·m^3/mol	Elf Atochem, 1996

Table 1: Physical and chemical properties (cont'd)

Property	Value, unit	Reference
Flash point, closed cup	22 - 25°C	Company data sheets [a]
	23.85°C	Billig, 1992
	24°C	Hahn *et al*, 1986
Explosion limits in air at room temperature and 1,013 hPa	1.7 - 9.8% (v/v)	Company data sheets [a]
Auto-flammability, ignition temperature	> 350 - 406°C	Company data sheets [a]
	390°C	Hahn *et al*, 1986

[a] Elf Atochem, 1996; ExxonMobil, 1998; Shell, 1994, 1999

[b] For a mixture of *d*- and *i*-isomers

[c] Reported as 11.4 mmHg

[d] Reported as 2.6 ppm

[e] Temperature assumed to be 20°C

[f] Presumably measured

[g] Calculated, reported as K_{oc} = 5.6 (Section 4.2)

[h] Calculated: molecular mass x vapour pressure / solubility in water

Commercial sBA typically has a purity ≥ 99.5%. Common impurities are: isobutanol (< 0.05%), dibutyl ether (< 0.03%), butyric acid (< 0.002%) and water (< 0.2%).

2.4 Conversion factors

Conversion factors for sBA concentrations in air at standard conditions (20°C and 1,013 hPa) are:

- 1 ppm = 3.082 mg/m^3
- 1 mg/m^3 = 0.324 ppm

In this report, converted values (rounded) are given in parentheses.

2.5 Analytical methods

2.5.1 In workplace air

The standard method for measuring sBA in air involves drawing a known volume of air (recommended sample volume 10 litres at a rate of 0.2 l/min) through a tube containing activated charcoal to trap the organic vapours present. The analyte is desorbed with carbon disulphide containing 1% 2-propanol, and the eluate is injected into a gas chromatograph (GC) equipped with a flame ionisation detector (FID) (NIOSH, 1994). The relatively high detection limit is sufficient for monitoring of airborne sBA concentrations in the range of current occupational exposure limit (OEL) values (Table 8).

A modification of the NIOSH method, in which sBA is desorbed with hydrogen sulphide, has been used by BASF (2000a). The analytical sensitivity is 2.2 ng sBA and the detection limit 0.06 mg sBA/m^3 (0.02 ppm) in 25 litres of sampled air. The method is suitable for personal and area measurements. After standardisation at BASF the method was certified by the competent German authority (Mess- und Prüfstellen der Länder, Kassel), renewable every 3 years.

2.5.2 In environmental media

For the determination of sBA in ambient air, the above NIOSH method for workplace air can be used. There are no standard methods for the analysis of water, soil or sediment. Substantial concentrations of sBA in the environment are not expected (Section 4.3.6 and 5.1).

2.5.3 In biological media

Concentrations of sBA and its metabolites methyl ethyl ketone (MEK; 2-butanone), 3-hydroxy-2-butanone and 2,3-butanediol in blood were determined by GC-FID using 10% Carbowax 20M on 60/80 mesh Chromosorb W. Various internal standards were added to blood, which was then de-proteinised with zinc sulphate and barium hydroxide before GC analysis. The limit of detection for each compound was at least 2 µg/ml of blood (Dietz and Traiger, 1979).

Alternatively, Angerer and Gundel (1977) determined alcohols and ketones in blood and urine by headspace capillary GC. Anticoagulated blood or urine (2 ml) was placed into a crimped vial and incubated at 40°C (blood) or 50°C (urine) for at least 1 hour. The head space was analysed by capillary column GC using a 25m Poropak Q stationary phase; the column temperature started at 100°C for 4 minutes and then was ramped at 10°C/min with various isothermal periods to 220°C. The retention time of sBA under those conditions was 17.3 minutes. The detection limits were 0.4 mg sBA/l blood and 0.2 mg sBA/l urine.

3. PRODUCTION, STORAGE, TRANSPORT AND USE

3.1 Production

sBA is produced commercially by the acid-catalysed addition of water to *n*-butenes. However, current trends are towards the employment of Raffinate II type feedstock, i.e. refinery streams containing predominantly ^{n}-butenes and saturated C4 hydrocarbons after removal of butadiene and isobutylene. In the traditional indirect hydration process, *n*-butenes are reacted with liquid sulphuric acid and the intermediate butyl sulphate esters hydrolysed (Billig, 1992). In another process variant, the olefins are hydrated directly at elevated temperatures and higher pressures (Hahn *et al*, 1986). All reaction and subsequent refining (distillation) steps are carried out in closed systems.

World-wide capacity of sBA is estimated at about 1,000 kt/y, and production 900 kt/y. The production volume of sBA in the USA has not been reported, but US production of MEK, the major industrial product of sBA, was estimated to be 635 x 10^6 pounds (288 kt)[a] in 1999 (ChemExpo, 1999). No data are available for Europe.

3.2 Storage

sBA can be stored or dispatched in untreated mild steel or enamelled steel drums, provided that ingress of moisture is prevented. Stainless steel containers are also suitable. Storage under dry nitrogen is recommended since this limits flammability hazards and minimises water pickup (Hahn *et al*, 1986). There is a report of an explosion that occurred during distillation of a sample of aged sBA, suggesting that dangerous levels of peroxides can form in sBA which has been stored in air (Pozdnev *et al*, 1977 as quoted in Billig, 1992).

3.3 Transport

sBA is transported in rail and road tank cars, and in drums as well as in tanker vessels and containers (Hahn *et al*, 1986).

3.4 Use

Most (> 95%) sBA produced world-wide is dehydrogenated for the synthesis of the solvent MEK (Billig, 1992).

sBA itself is also used as solvent: in particular, when mixed with aromatic hydrocarbons it is especially suitable as a solvent for alkyd resins and ethylcellulose lacquers (Billig, 1992). Some sBA is used in the manufacture of plasticisers, paints and varnishes, inks, perfumes, dyestuffs, fruit essences, wetting agents and lubricating oil additives (e.g. zinc dithiophosphates).

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[a] 1 pound = 1 lb = 0.4535924 kg

4. ENVIRONMENTAL DISTRIBUTION AND TRANSFORMATION

4.1 Emissions

sBA is released to the environment from natural and human (anthropogenic) sources.

4.1.1 Natural sources

sBA occurs naturally as a result of fermentation of carbohydrates, for example in alcoholic beverages (IPCS, 1987). It was identified as a volatile component of baked potatoes (Coleman *et al*, 1981), Beaufort cheese (Dumont and Adda, 1978), roasted filberts (Kinlin *et al*, 1972), fried bacon (Ho *et al*, 1983), milk (Urbach, 1987), chickpea (*Cicer arietinum* L.) (Rembold *et al*, 1989), Parma ham (Hinrichsen and Pedersen, 1995), mussels (Yasuhara and Morita, 1987), dry beans, split peas and lentils (Lovegren *et al*, 1979), Portuguese bagaceiras (grape marc) (Silva *et al*, 1996) and apple and pear juice concentrate (Drawert *et al*, 1962). In addition, Shahidi *et al* (1986) reported the presence of sBA in beef and pork meat. The concentration levels are reported in Section 5.2.1.

sBA was measured, along with 21 other oxygenated volatile organic compounds (VOCs), in biogenic emissions from birch trees *in situ* on locations near Vienna, Austria; sBA was emitted at a rate of 13.7 ng/g biomass/h (König *et al*, 1995). sBA was detected in kiwi fruit flowers (*Actinidia chinensis*), where it represented 0.02% of the total number of 87 VOCs (Tatsuka *et al*, 1990). sBa was also found to be a major component of compost gas (Day *et al*, 1998). Identification of VOCs in these studies was by GC combined with mass spectrometry (MS).

Freeze vacuum distillation and GC-MS were used for the isolation and determination of VOCs in poultry manure. sBA concentrations of 0.15, 4.63 and 6.58 mg/kg were measured at different stages (0, 9 and 28 days, 3 samples) of anaerobic fermentation at 28 to 29°C (Yasuhara, 1987).

An sBA concentration of 30.75 $\mu g/m^3$ was detected in landfill gas from a municipal solid waste treatment plant in Connecticut (USA) (Capenter and Bidwell, 1996).

4.1.2 Emissions during production and use

sBA may be released to the environment during its production, transport, storage, and use. Most of sBA released into the atmosphere arises from MEK manufacture.

In the Netherlands, industrial emission levels of butyl alcohols in air and water were registered per province from 1974 to 1982. Total process emissions of sBA were 33 t/y to air and 496 t/y to water (Ministerie van VROM, 1991).

In the USA, the Toxics Release Inventory (US-EPA, 1999a) lists the reported releases (annual quantities emitted) from industrial facilities having 10 or more full-time employees and manufacturing or processing ≥ 25,000 lbs (11,340 kg) or otherwise use ≥ 10,000 lbs (4,536 kg) of sBA (Table 2).

Table 2: Industrial emissions reported [a] in the USA in 1997 *(US-EPA, 1999a)*

On-site releases	**(lb)**	**(kg)**
Total air emissions	959,349	435,153
Surface water discharges[b]	11,965	5,427
Underground Injection	152,939	69,372
On-site land releases	10	4.5
Total on-site releases	1,124,263	509,957
Transfers off-site to disposal	17,496	7,936
Total on- and off-site releases	1,141,759	517,893

[a] Total facilities reporting: 120

[b] Excluding emissions from waste-water treatment plants (WWTPs)

These estimated release figures represent a worst-case estimate, because they are based on conservative assumptions and do not take into consideration any breakdown on-site by biological or physical means such as waste-water treatment, incineration and flaring (US-EPA, 1999b).

4.1.3 Other sources

sBA was identified, by gas liquid partition chromatography, in exhaust gases from petrol driven motor vehicles; it represented 4.3% of the exhaust gases (Hughes and Hurn, 1960). Nowadays, this figure is probably lower due to the introduction of catalytic converters.

4.2 Environmental distribution

An indication of tendency of a chemical to partition over the environmental compartments can be obtained using a Mackay level I fugacity model (Mackay, 1991). This model calculates the theoretical distribution in a "unit world", assuming steady-state equilibrium, continuous chemical input, no transfer between compartments and no degradation of the chemical. The absolute values resulting from the calculation are not relevant, but the relative outcome can be used to identify compartments of potential concern. The fugacity calculation for sBA shows that it is not expected to adsorb significantly to soil or sediment, while the majority partitions to water and air (Table 3).

Table 3: Partitioning into the environment *(Schulte-Körne, 2000)*

Compartment	(%)
Air	24
Water	75
Soil	0.3
Biota	0.000
Sediment	0.02
Suspended matter	0.000

The environmental partitioning of sBA has been refined using the EQC Level III model (Mackay *et al*, 1996). The Level III model simulates a situation in which a chemical is emitted at a constant rate into one or more of the air, water, soil and sediment compartments, in each of which it may degrade. The steady-state distribution between compartments is calculated. On account of the resistance to mass transfer between compartments, the various phases are not in equilibrium and the steady-state partitioning depends on the compartment(s) into which the chemical is injected, i.e. its "mode of entry".

EQC modelling has been performed for sBA using the physical properties given in Table 1 and an atmospheric lifetime of 55.7 hours (2.7 d), corresponding to a half-life of 38.6 hours (1.6 d) (Section 4.3.1). Degradation in other media was neglected. Table 4 below gives the percentages of sBA calculated to be present in each compartment.

Table 4: Partitioning (%) into the environment *(Kniestedt, 2003)*

Compartment	Level III, with emissions to air alone	to water alone
Air	77.5	0.3
Water	14.9	99.5
Soil	7.57	0.03
Sediment	0.02	0.17

While the Level III simulation with emissions of sBA to air alone leads to partitioning to air and water that is closely similar to the Level I equilibrium situtation, a much greater steady-state proportion of sBA is found in the water compartment when the emissions are to water alone. This is due to the resistances to inter-media transfer (in particular from water to air) introduced in the Level III model.

Based on sBA concentrations measured in a wastewater holding bay (eastern Southampton, UK), fluxes of volatilisation of 11.63 and 0.044 ng sBA/cm^2/h were estimated in winter (wind 8.4 m/s, air 2.5°C, water 5.3°C) and summer (wind 3.3 m/s, air 30.3°C, water 18.2°C) conditions, respectively (Bianchi and Varney, 1997).

Using a Henry's Law constant of 0.922 Pa·m^3/mol at 25°C and 0.0972 Pa·m^3/mol at 0°C, the volatilisation half-life of sBA in a model river (depth 1 m, flow 1m/s, wind velocity 3 m/s) was estimated to be 3.5 and 30 days at 20°C and 0°C, respectively (Thomas, 1990).

Based on a water solubility of 180 g/l (Matsuda *et al*, 1993 cited in Beilstein, 2002) and using the recommended regression equation (Lyman, 1990), a K_{oc} of 5.6 has been estimated. Therefore, sBA should not adsorb significantly to soil or sediment.

A K_{oc} value of 2.4 can be calculated by means of PcK_{oc} software (SRC, 1999a), using the molecular topology/fragment contribution method of Meylan *et al* (1992).

4.3 Environmental fate and biotransformation

4.3.1 Atmospheric fate

sBA is a VOC which rapidly reacts with photochemically produced hydroxyl radicals (·OH). Several values for the rate constant (k_{OH}) of this reaction have been measured, most recently 8.1 x 10^{-12} cm^3/molecule/s, said to be in agreement with previous laboratory results (Baxley and Wells, 1998). The Atmospheric Oxidation Program (Meylan and Howard, 1993) predicts a similar value of 9.98 x 10^{-12} cm^3/molecule/s. Based on these values, the average atmospheric half-life ($t_{1/2}$) for sBA, calculated according to the equation $t_{1/2} = \ln 2/k_{OH} \times [\cdot OH]$, and assuming a global average concentration of 0.5 x 10^6 ·OH/cm^3, would be 38.6 hours (1.6 d), and the life-time [a] 55.7 hours (2.3 d).

When emitted to the atmosphere, sBA may contribute to the formation of tropospheric ozone through oxidation of NO in NO_2, oxidation of intermediate species produced by its degradation and further photolysis of NO_2 to NO and atomic oxygen. The experimental half-life for photodecomposition of sBA (initial concentration 5 ppm, 15 mg/m^3) in the presence of NO was 4.0 hours (Dilling *et al*, 1976). Derwent *et al* (1998) calculated a photochemical ozone creation potential (POCP) of 40 for sBA compared to ethylene (100) which is used as a reference.

Several intermediate oxidation species have been observed in the laboratory (atmospheric chamber), the two major compounds being MEK (yield 60%) and acetaldehyde (29%) (Baxley and Wells, 1998).

[a] Lifetime (L 1) is the time necessary for 63% degradation: it is equal to the "half-life" divided by In 2 (= 0.69)

4.3.2 Aquatic fate

As explained in Section 4.2, sBA will distribute predominantly to the aquatic environment. Rapid degradation and full mineralisation with respective half-lives of 1 to 7 days and 2 to 14 days in surface and ground water were estimated from aerobic biodegradation characteristics (Howard *et al*, 1991).

4.3.3 Terrestrial fate

Based on the biodegradation results presented in the following section, sBA will likely biodegrade in soil with half-life of 1 to 7 days (Howard *et al*, 1991). Due to a high vapour pressure and a low adsorption to soil, volatilisation should also occur from dry soil. If released on land, sBA is not expected to persist in soil.

Supporting this assumption, no sBA was found in ground water under a paint factory where sBA and other solvents were stored in leaking underground storage tanks (Botta *et al*, 1984). It is presumed to have degraded in the subsoil and ground water.

4.3.4 Biodegradation

Aerobic

The available studies are summarised in Table 4. Several authors reported that after 1 day approximately 9 to 58% of sBA is degraded (McKinney and Jeris, 1955; Gerhold and Malaney, 1966). After 5 days, biodegradation of between 33 and 98.5% was achieved (Hammerton, 1955; Wagner, 1974; Dore *et al*, 1975; Pitter, 1976; Bridié *et al*, 1979a), and between 10 and 20 days, the reported values ranged from 44 to 73.5% (Lamb and Jenkins, 1952; CITI, 1992). Ettinger (1956) found 44 to 77% degradation after 5 to 10 days.

In a semi-automatic activated sludge system simulating WWTP, 98% BOD reduction was observed in 4 hours (Hatfield, 1957).

Based on these results, it is concluded that complete aerobic biodegradation of sBA occurs quite rapidly, within a few days.

A high rate of oxidation (15.3 - 16.8 μmol/h per mg protein) of sBA to MEK was observed with various C_2 to C_4 gaseous *n*-alkane-grown bacteria isolated from lake water (Warinanco, Linden, New Jersey, USA) (Hou *et al*; 1983). However, extensive data demonstrated that MEK is readily biodegradable (ECETOC, 1983).

Table 4: Aerobic degradation tests

Guideline or method	Time (d)	Inoculum	Initial concentration (mg sBA//l)	Parameter and result (% removal)	Reference	CoRa
				BOD		
Batch-wise fill-and-draw	0.17 (4 h)	Adapted activated sludge (1,620 mg/l)	550	96	Hatfield, 1957	2e
				COD		
COD removal assay	5	Adapted activated sludge (100 mg/l) from sewage plant	200	98.5b	Pitter, 1976	2e
				ThOD		
Warburg respirometer	0.96 (23 h)	Adapted activated sludge (1,050 mg/l)	500	58	McKinney and Jeris, 1955	2e
Warburg respirometer	1	Activated sludge (2,500 mg/l) from sewage plant	500	9.3	Gerhold and Malaney, 1966	2c
APHA, 1971, standard method 219	5	Activated sludge from sewage plant	NS	83	Bridié *et al*, 1979a	2g
Sewage die-away (equivalent to OECD 301A)	5	Activated sludge	6,000	81.7	Wagner, 1974	2c
AFNOR, 1969 NF T90-103, oxygen consumption	5	NS	NS	33	Dore *et al*, 1975	2g
Sewage die-away	5	River water	3	55	Hammerton, 1955	3a
OECD 301C	14	Activated sludge (30 mg/l)	100	73.5	CITI, 1992	2c
Not stated	5	Activated sludge	2.5	0	Ettinger, 1956	4b
	10			44.2		
	15			69.2		
	20			72.3		
	30			73.2		
	40			75.4		
	50			77.0		

[a] Code of Reliability (Appendix B)
[b] 55 mg COD/g/h
NS Not stated
BOD Biological oxygen demand
COD Chemical oxygen demand
ThOD Theoretical oxygen demand, i.e. the calculated amount of oxygen (O_2) needed for complete oxidation to water and carbondioxide (CO_2)

Anaerobic

Using the Hungate serum bottle technique, sBA, at an initial concentration of 500 mg/l, was totally degraded (100%) at a rate of 42 mg/l/d by an acetate-enriched methanogenic culture after a lag time of 14 days. After 52 days of acclimation in anaerobic filters the utilisation efficiency was 93% at the concentration of 110 mg sBA/l (Lin Chou *et al*, 1979; CoR 2e).

At a hydraulic retention time (HRT) of 2 days and sBA volumetric loading rate of 9 kg COD/m^3, anaerobic hybrid reactors achieved total and soluble COD removal efficiencies of 98.5% in less than 5 times the HRT (Henry *et al*, 1996; CoR 2e).

4.3.5 Bioaccumulation

A measured bioconcentration factor (BCF) is not available.

Using the log K_{ow} value of 0.61 (Table 1) and the equation derived by Veith *et al* (1979), valid if log $K_{ow} \leq 6$,

$$\log BCFfish = 0.85 \times \log K_{ow} - 0.70 \qquad \text{(Eq.1)}$$

gives a BCF of 0.66, indicating that the bioconcentration of sBA in aquatic organisms should be negligible. Thus, sBA is not expected to bioaccumulate.

The BCF calculated by means of BcfWin software (SRC, 1999b), using a different algorithm based on log K_{ow} (Meylan *et al*, 1999), is 3.16, the lowest value by default.

4.3.6 Summary and evaluation

sBA enters the environment from natural sources (biomass, fermentation) as well as from its production, transport, storage and use in the manufacture of MEK, as a solvent, and as an ingredient in paint remover and industrial cleaning agents. sBA is readily biodegradable by aerobic and anaerobic processes. In contact with soil, sBA is mobile, is not expected to adsorb significantly to soil and sediment and is likely removed from soil by volatilisation and biodegradation with an estimated half-life of 1 to 7 days. If released in water, biodegradation is likely also to be the primary factor affecting its loss. In a model river, the volatilisation half-life is estimated to be 3.5 days and 30 days at 20°C and 0°C, respectively. When emitted into the atmosphere, model calculations show a minimal contribution of sBA to the formation of tropospheric ozone. sBA will be removed by reaction with photochemically produced hydroxyl radicals with an half-life of 24 hours via the formation of MEK and acetaldehyde as intermediate oxidation species. Based on a log K_{ow} of 0.61, bioaccumulation in aquatic organisms is not expected to occur.

5. ENVIRONMENTAL AND HUMAN EXPOSURE

5.1 Environmental levels

5.1.1 In air

Extremely low concentrations (not quantified) of sBA were detected in the air of the Black Forest and in suburban air in the city of Tübingen in Germany, as judged by qualitative examination of the chromatograms (Jüttner, 1986). Sample points at Tucson (Arizona, USA) and at two rural sites about 40 km apart failed to detect sBA in tropospheric air and rain (Snider and Dawson, 1985). Very low airborne concentrations of sBA, < 0.1 - 5.4 μg/m^3 (range 0.3 - 16.6 μg/m^3) in summer and 0.5 - 9.6 μg/m^3 (1.5 - 29.6 μg/m^3) in winter, were quantified in ambient air above an estuary (Southampton, UK) over a 2-year period (Bianchi and Varney, 1992). No sBA was detected in air in the Allegheny Mountain Tunnel of the Pennsylvania Turnpike (USA) in 1979 (Hampton *et al*, 1982).

In a simulated VOC partition experiment in a redundant wastewater holding bay in the eastern Southampton dockland area (UK), a mean (8-h TWA) concentration of 3.5 μg sBA/m^3 (range 0.28 - 7.4 μg/m^3) was measured over a 14-month period following the addition of sBA to the water. The levels were considered typical of those encountered at a waste water treatment plant (Bianchi and Varney, 1997).

The available data are summarised in Table 5.

Table 5: Concentrations in Air

Sample	Location	Analytical method	Results	Reference
Forest air	Southern Black Forest, Germany	GC-MS	sBA was identified but not quantified	Jüttner, 1986
Suburban air	Tübingen, Germany	GC-MS	sBA was identified but not quantified	Jüttner, 1986
Tropospheric air and precipitation	Tucson, Arizona, USA and two rural sites about 40 km distant	GC-FID	sBA was not detected	Snider and Dawson, 1985
Ambient air	Water estuary, Southampton, UK	GC-MS	< 0.1-5.4 µg sBA/m^3 in summer and 0.5 - 9.6 µg sBA/m^3 in winter, over a 2-y period	Bianchi and Varney, 1992
Air	Allegheny Mountain Tunnel of the Pennsylvania Turnpike, USA	GC-MS	sBA was not detected	Hampton et al, 1982
Air above estuary	Redundant wastewater holding bay in the eastern Southampton dockland area, UK	GC-MS	3.5 + 1.8 µg sBA/m3 over a 14-month period	Bianchi and Varney, 1997

5.1.2 In water

Bianchi and Varney (1997) measured simulated concentrations of 3,790 µg sBA/l (range 18.8 - 7,530 µg/m^3) over a 14-month period, in a VOC partition experiment in a redundant waste holding bay in the eastern Southampton dockland area, UK (Section 5.1.1).

5.1.3 In soil

sBA was identified but not quantified in several trench leachate samples collected from commercially-run low-level radioactive waste disposal sites in USA (Francis *et al*, 1980). In leachates from 1 of 5 landfill sites in Connecticut towns, the concentrations ranged from 6,230 to 14,882 µg/l (Sawhney and Kozloski, 1984). A lower level of 49.1 µg/l was found in leachate from municipal waste landfills in Japan (Yasuhara *et al*, 1993). These, and other data are summarised in Table 6.

Table 6: Concentrations in landfills

Sample	Location	Analytical method	Result	Reference
Landfill gas	Municipal solid waste, Connecticut, USA	GC-MS	30.75 µg sBA/m^3	Capenter and Bidwell, 1996
Trench leachate	Low-level radioactive waste disposal sites, USA	GC-MS	sBA was identified but not quantified among 75 other compounds	Francis *et al*, 1980
Leachates	Landfill sites of Connecticut towns, USA	GC-MS	6,230 to 14,882 µg sBA/l in 1 of 5 samples	Sawhney and Kozloski, 1984
Leachates	Landfill of municipal wastes in Japan	GC-MS	49.1 µg sBA/l	Yasuhara *et al*, 1993
Sanitary landfill gas	Several locations in Germany	GC-MS	sBA was identified but not quantified among more than hundred compounds	Bruckmann and Mülder, 1982
Ground water	Land irrigated with sewage, China	Not stated	sBA was identified but not quantified among 167 compounds	Jieying *et al*, 1986

5.2 Human exposure levels and hygiene standards

5.2.1 Non-occupational exposure

sBA concentrations in various foodstuffs are presented in Table 7. The mean levels ranged from 32 ng/kg in beans to 270 µg/kg in mussels; in a sample of grape marc, high levels of up to 133 mg sBA/l were found. In several other studies and foodstuffs, traces of sBA were identified without further quantitation.

Table 7: Concentrations in Food

Food sample	Analytical method	Results	Reference
Baked potatoes	GC-MS	sBA was identified among 228 other volatile compounds with a relative concentration of 0.21 compared to ethyl acetate (the most abundant compound)	Coleman *et al*, 1981
Beaufort cheese	GC-MS	sBA was identified among 140 volatile compounds	Dumont and Adda, 1978
Fried bacon	GC-MS	sBA was identified among 135 compounds	Ho *et al*, 1983
Roasted filbert	GC-MS	sBA was identified among 229 compounds	Kinlin *et al*, 1972
Milk	GC-MS	sBA was identified among 60 compounds	Urbach, 1987
Chickpea (Cicer arietinum L.)	GC-MS	sBA was identified among 132 compounds	Rembold *et al*, 1989
Parma ham at different stages of manufacturing	GC-MS sBA was quantified in comparison to a *n*-dodecane standard curve	Very low levels of sBA (2 - 19 ng dodecane equivalents) were observed, compared to ethanol (1,054 - 12,769 ng dodecane equivalents)	Hinrichsen and Pedersen, 1995
Mussel	GC-MS	270 µg/kg	Yasuhara and Morita, 1987
Dry bean	GC-MS	53 ng/kg	Lovegren *et al*, 1979
Split pea	GC-MS	89 ng/kg	Lovegren *et al*, 1979
Lentil	GC-MS	32 ng/kg	Lovegren *et al*, 1979
Portuguese bagaceira (grape marc)	GC-MS	50 ± 37 mg/l (0.0 133 mg/l)	Silva *et al*, 1996
Apple and pear juice concentrate	GC-FID	sBA was identified	Drawert *et al*, 1962

In indoor air, sBA was detected by GC-MS together with 149 other VOCs in the emissions from furniture coatings (Salthammer, 1997). It was also identified (measured by GC-MS and GC-FID but not quantified) in 4 out of 12 indoor air samples from offices and restaurants in Rio de Janeiro and São Paulo (Brazil) (Santos *et al*, 1997).

5.2.2 Occupational exposure

In an occupational exposure survey conducted by 24 occupational health service institutions in Japan, sBA was detected in 8% of the workplaces, primarily in degreasing, cleaning, wiping, surface coating and painting industries (Ukai *et al*, 1997).

From 1979 to 1999, extensive workplace exposure measurements were undertaken within a chemical company at all sites involved in the production and use of sBA (BASF, 2000b). The measurement method was comparable to the NIOSH method, detailed in Section 2.5.1. The sampling method was based on personal air sampling, the sampling strategy is unknown. The frequency of measurement (10/site on average) could be kept low due to compliance with hygiene standards (Section 5.2.3). The results are summarised in Table 6. The general representativeness of these results for all production and down-stream scenarios, however, cannot be evaluated (see also Section 10).

Table 6: Workplace (8-h TWA) concentrations [a] at BASF (2000b)

Concentration	ppm[b]	mg/m^3
Range	0.03 - 6.5	0.09 - 20
Mean	0.2	0.6
95%	≤ 0.62	≤ 1.91
90%	≤ 0.62	≤ 1.91
50% (median)	≤ 0.4	≤ 1.2

[a] 218 personal samples at 71 sites

[b] Reported values, converted following Section 2.4

5.2.3 Hygiene standards

Several industrialised countries have adopted occupational exposure limit values (OELs) (Table 8). Some OELs include a skin notation (for which no documented rationale is available).

Table 8: Occupational exposure limit values

Country	TWA (ppm)	(mg/m^3) [a]	STEL (ppm)	(mg/m^3) [a]	Notation	Reference
Belgium	100	303	-	-	-	ACGIH, 2002 [b]
Denmark	50	150	-	-	Skin	Arbejdstilsynet, 2000
Finland	100	303	-	-	-	ACGIH, 2002 [b]
France	100	300	-	-	-	INRS, 1999
Italy	100	303	-	-	-	ACGIH, 2002 [b]
Japan	100	300	-	-	-	JSOH, 1999
Netherlands	150	450	-	-	-	Sdu, 1999
Norway	-	-	25	75	Skin	Arbeidstilsynet, 1997
Switzerland	100	303	-	-	-	ACGIH, 2002 [b]
UK	100	308	150	462	-	HSE, 2000
USA	100	-	-	-	-	ACGIH, 2002 [b]
	100	305	150	455	-	NIOSH, 2000
	150	450	-	-	-	OSHA cited in NIOSH, 2000

TWA Time-weighted average concentration (8-h working period)

STEL Short-term exposure limit (15 min, unless specified otherwise)

[a] Official values; some countries use different conversion factors and/or other ambient temperature

[b] OELs in other countries are also directly linked to the value published by ACGIH, including Australia, Bulgaria, Colombia, Jordan, Korea, New Zealand, Singapore and Vietnam

No environmental or public health standards are available for sBA in indoor air, drinking water and food residues.

5.2.4 Other standards

In the USA, an Immediately Dangerous to Life or Health (IDLH) concentration of 2,000 ppm (6,000 mg/m^3) was established, based on acute inhalation toxicity data in animals. This value is considered as a protective measure and includes conservative assumptions (NIOSH, 1996).

In Germany, sBA is classified as a weakly hazardous compound for the aquatic environment (Wassergefährdungsklasse, WGK 1) (UBA, 2000).

5.2.5 Summary

sBA is a ubiquitous environmental chemical that is present in low and variable concentrations e.g. in ambient air, edible plants and waste waters. Since these data are so variable it is not possible to arrive at a figure representative of human exposure to sBA.

Occupational exposure limit values for sBA vapours in different countries range between 50 and 150 ppm (150 - 450 mg/m3) for the TWA values.

6. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

6.1 Micro-organisms

sBA has been tested for its toxicity to bacteria and protozoa (Table 9).

Table 9: Toxicity to micro-organisms

Organism	Biological endpoint / Parameter	Method	Time	Concentration (mg/l)	Reference	CoR[a]
Bacteria	**Growth inhibition**					
Pseudomonas putida	EC_3	Bringmann-Kühn	16 h	500	Bringmann and Kühn, 1977a, 1980a	1d
Microcystis aeruginosa	EC_3	Bringmann-Kühn	8 d	≥ 312 [c]	Bringmann and Kühn, 1978a,b	1d
	Germination inhibition					
Bacillus subtilis spores	EC_{50}	NS	NS	1,630 [b]	Yasuda-Yasaki *et al*, 1978	3a
Protozoa	**Growth inhibition**					
Uronema parduczi	Toxicity threshold [d]	Bringmann-Kühn	20 h	1,416	Bringmann and Kühn, 1980b	1d
Chilomonas paramaecium	Toxicity threshold [d]	Bringmann-Kühn	48 h	745	Bringmann *et al*, 1980	1d
Entosiphon sulcatum	Toxicity threshold [d]	Bringmann-Kühn	72 h	1,282	Bringmann and Kühn, 1978c, 1980a	1d

[a] Code of Reliability (Appendix B)

[b] Reported as 22 mmol/l

[c] Erroneously listed as *n*-butanol

[d] Screening test showing the onset of adverse effects (3 - 5% growth inhibition)

NS Not stated

The results show that sBA has a low order of toxicity to micro-organisms; the effect levels range from 500 to more than 1,600 mg/l, depending on the species and test method.

6.2 Aquatic organisms

sBA has been tested for its toxicity to invertebrates and fish (Table 11).

Table 10: Toxicity to fish and invertebrates

Organism	Biological endpoint / Parameter	Method	Time (h)	Concentration (mg/l)	Reference	CoR[a]
Fish	**Lethality**					
Pimelas promelas	LC_{50}	Static	96	3,670	Geiger *et al*, 1986	1d
Carassius auratus	LC_{50}	Static	24	4,300	Bridié *et al*, 1979b	1c
Leuciscus idus	LC_{50}	Static	48	3,520, 3,540	Juhnke and Lüdemann, 1978	2c
Invertebrates	**Immobility**					
Daphnia magna	EC50	Static	24	3,750	Bringmann and Kühn, 1977b	2c
Daphnia magna	EC50	Static	24	2,300	Bringmann and Kühn, 1982	1d
	Excystment					
Artemia salina	EC50	Static	NS	3,800	Smith and Siegel, 1975 cited in IPCS, 1987	3a

[a] Code of Reliability (Appendix B)
NS Not stated

The results show that sBA is non-toxic invertebrates and to fish; all LC_{50} values are far greater than 1,000 mg sBA/l. No chronic data are available.

Applegate *et al* (1985; CoR 3a) reported a 24-h no-observed effect concentration NOEC of > 5 mg sBA/l for larvae of the sea lamprey *Petromyzon marinus* from the Great Lakes (USA). The value was taken from a study in which a large number of substances were screened for possible lamprecidal properties at a low concentration of 5 mg/l, the only concentration tested.

Table 11 shows that sBA has a low toxicity to algae.

Table 11: Toxicity to algae

Organism	Biological endpoint / Parameter	Method	Time	Concentration (mg/l)	Reference	CoR[a]
	Growth inhibition					
Chlorella pyrenoidosa	EC_{50}	NS	NS	8,900	Jones, 1971 cited in IPCS, 1987	3a
Scenedesmus quadricauda	EC_3	Bringmann-Kühn	8 d	≥ 95 [b]	Bringmann and Kühn, 1977a, 1978a,b, 1980a	1d

[a] Code of Reliability (Appendix B)
[b] Erroneously listed as *n*-butanol in Bringmann and Kühn, 1977a, 1978a,b
NS Not stated

6.3 Terrestrial organisms

No data are available.

6.4 Summary and evaluation

sBA is readily biodegradable in water. It is of limited toxicity to aquatic organisms. In studies in fish and daphnia, the LC_{50} values are generally in the range of 3,000 to 4,000 mg/l. In algae studies the effect levels are above the highest levels tested in the studies. It is concluded that sBA poses minimal hazard to aquatic organisms.

sBA is not expected to bioaccumulate, nor is it adsorbed on soils. Long-term adverse effects to the aquatic environment are not expected.

Because of its rapid photochemical degradation, accumulation in the atmosphere is not anticipated. Measured concentrations are very low.

7. KINETICS AND METABOLISM

7.1 Absorption, metabolism and exretion in vivo

7.1.1 Animals

There are several animal studies indicating that sBA is rapidly absorbed, metabolised to MEK and other subsequent metabolites, and excreted.

Following oral application of 8.3 mmol sBA/kgbw (approximately 600 mg/kgbw) to rabbits, 14 to 15% of the dose was excreted in urine as a glucuronic acid conjugate, while most of the remainder was metabolised and partially exhaled as MEK (Kamil *et al*, 1953).

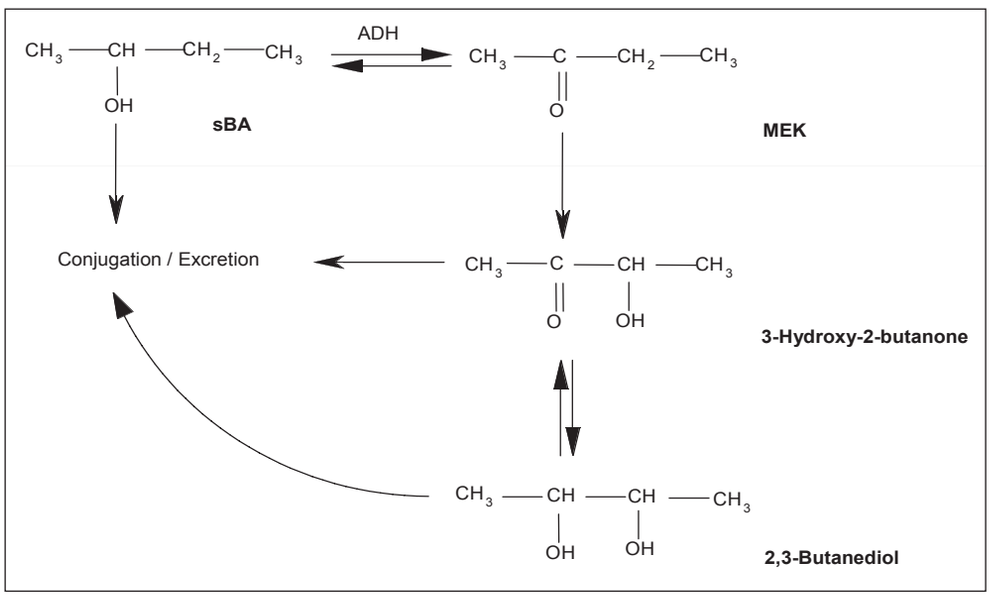
Saito (1975) administered sBA (2 ml/kgbw, equivalent to 1.6 g/kgbw) orally to rabbits and collected blood samples for GC analysis. Approximately 1,000 mg sBA/l blood was found after 1 hour, 700 mg sBA/l after 7 hours and trace amounts after 10 hours. sBA was metabolised via alcohol dehydrogenase (ADH) to MEK that was also detected in blood, where it reached a maximum concentration of 480 mg/l after 6-hours. Some sBA was excreted directly via exhalation (3.3% of the administered dose) and urine (2.6%), while the majority of MEK was exhaled (22.3% of the original sBA dose) and urine (4.1%).

Traiger and Bruckner (1976) determined a half-life of 2.5 hours for the elimination of sBA from blood of rats administered an oral dose of 2.2 ml/kgbw (equivalent to 1.77 g/kgbw). One hour after administration, a maximal blood level of 800 mg sBA/l was reached; the MEK level at that time point was 430 mg/l, rising to a maximum of 1,050 mg/l at 4 hours after sBA administration.

DiVincenzo *et al* (1976) studied the metabolism and clearance of MEK, the primary sBA metabolite, in the serum of male guinea pigs following a single intraperitoneal (*i.p.*) dose of 450 mg MEK/kgbw as a 25% solution in corn oil. The serum half-life of MEK was determined to be 270 minutes, and the clearance time 12 hours. sBA, 3-hydroxy-2-butanone and 2,3-butanediol were identified by GC-MS as the serum metabolites of MEK. Reduction at the carbonyl group of MEK was believed to have led to the formation of sBA, which was then likely to be eliminated as o-sulphates or o glucuronides in urine or as CO_2 through endogenous intermediary metabolism, or incorporated into tissues. Oxidation of MEK appeared to proceed by hydroxylation of the ω-1 carbon to form 3-hydroxy-2-butanone and further reduction to 2,3-butanediol.

Taking account of these studies, the following metabolic scheme can be proposed for sBA (Figure 1):

Figure 1: Metabolic pathways of sBA



Dietz *et al* (1981) developed a physiologically-based pharmacokinetic (PBPK) model for sBA and its metabolites MEK, 3-hydroxy-2-butanone and 2,3-butanediol in rats. The model examined the observed blood levels of sBA and its metabolites after oral administration of sBA, and was compared to blood levels of these compounds following oral exposure to MEK. The predicted blood concentrations of sBA and the metabolites were in good agreement with the observed data. The authors reported that 97% of sBA administered orally at 1,776 mg/kgbw to rats was oxidised via ADH to MEK. Equimolar doses of MEK (1,690 mg/kgbw) produced similar maximum blood concentrations (Cmax) and areas under the concentration curve (AUC) for both MEK and 2,3-butanediol (Table 12).

Table 12: Blood metabolite concentrations after oral administration of sBA or MEK to Rats (Dietz et al, 1981)

	sBA	MEK	3-Hydroxy-2-butanone	2,3-Butanediol
Following sBA dose[a]				
Cmax (mg/ml)	0.59 (2 h)	0.78 (8 h)	0.04 (12 h)	0.21 (18 h)
AUC (mg·h/l)	3,254	9,868	443	3,167
Following MEK dose[b]				
Cmax (mg/ml)	0.033 (6 h)	0.95 (4 h)	0.027 (8 h)	0.26 (18 h)
AUC (mg·h/l)	414	10, 899	382	3,863

[a] 1,776 mg sBA/kgbw, or 2.2 ml/kgbw of a 22% aqueous solution

[b] 1,690 mg MEK/kgbw, or 2.1 ml/kgbw of a 21% aqueous solution

AUC Area under the concentration curve

Since the quantities of MEK and subsequent metabolites derived from sBA dosing are similar to those obtained after dosing with MEK itself, they could be expected to possess similar toxicological properties. Dietz *et al* (1981) used these metabolic and kinetic data to propose that the potentiation of carbon tetrachloride hepatotoxicity by sBA occurs via a metabolite, probably 2,3-butanediol. Dietz and Traiger (1979) showed earlier that production of 3-hydroxy-2-butanone and 2,3-butanediol via sBA metabolism in rats was likely to contribute to the augmented necrogenic effect of carbon tetrachloride seen after pre-treatment with sBA. These considerations, however, may not account for acute toxicity arising from high bolus doses of sBA, or for any portal of entry effects.

7.1.2 Humans

The kinetics of inhaled MEK were studied in human volunteers (9 healthy males) exposed in an exposure chamber to 200 ppm MEK (600 mg/m^3) for 4 hours on two separate occasions, the first with only sedentary activity, and the second which included 3 x 10-min exercise. Relative pulmonary uptake was 53% throughout the 4-h inhalation exposure periods. Blood MEK concentrations rose steadily throughout the exposure periods without achieving a steady state. Exercise increased markedly the overall blood MEK level in comparison to sedentary activity. Only 2 to 3% of the absorbed dose was excreted unchanged by exhalation. [Comment by the Task Force: This value is much lower than the pulmonary excretion reported by Munies and Wurster (1965) after an oral dose of 30% MEK, which likely yielded much higher, and thus exhalable, plasma peak levels]. The metabolite 2,3 butanediol, which was reported in the animal studies, was also detected in the urine of humans, with maximum rates of excretion at about 6-12 hours from the beginning of exposure. About 2% of the absorbed MEK were excreted in the urine as 2,3-butanediol. The main portion of the inhaled MEK appears to be metabolised via pathways of the intermediary metabolism, e.g. converted to acetate or acetoacetate through the intermediate metabolite 3-hydroxy-2-butanone (Liira *et al*, 1988).

7.2 In vitro metabolism

No data are available.

7.3 Evaluation

Data from studies of the metabolism and pharmacokinetics of sBA in animals (notably rats) indicate that sBA is rapidly absorbed and distributed through the blood. While a minor part of the sBA is excreted directly into urine, partly in the form of conjugates, the majority is metabolised by oxidation to MEK (in rats). The primary metabolite MEK is subsequently converted to metabolites that are exhaled, excreted in urine, or incorporated into endogenous metabolic processes. Assuming the same basic principles of metabolic transformation in rats and humans, the approximate capacity to oxidise sBA to MEK should be of a similar order of magnitude. In quantitative terms, however, there may be some limitations for complete equivalency of rats and humans. Thus, the Task Force proposes an adaptation factor for potential species differences, accounting for more rapid oxidation or conjugation rates in rats. In support of this proposal, a study in rabbits points to the fact that large animals (with slow metabolism) may favour the conjugate pathway to a greater extent. On the other hand, rats might again metabolise more rapidly the resulting MEK.

In the absence of quantitative human data, allometric scaling (Feron *et al*, 1990) should be used to make an assumption of critical effect levels in humans, employing a factor of 0.254 for extrapolation from rats to humans.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO TEST SYSTEMS

8.1 Acute toxicity

sBA has a low order of acute toxicity to mammals by the oral, dermal and inhalation routes of exposure. The available data are reviewed below.

8.1.1 Oral

Oral LD_{50} values in laboratory animals range from approximately 2.2 to 6.5 g/kgbw (Table 13).

Table 13: Oral Toxicity

Species, strain and sex	LD_{50}, range (mg/kgbw)	Remark	Reference	CoR
Rat				
Fischer 344, M and F	2,193 (1,608-4,146)	Undiluted sBA (99.5%) by gavage	Price, 1986	1a
Carworth-Wistar, M	6,480 (5,730-7,320)	Diluted sBA, 20% in corn oil	Mellon Institute, 1951; Smyth *et al*, 1954	2g
Rabbit				
Rabbit, NS	4,890 [a]	ND_{50} [b] = 1,036 mg/kgbw [c]	Munch, 1972	3a

[a] Reported as 66 mmol/kgbw. Represents Certain Lethal Dose of 65.5 mmol/kgbw that produced death in about 24 hours in practically all animals, as reported earlier by Munch and Schwartze (1925; CoR 3a). Because of this inconsistency, a CoR of 3a is assigned to both references.

b Narcotic dose producing stupor and loss of voluntary movements in half of the animals

c Reported as 14 mmol/kgbw. Represents Minimum Narcotic Dose of 13.7 mmol/kgbw that produced light narcosis in practically all animals (Munch and Schwartze, 1925).

NS Not stated

Clinical signs reported in these studies included gait and/or posture abnormalities, coma, prostration (Price, 1986) and narcosis (Munch, 1972).

8.1.2 Dermal

The dermal LD_{50} value for sBA in rats was greater than 2 g/kgbw in one study (Table 14). No clinical signs were reported.

Table 14: Dermal Toxicity

Species, strain and sex	Result	Remark	Reference	CoR
Rat, Fischer 344, M and F	No mortality at 2,000 mg/kgbw	Undiluted sBA (99.5%), applied to the skin under an occlusive patch	Price, 1986	1a

8.1.3 Inhalation

Studies by Mellon Institute (1951) and Smyth *et al* (1954) suggest that the 4-h LC_{50} value for sBA was between 8,000 and 16,000 ppm in rats. These data and results following 7-h exposure (Nelson *et al*, 1989) are presented in Table 15.

Table 15: Inhalation toxicity in rats

Species, strain and sex	Exposure duration (h)	Concentration (ppm)	Concentration (mg/m^3)	Result	Reference	CoR
Rat						
Carworth-Wistar, M and F	4	16,000	49,000	5/6 rats killed	Mellon Institute, 1951	2g
Carworth-Wistar, M and F	4	8,000	25,000	1/6 rats killed	Smyth *et al*,1954	3a
Sprague-Dawley,F	7	10,000	31,000	6/6 rats killed	Nelson *et al*, 1989	2e

Vapour concentrations of 32.3 mg/l (10,500 ppm) for 225 minutes and 48.5 mg/l (15,700 ppm) for 160 minutes were fatal to mice (Weese, 1928). Clinical signs were not reported in these studies.

Other authors observed clinical signs of acute intoxication following exposure to high levels of sBA in laboratory animals, including variable expressions of central nervous system (CNS) depression. Among the clinical effects reported were restlessness, ataxia, prostration, decreased respiratory rate, and narcosis (Price, 1986; CoR 1a; Hansen and Nielsen, 1994; CoR 2e).

Starrek (1938) exposed groups of 2 mice to increasing concentrations of sBA vapour for decreasing lengths of time and found that the exposure durations necessary to induce ataxia, prostration, or deep narcosis were inversely proportional to the vapour concentrations. At 3,330 ppm (10,260 mg/m^3) ataxia, prostration, and narcosis became evident in 51 to 100 minutes, 120 to 180 minutes, and 300 minutes, respectively, whereas at 19,800 ppm (61,000 mg/m^3) these signs appeared in 7 to 8 minutes, 12 to 20 minutes, and 40 minutes, respectively. There were no signs of toxicity observed in mice that were exposed for 7 hours to 1,650 ppm (5,090 mg/m^3).

8.2 Skin, respiratory and eye irritation, sensitisation

8.2.1 Skin irritation

Studies in which neat sBA was applied to the skin of rabbits revealed no to slight irritation of the skin (Table 16).

Table 16: Skin Irritation studies in rabbits

Test method	Test condition	Exposure period (h)	Result	Reference	CoR
OECD 404	Undiluted sBA [a] (0.5 ml) under semi-occluded patch	4	No irritation	Price, 1986	1a
NS	Undiluted sBA (0.01 ml)	NS	Slight irritation, score 1/10	Mellon Institute, 1952; Smyth *et al*, 1954	2g

[a] 99.5% pure

NS Not stated

8.2.2 Eye irritation

Application of undiluted sBA resulted in moderate to severe irritation of the eye in rabbits (Table 17).

Table 17: Eye Irritation studies in rabbits

Test method	Test condition	Result	Reference	CoR
OECD 405	Undiluted sBA [a] (0.1 ml) instilled into the conjunctival sac of the eye	Moderate conjunctival inflammation in all 6 rabbits with slight, transitory iritic damage and/or corneal opacity in 3 rabbits. Intense, extensive corneal opacity and complete loss of iritic response developed in one rabbit.	Price, 1986	1a
NS	Undiluted sBA (0.02 and 0.1 ml) instilled into the	Irritating (score 4/10), injury minor from 0.02 ml severe from 0.1 ml conjunctival sac of the eye	Mellon Institute, 1952; Smyth *et al*, 1954	2g

[a] 99.5% pure

NS Not stated

In the study of Price (1986), sBA was corrosive to the eye, as evidenced by the progressive corneal opacity in one rabbit, that was killed on day 7. All other rabbits had mild effects that recovered completely by day 7.

8.2.3 Respiratory tract irritation

An Alarie test conducted in mice determined an RD_{50} [a] value of 11,800 ppm for sBA vapour (Hansen and Nielsen, 1994; CoR 2e).

8.2.4 Sensitisation

sBA was found to be inactive when tested in guinea pigs in Magnusson-Kligman maximisation tests performed according to OECD guidelines (Price, 1986; CoR 1a; Elf Atochem, 1997; CoR 1a).

8.2.5 Evaluation

sBA liquid is non-irritant to the skin, but irritant to the rabbit eye. It is a weak irritant to the respiratory tract of mice.

No evidence was found of skin sensitising potential on the part of sBA in a guinea pig maximisation test.

8.3 Repeated dose toxicity

8.3.1 Oral

No specific oral repeat-dose toxicity studies have been conducted with sBA.

Information on subchronic toxicity of sBA administered by the oral route can be deduced from a 2-generation reproductive toxicity study in which sBA was initially administered to the F_0 generation at concentrations of 0, 0.3, 1.0 or 3.0% (0, 3, 10 or 30 g/l) in the drinking water (Cox *et al*, 1975; Gallo *et al*, 1977) (Section 8.6.1). Due to toxicity, the highest level was reduced to 2.0% for treatment of the second generation (F_1) for 12 weeks. The F_1 generation animals (30/sex/group) were reared to maturity (up to week 12), mated to produce a F_2 generation, then killed for organ weights, and gross and microscopic pathological evaluations (10/sex/group). Haematological, biochemical, and urinary examinations were conducted terminally on the F_1 rats. A series of mild kidney changes (non-reactive tubular degeneration, tubular casts, foci of tubular regeneration, microcysts) were observed in animals treated at 2.0% sBA. The authors concluded that these findings were not a result of direct toxicity and did not have clear pathologic significance. They were considered to be non-specific effects due increased renal work load, possibly from increased urine volume and pressure at the high dose of sBA (Cox *et al*, 1975). No other findings of note were reported. The NOAEL for reproduction parameters was 1.0%, estimated by the authors to be 1,500 mg/kgbw/d or 1,771 mg/kgbw/d by the Integrated Risk Information system (IRIS) (US-EPA, 1993).

[a] Concentration expected to cause a 50% decrease in respiratory rate over a 10-min exposure period

8.3.2 Dermal

No data are available.

8.3.3 Inhalation

Three inhalation toxicity studies of limited duration have been reported for sBA. These studies were conducted primarily to assess narcotic effects, impact on liver and kidney mixed function oxidases, and developmental toxicity.

Weese (1928) exposed mice to a high vapour concentration of 0.1 cm^3 sBA/5 l air (20,000 ppm; 62,000 mg/m^3) for up to 117 hours (almost 5 days). and noted narcotic effects but no deaths in the animals. Aarstad *et al* (1985) studied cytochrome P450 (CYP) concentrations and found an induction of CYP enzymes in the livers (33% increase) and kidneys (47% increase) of rats that inhaled 2,000 ppm sBA (6,000 mg/m^3) for 3 days and 500 ppm (1,500 mg/m^3) for 5 days.

Additional information on subchronic effects by inhalation may be gained from the reproductive toxicity study by Nelson *et al* (1989) (Section 8.6.2).

8.3.4 Evaluation

There are few repeated-exposure toxicity studies that have been conducted for sBA specifically. However, significant information indicating a low subchronic toxicity potential for sBA is available from a 2-generation study with sBA and also from toxicity studies conducted on MEK (Section 9), the major initial metabolite of sBA. Based on these data, sBA appears to be of low subchronic toxicity via the inhalation and oral exposure routes.

8.4 Genotoxicity

8.4.1 *In vitro*

Gene mutation

sBA was found to be not genotoxic *in vitro* in bacteria and yeast, with or without metabolic activation (Table 18). Cytotoxicity was not seen in these studies, except for one test on TA100 at high concentration.

Table 18: Gene mutation assays in bacteria and yeast, with or without metabolic activation [a]

Species, strain	Concentration, test condition	Endpoint / Result [b]	Remark	Reference	CoR
	(mg/plate)	**Histidine reversion**			
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Up to 10, pre-incubation	**-ve** **-ve**	Cytotoxic at 10 mg/plate on TA100 without S9	Elf Atochem, 1989	1a
Salmonella typhimurium TA98, TA100, TA1535, TA1537, TA1538	Up to 4, plate incorporation	**-ve**		Brooks *et al*, 1988	1a
Escherichia coli WP2 uvrA pKM101	Up to 4, plate incorporation	**-ve**		Brooks *et al*, 1988	1a
	(mg/ml)	**Gene conversion**			
Saccharomyces cerevisiae JD1	Up to 5	**-ve**		Brooks *et al*, 1988	1a

[a] Aroclor 1254-induced rat liver S9-mix

[c] -ve, negative: not mutagenic

Chromosomal damage

No clastogenic activity was seen in a chromosomal aberration assay with cultured Chinese hamster ovary (CHO) cells treated with sBA up to 5 mg/ml, with or without metabolic activation (rat S9), in the absence of cytotoxicity (Brooks *et al*, 1988).

8.4.2 In vivo

Barilyak and Kozachuk (1988; CoR 3a) reported that intragastric administration to rats of sBA, and 11 other alcohols, at 1/5th of the LD_{50} level, resulted in clastogenic effects to bone marrow cells. The authors noted that exposure to all 12 alcohols examined increased the numbers of polyploid cells, cells with chromosome gaps, and cells with chromosomal aberrations. The results of this study appear to be rather unique since alcohols in general do not exert such effects (ECETOC, 1995; Boatman, 2001; Boatman and Knaak, 2001). Further doubt is cast on this finding by the results of two *in vivo* assays with MEK, the primary metabolite of sBA, which did not show an increase in micronucleated polychromatic erythrocytes (Section 9.2).

8.5 Chronic toxicity and carcinogenicity

sBA has not been evaluated for chronic toxicity or carcinogenicity. However, given the lack of genotoxic potential and low order of repeated dose toxicity, sBA is not considered potentially carcinogenic.

8.6 Reproduction, embryotoxicity and teratogenicity

8.6.1 Reproductive toxicity

In a 2-generation reproductive toxicity study, sBA was initially administered at concentrations of 0, 0.3, 1.0 or 3.0% (0, 3, 10 or 30 g/l) in the drinking water of male and female Wistar rats (30/sex/group). There were no signs of toxicity in terms of growth and reproduction efficiency at 0.3 and 1.0%. In the group exposed to 3.0%, there was a reduction in body weight gain during the 8-wk pre-mating period, in the number of pups born, and in pup body weight, but fertility was not affected. Due to toxicity, the concentration was reduced to 2.0% at the high dose for the second generation. In the second generation, the high dose level caused a slight but not significant depression in growth of weanling rats. The NOAEL for reproduction parameters was 1.0%, estimated by the authors to be 1,500 mg/kgbw/d (Cox *et al*, 1975; CoR 1b; Gallo *et al*, 1977; CoR 4a) or 1,771 mg/kgbw/d by IRIS (US-EPA, 1993).

8.6.2 Developmental toxicity

Oral

In the course of the 2-generation reproductive toxicity of Cox *et al* (1975) (Section 8.6.1) a teratogenic phase was added in which the parent dams (28 - 30/group) were re-bred (2nd litter) and subjected to Caesarean section on day 20 of gestation. At 2.0%, sBA caused a significant depression in foetal weight, with evidence of retarded skeletal maturation, but no skeletal or visceral malformations. The authors concluded that these changes were consistent with mild toxicity and were reminiscent of stress lesions. At 0.3 and 1.0%, there were no effects. The NOAEL for developmental parameters was 1.0%, estimated to be 1,500 mg/kgbw/d by the authors (Cox *et al*, 1975; CoR 1d; Gallo *et al*, 1977; CoR 4a) and 1,771 mg/kgbw/d by IRIS (US-EPA, 1993).

Inhalation

In a developmental toxicity study, groups of 15-16 rats were exposed (7 h/d) by inhalation to 0, 3,500, 5,000 or 7,000 ppm sBA (0, 10,800, 15,000 or 22,000 mg/m^3) on days 1 to 19 of gestation; the dams were sacrificed on day 20. At 7,000 ppm, narcosis was observed in all animals. At 5,000 ppm, the dams were partially narcotised with locomotion activity impaired. Maternal weight gain and food consumption were significantly reduced in all dose groups. The number of live foetuses was significantly reduced and resorptions were increased in the high exposure group only. Foetal body weights were significantly reduced in the mid- and high dose groups. There was no evidence of teratogenic effects or selective developmental toxicity. For maternal toxicity the NOAEL was < 3,500 ppm. For developmental toxicity the NOAEL was 3,500 ppm (Nelson *et al*, 1989; CoR 1b).

8.6.3 Evaluation

sBA has not produced toxic effects to reproduction or teratogenic effects in the developing embryo/foetus of laboratory animals. Developmental effects, such as delayed development, have been produced in laboratory animals with sBA, but only at doses that also produced toxicity in the dams. Further support for a lack of developmental toxicity is provided by studies conducted on MEK, the major initial metabolite of sBA (Section 9.3).

8.7 Neurotoxicity

Short-term exposure to sBA, like many other organic solvents, produces reversible depression of CNS activity at high concentrations (Snyder and Andrews, 1996; CoR 4b). Laboratory animals that were exposed to acutely-toxic doses of sBA exhibited clinical signs of CNS depression that were reversible in survivors upon termination of exposure (Section 8.1).

One, limited, acute study of neurotoxicity in laboratory animals is reported for sBA. A simple functional test, the tilted plane test, was conducted in rats that received a single oral dose of sBA and the results compared with analogous doses of ethanol, propanols, and other butanols. An sBA dose of 0.0163 mol/kgbw (approximately 1.21 g/kgbw) produced a greater intoxication effect than ethanol (relative molar intoxicating effect values of 4.4 and 1 for sBA and ethanol, respectively) and exhibited a slower recovery to normal behaviour (Wallgren, 1960; CoR 3c).

There are also reported several *in vitro* neurological studies that included sBA among groups of alcohols studied to establish neurological mechanisms of acute alcohol intoxicating effects (Lyon *et al*, 1981; Rand and Li, 1994; Tanii *et al*, 1995). Those studies, however, are of low value in assessing functional neurological effects associated with acute sBA exposure (CoR 3c).

The potential for neurotoxicity associated with repeated exposure to sBA has not been specifically evaluated. sBA caused partial narcosis at 5,000 ppm (15,000 mg/m^3) in pregnant rats in the developmental toxicity study by Nelson *et al* (1989) (Section 8.6.2). The few repeated exposure studies available (Section 8.2) did not indicate enduring adverse CNS effects; however, the experimental design of those studies does not permit definitive assessment.

Further support of an anticipated low neurotoxicity potential for sBA following repeated exposure may be gained from toxicity studies conducted on MEK, the major initial metabolite of sBA (Section 9.4).

8.8 Other effects

sBA inhibited the contraction of depolarised guinea pig ileum induced by calcium chloride (Yashuda *et al*, 1976), produced an increase in cyclic AMP in human peripheral lymphocytes (Atkinson *et al*, 1977) and enhanced microsomal enzymes and metabolism (Aarstad *et al*, 1985; Traiger *et al*, 1989; Page and Carlson, 1993; Gadberry and Carlson, 1994). Also, sBA potentiated the toxicity of carbon tetrachloride (Cornish and Abefuin, 1967). The experimental designs of these studies, however, limit their application to the hazard assessment of sBA (CoR 3c).

Inhalation exposure of rats to high concentrations of sBA induced microsomal P450 activity in liver and kidney. Orally administered sBA also induced microsomal mixed function oxidase activity, which may have contributed to the potentiation of carbon tetrachloride hepatotoxicity (Traiger and Bruckner, 1976; CoR 2e). MEK has also been reported to potentiate the hepatotoxicity of halogenated hydrocarbons (Section 9.6), and this corroborates the same effect reported for sBA.

9. OTHER CONSIDERATIONS AND SUPPORTIVE DATA ON METHYL ETHYL KETONE

Additional insight into the overall toxicological profile of sBA can be gained from available toxicity studies on MEK [a], the major initial metabolite of sBA. The metabolic relationship between sBA and MEK has been established in pharmacokinetic studies (Section 7).

This does not necessarily mean that MEK data can principally serve as a surrogate for absent studies on sBA. The oxidative conversion of sBA to MEK, mediated by ADH, is rate-limited and does not allow sBA to be oxidised all at once (Section 7.3). Consequently, it is possible that sBA may have toxicological properties that are attributable to the parent compound itself, i.e. local effects such as irritation and acute toxicity. The use of MEK data (discussed below) is therefore confined to the examination of possible low to medium dose effects of this metabolite that might be of relevance for sBA.

The toxicology profile for MEK has been critically reviewed by a number of organisations (ATSDR, 1992; IPCS, 1993) and earlier by ECETOC (1983). The overall conclusion was that MEK is of low concern for adverse health effects.

9.1 Subchronic toxicity

MEK produces minimal or no systemic effects in laboratory animals following repeated exposure at high doses. This is supported by a number of subchronic toxicity studies that were conducted using multiple experimental animal species and a variety of exposure routes (ATSDR, 1992; IPCS, 1993).

The most comprehensive subchronic toxicity study available for MEK is a study in Fischer 344 rats (15/sex/group) that were exposed (6 h/d, 5 d/wk) to 0, 1,250, 2,500 or 5,000 ppm MEK vapour (0, 3,750, 7,500 or 15,000 mg/m^3) for 90 days. The animals were examined for clinical signs of toxicity and changes in body weight, clinical pathology parameters (haematology and serum chemistry), gross pathology and histopathology, and neuropathology. The results indicated that none of the exposure concentrations were lethal or even significantly harmful. There were no adverse effects on the clinical health or growth of male or female rats, with the exception of a depression of mean body weight in the 5,000 ppm groups. The female rats exposed to 5,000 ppm showed slightly increased liver weight, slightly decreased brain and spleen weights, and slightly altered blood chemistry in comparison with controls. Male rats at 5,000 ppm exhibited only a slightly increased liver weight. At the lower concentrations (1,250 and 2,500 ppm), there was slightly increased liver weight for female rats and no significant differences for males. Pathological examination did not reveal any lesions that could be attributed to MEK (Cavender *et al*, 1983; CoR 1d). The increase in liver weights and altered serum enzyme activities indicate a MEK treatment-related effect. However, since histopathological lesions were not observed, those responses are likely to be the result of a physiologic adaptation mechanism. Hence a NOAEL of 5,000 ppm can be concluded.

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[a] Methyl ethyl ketone, CAS No. 78-93-3, formula CH_3-CO-CH_2-CH_3, molecular mass 72.11; 1 ppm = 2.998 mg/m^3 at 20°C

In the study of Cavender *et al*, there were no findings of respiratory tract irritation, which differed from the outcome of an earlier subchronic inhalation toxicity study in Wistar rats (5 males/group) in which all animals exposed to 6,000 ppm (18,000 mg/m^3) died suddenly during the 7th week, with pathologically confirmed bronchopneumonia (Altenkirch *et al*, 1978; CoR 3b). The significance of the respiratory tract effect and its pathogenesis, found in the one study but not the other, is unclear. Respiratory effects may be considered to be more related to concentration than to (systemic) dose. In conclusion, the respiratory effects found with MEK may have no relevance to sBA toxicity.

9.2 Genotoxicity

9.2.1 *In vitro*

MEK has been evaluated in 11 *in vitro* tests for genotoxicity, including assays on bacteria (*S. typhimurium*) for histidine reversion, yeast (*S. cerevisiae*) for mitotic gene conversion and induction of mitotic aneuploidy, rat liver RL4 cells for chomosome aberrations, BALB/3T3 cells for cell transformation and primary rat hepatocytes for unscheduled DNA synthesis. Almost all results, except for two tests for aneuploidy in yeast, have been negative, as reviewed by IPCS (1993).

9.2.2 *In vivo*

When MEK [a] dissolved in corn oil was administered *i.p.* to mice at 1.96 ml/kgbw (LD_{20} value, equivalent to 1.58 mg/kgbw], and micronucleated polychromatic erythrocytes in bone marrow cells were determined at 12, 24 and 72 hours, there was no increase in micronucleated erythrocytes at any time interval (O'Donoghue *et al*, 1988; CoR 1d). Similarly, MEK administered *i.p.* to Chinese hamsters at 411 mg/kgbw caused no effect on bone marrow cells (Basler, 1986; CoR 2c).

9.2.3 Conclusion

The fact that MEK was negative *in vivo* indicates that the metabolic precursor sBA would also be without genotoxic activity *in vivo*.

[a] Relative density D420 = 804 - 806 (ECETOC, 1993)

9.3 Reproductive and developmental toxicity

9.3.1 Reproductive toxicity

MEK has not been evaluated for effects on reproductive function, but has been assessed for structural changes to male and female reproductive organs. In the subchronic toxicity study by Cavender *et al* (1983; CoR 1d) (Section 9.1), histopathological examinations were conducted on the testes, epididymides, seminal vesicles, vagina, cervix, uterus, oviducts, ovaries and mammary glands of rats that were exposed to MEK vapour at concentrations up to 5,000 ppm (15,000 mg/m^3) for 90 days. No exposure related lesions to the reproductive organs of either sex were found in this study.

9.3.2 Developmental toxicity

MEK has been studied in both rats and mice, whereas sBA has been studied only in the rat (Section 8.6.2).

In the earliest developmental toxicity study conducted for MEK, pregnant Sprague-Dawley rats were exposed to MEK at concentrations of 0 (47 females/group), 1,000 (29/group) or 3,000 ppm (21/group) (0, 3,000 or 9,000 mg/m^3) on days 6 to 15 of gestation. No maternal effects or foetal resorptions were seen. At 1,000 ppm, there was a decrease in foetal body weight and crown-rump length, but this was not observed in the 3,000 ppm rats. There were no significant increases in gross, soft tissue, or skeletal effects in litters of dams exposed to 1,000 ppm MEK. In the 3,000 ppm group, there was a significant increase in the number of foetuses and litters with gross anomalies. No statistically significant specific soft tissue malformations or alterations were seen, but the total number of litters with abnormal foetuses was significantly greater than controls. The authors concluded that MEK was embryotoxic, foetotoxic and potentially teratogenic (Schwetz *et al*, 1974; CoR 2e). In an attempt to confirm these effects, the same group (Deacon *et al*, 1981; CoR 2e) conducted a further study, identical in experimental design except for the inclusion of an additional level of exposure at 400 ppm (1,200 mg/m^3). Decreased maternal body weight and increased water consumption were seen in the 3,000 ppm group; no other maternal effects were noted. This second study supported the previous findings of skeletal anomalies in the high-dose group. Skeletal abnormalities, including delayed ossification of cervical centre, sternebral malformations and asymmetric pelvis were observed at 3,000 ppm. No statistically significant differences in external soft tissue abnormalities were found in the offspring of dams exposed to 3,000 ppm MEK or less during gestation, nor were there effects observed on the number of live foetuses/litter or on foetal crown-rump length. Thus, this study did not confirm the effects observed earlier by Schwetz *et al* (1974) at the mid-dose only and the authors (Deacon *et al*) concluded that MEK was slightly foetotoxic, but not embryotoxic or teratogenic at 3,000 ppm.

In a study with pregnant Crl:CD-1 Swiss albino mice (23 - 28 females/group), MEK was administered (7 h/d) by inhalation at approximately 0, 400, 1,000 and 3,000 ppm vapour (0, 1,200, 3,000 or 9,000 mg/m^3). The only maternal effect observed was a concentration-related increase in relative liver and kidney weight, which was statistically significant in the 3,000 ppm dams. A reduction in mean foetal body weight was statistically significant in males at this maternal dose level. There was no increase in the incidence of intrauterine death, but there was a significant trend for an increased incidence of misaligned sternebrae, when measured on a foetus, but not litter, basis. There were a small number of foetuses with malformations in exposed groups but the increases were not statistically significant (Schwetz *et al*, 1991; CoR 1d).

The evaluation of European Commission "Group Specialised Experts in the fields of Carcinogenicity, Mutagenicity and Reproductivity" concluded that MEK did not require classification for developmental toxicity due to the lack of selective reproductive toxicity in one study and the small number of overall foetuses with gross malformations (EC, 1998a,b).

In a limited developmental neurotoxicity study, *n*-hexane [a] (500 - 1,500 ppm [1,800 - 5,400 mg/m^3]), MEK (800 - 1,500 ppm [2,400 - 4,500 mg/m^3]) and a mixture of n hexane and MEK (1,200:300 ppm [4,300:900 mg/m^3]) were administered (23 h/d, 7 d/wk) by inhalation to Wistar rats (8/group) throughout gestation and postnatal development. Controls were without solvent exposure. Three pregnant rats exposed to 800 ppm MEK failed to deliver litters. While all control dams in the MEK experiment delivered litters, 6 of the 16 control dams in the n hexane experiment failed to produce litters (Stoltenburg-Didinger *et al*, 1990; CoR 3a,b). It follows that the reliability of the results in the MEK-exposed group is questionable. This study is also very poorly reported, with little information or data provided on MEK alone.

9.3.3 Evaluation

The developmental toxicity studies do not rule out the possibility of developmental toxicity on the part of MEK at high dose levels. For sBA, the available studies (in rats) do not indicate a similar potential for developmental toxicity. This, however, is not regarded as contradictory, since the rate-limiting steps of sBA oxidation appears to preclude similar peak levels as those with MEK (Section 7.3). A clear NOAEL of 3,500 ppm (10,800 mg/m^3) for developmental toxicity (Section 8.6.2) can be ascribed to sBA.

[a] C_6H_{14}, molecular weight 86.17; 1 ppm = 3.583 mg/m^3 at 20°C

9.4 Neurotoxicity

A number of repeated exposure studies have been conducted to assess the potential for MEK to produce neurotoxic effects. These studies included multiple (mammalian and avian) species and utilised a variety of exposure routes. Evaluations for peripheral nervous system effects have been of special interest because of the proven peripheral neuropathy induced by the homologous ketone solvent, methyl *n*-butyl ketone.

Sprague-Dawley rats (12/group, sex not stated) were exposed (24 h/d, 7 d/wk) by inhalation to 1,125 ppm MEK (3,373 mg/m^3) for up to 5 months without effect (Saida *et al*, 1976; CoR 2e). Wistar rats exposed to MEK for 7 weeks were without evidence of neuropathological lesions (Altenkirch *et al*, 1978); similarly, repeated exposure for 90 days produced no neurological abnormalities (Cavender *et al*, 1983) (the latter two studies are detailed in Section 9.1). These three findings were confirmed by Krasavage and O'Donohogue (1977; CoR 2e) and Egan *et al* (1980; CoR 2e). MEK injected (2 x/d, 5 d/wk) *s.c.* for 8.5 months did not produce nervous system damage in cats (Spencer and Schaumburg, 1976; CoR 2e) or dogs (O'Donohogue, 1976; CoR 2e). Finally, nervous system damage was not produced following dermal application (O'Donohogue *et al*, 1978; CoR 2d). The overall evidence from these repeated exposure studies indicates that MEK does not produce permanent structural damage to the nervous system or changes in behaviour.

9.4.1 Potentiation of hexacarbon neurotoxicity

Although MEK is not considered to be neurotoxic when administered alone, it has been shown to potentiate hexacarbon-induced peripheral neuropathy in laboratory animals. Co-exposure of MEK with doses of *n*-hexane, methyl *n*-butyl ketone, ethyl *n*-butyl ketone or 2,5-hexanedione that were high enough or given for a sufficient period of time, caused clinical signs of the resulting peripheral neuropathy to be more severe or occur earlier. Doses of hexacarbons too low to produce signs of neuropathy, when combined with MEK, resulted in subtle changes such as reduced nerve conduction velocity, elevated microsomal enzymes and reduced clearance of 2,5-hexanedione (Altenkirch *et al*, 1978, 1979, 1982a,b).

The potentiation of hexacarbon neurotoxicity is not unique to MEK, but is shared by other short chain aliphatic ketones such as methyl *n*-propyl ketone, methyl *n*-amyl ketone, methyl *n*-hexyl ketone, and methyl isobutyl ketone; none of which appear to be intrinsically neurotoxic. The mechanism by which MEK potentiates hexacarbon neurotoxicity is not well understood. Metabolic interactions may contribute but are not thought to be completely responsible for the potentiation (IPCS, 1993). No potentiation of neurotoxicity has been reported with sBA, but because it can be metabolised to MEK, sBA may also potentiate neurotoxicity of certain chemicals.

9.5 Potentiation of haloalkane toxicity

Exposure to MEK alone produces only slight toxic effects to the liver of rats. However, when MEK was administered several days prior to the hepatotoxic haloalkanes chloroform or carbon tetrachloride, the hepatotoxicity was potentiated. This effect is shared by many oxygenated solvents, and is due, at least in part, to an induction of the cytochrome P450 isoenzymes, which metabolise haloalkanes to toxic free radical intermediates. An oral dose as low as 0.072 g/kgbw of MEK potentiated effects of chloroform administered 18 hours later, but inhalation exposure (10 h/d) of rats to 600 ppm (1,800 mg/m^3) of MEK for 10 days had little effect on cytochrome P450 enzymes in the liver (IPCS, 1987).

Studies have suggested that the common metabolite 2,3-butanediol may be responsible for the potentiation effects of both sBA and MEK (Dietz and Traiger, 1979; CoR 2e; Dietz *et al*, 1981; CoR 2e). There are no reports of MEK potentiation of haloalkane toxicity in humans.

10. EFFECTS ON HUMANS

10.1 Acute and subchronic toxicity

No adverse systemic effects have been reported in man from acute or repeated exposure to sBA. As sBA is a volatile organic solvent, excessive exposure by inhalation may result in headache, and other signs of central nervous system depression.

10.2 Irritation and sensitisation

sBA vapour is a weak sensory irritant in humans. Cometto-Muñiz and Cain (1993) evaluated odour detection and nasal irritation effects in groups of human volunteer anosmic subjects (lacking olfaction) and normosmic subjects (with normal olfaction) that self-inhaled sBA vapour from squeeze bottles. The average nasal irritation (pungency) and odour thresholds for sBA vapour were 5,711 and 95 ppm (17,601 and 293 mg/m^3), respectively. This suggests that the odour of sBA can be detected at low vapour concentrations, but high vapour concentrations are required to produce nasal irritation. (The threshold odour concentration is 8.0 mg/m^3, see Table 1).

sBA exposure in humans has been associated with a few clinical reports of allergic contact dermatitis (Fregert *et al*, 1969, 1971; Ludwig and Hausen, 1977). These case reports are considered unreliable, mainly because of deficiencies in reporting, and hence must be interpreted with caution.

11. FIRST AID AND SAFE HANDLING ADVICE

11.1 First aid and medical treatment

There is no specific treatment or antidote for over-exposure to sBA. Supportive medical treatment as indicated by the patient's condition is recommended.

11.1.1 Skin and eye injuries

Clothing contaminated with sBA should be removed and either discarded or laundered before re-use. Affected areas of skin should be washed with copious quantities of water. The skin should be rinsed for at least 10 minutes. If the eyes are splashed, they should be irrigated immediately with eyewash solution or clean water, holding the eyelids apart for at least 10 minutes. A physician should be consulted.

11.1.2 Inhalation

The subject exposed to sBA should be taken into fresh air, kept warm and at rest if difficulty in breathing is experienced. If the patient stops breathing, artificial respiration should be administered until qualified medical personnel is able to take over. Medical aid should be summoned immediately.

11.1.3 Ingestion

If sBA has been swallowed, do not induce vomiting as aspiration into the lungs may cause chemical pneumonitis. Never give anything by mouth to an unconscious person. A physician should be consulted immediately.

11.2 Safe handling

11.2.1 Safety at work

In order to avoid danger of fire and explosion, good ventilation at workplace and storage is essential. The industrial hygiene standards must be met. Gloves (rubber) and eye protection (close-fitting protective goggles) should be worn. Contamination of skin and clothes are to be avoided.

11.2.2 Storage safety

The material is to be stored in tightly closed vessels under cool and dry conditions.

11.2.3 Fire safety and extinguishers

A fire extinguisher should be kept at hand. Suitable extinguishing media: water spray, dry media, alcohol-resistant foam or CO_2. Containers are to be kept cool by spraying with water if exposed to fire. Foam should be applied in large quantities, since it is subject to degradation by the product.

11.2.4 Protection against fire and explosion

Measures to avoid electrostatic charges should be taken. Avoid, sources of open fire and ignition.

11.3 Management of spillage and waste

Ensure adequate ventilation and extinguish ignition sources. Damm-off and pump larger amounts into containers, soak up residue with absorbent material and disposed of in accordance with local regulations.

APPENDIX A: ABBREVIATIONS

ADH	Alcohol dehydrogenase
AUC	Area under the curve
BCF	Bioconcentration factor
bw	Body weight
BOD	Biological oxygen demand
COD	Chemical oxygen demand
CoR	Code of reliability (Appendix B)
CYP	Cytochrome P450
FID	Flame ionisation detector
GC	Gas chromatography
h	Hour
HRT	Hydraulic retention time
i.p.	Intraperitoneal
IDLH	Immediately dangerous to life or health
min	Minute
MEK	Methyl ethyl ketone
MS	Mass spectrometry
NOAEL	No-observed adverse effect level
NS	Not stated
OEL	Occupational exposure limit (value)
PBPK	Physiologically-based pharmacokinetic
POCP	Photochemical ozone creation potential
QSAR	Quantitative structure-activity relationship
s	Second
sBA	*sec*-Butanol
s.c.	Subcutaneous
STEL	Short-term exposure limit (value)
ThOD	Theoretical oxygen demand
TWA	Time-weighted average (concentration)
VOC	Volatile organic compound
wk	Week
WWTP	Wastewater treatment plant
y	Year

APPENDIX B: CRITERIA FOR RELIABILITY CATEGORIES

Adapted from Klimisch *et al* (1997)

Code of Reliability (CoR‡)	**Category of reliability**
1	Reliable without restriction
1a	GLP guideline study (OECD, EC, EPA, FDA, etc...)
1b	Comparable to guideline study
1c	Test procedure in accordance with national standard methods (AFNOR, DIN, etc...)
1d	Test procedure in accordance with generally accepted scientific standards and described in sufficient detail
2	Reliable with restrictions
2a	Guideline study without detailed documentation
2b	Guideline study with acceptable restrictions
2c	Comparable to guideline study with acceptable restrictions
2d	Test procedure in accordance with national standard methods with acceptable restrictions
2e	Study well documented, meets generally accepted scientific principles, acceptable for assessment
2f	Accepted calculation method
2g	Data from handbook or collection of data
3	Not reliable
3a	Documentation insufficient for assessment
3b	Significant methodological deficiencies
3c	Unsuitable test system
4	Not assignable
4a	Abstract
4b	Secondary literature
4c	Original reference not yet available
4d	Original reference not translated (e.g. Russian)
4e	Documentation insufficient for assessment

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No. 85 Recognition of, and Differentiation between, Adverse and Non-adverse Effects in Toxicology Studies
No. 86 Derivation of Assessment Factors for Human Health Risk Assessment

No. 87 Contact Sensitisation: Classification According to Potency
No. 88 Environmental Risk Assessment of Difficult Substances
No. 89 (Q)SARS: Evaluation of the commercially available software for human health and environmental endpoints with respect to chemical management applications
No. 90 Persistence of Chemicals in the Environment
No. 91 Aquatic Hazard Assessment II

Joint Assessment of Commodity Chemicals (JACC) Reports

No.	Title
No. 1	Melamine
No. 2	1,4-Dioxane
No. 3	Methyl Ethyl Ketone
No. 4	Methylene Chloride
No. 5	Vinylidene Chloride
No. 6	Xylenes
No. 7	Ethylbenzene
No. 8	Methyl Isobutyl Ketone
No. 9	Chlorodifluoromethane
No. 10	Isophorone
No. 11	1,2-Dichloro-1,1-Difluoroethane (HFA-132b)
No. 12	1-Chloro-1,2,2,2-Tetrafluoroethane (HFA-124)
No. 13	1,1-Dichloro-2,2,2-Trifluoroethane (HFA-123)
No. 14	1-Chloro-2,2,2-Trifluoromethane (HFA-133a)
No. 15	1-Fluoro 1,1-Dichloroethane (HFA-141B)
No. 16	Dichlorofluoromethane (HCFC-21)
No. 17	1-Chloro-1,1-Difluoroethane (HFA-142b)
No. 18	Vinyl Acetate
No. 19	Dicyclopentadiene (CAS: 77-73-6)
No. 20	Tris-/Bis-/Mono-(2 ethylhexyl) Phosphate
No. 21	Tris-(2-Butoxyethyl)-Phosphate (CAS:78-51-3)
No. 22	Hydrogen Peroxide (CAS: 7722-84-1)
No. 23	Polycarboxylate Polymers as Used in Detergents
No. 24	Pentafluoroethane (HFC-125) (CAS: 354-33-6)
No. 25	1-Chloro-1,2,2,2-tetrafluoroethane (HCFC 124) (CAS No. 2837-89-0)
No. 26	Linear Polydimethylsiloxanes (CAS No. 63148-62-9)
No. 27	n-Butyl Acrylate (CAS No. 141-32-2)
No. 28	Ethyl Acrylate (CAS No. 140-88-5)
No. 29	1,1-Dichloro-1-Fluoroethane (HCFC-141b) (CAS No. 1717-00-6)
No. 30	Methyl Methacrylate (CAS No. 80-62-6)
No. 31	1,1,1,2-Tetrafluoroethane (HFC-134a) (CAS No. 811-97-2)
No. 32	Difluoromethane (HFC-32) (CAS No. 75-10-5)
No. 33	1,1-Dichloro-2,2,2-Trifluoroethane (HCFC-123) (CAS No. 306-83-2)
No. 34	Acrylic Acid (CAS No. 79-10-7)
No. 35	Methacrylic Acid (CAS No. 79-41-4)
No. 36	n-Butyl Methacrylate; Isobutyl Methacrylate (CAS No. 97-88-1) (CAS No. 97-86-9)
No. 37	Methyl Acrylate (CAS No. 96-33-3)
No. 38	Monochloroacetic Acid (CAS No. 79-11-8) and its Sodium Salt (CAS No. 3926-62-3)
No. 39	Tetrachloroethylene (CAS No. 127-18-4)
No. 40	Peracetic Acid (CAS No. 79-21-0) and its Equilibrium Solutions
No. 41	*n*-Butanol (CAS No. 71-36-3)
No. 42	Tetrafluoroethylene (CAS No. 116-14-3)

Special Reports

No.	Title
No. 8	HAZCHEM; A Mathematical Model for Use in Risk Assessment of Substances
No. 9	Styrene Criteria Document
No. 10	Hydrogen Peroxide OEL Criteria Document (CAS No. 7722-84-1)
No. 11	Ecotoxicology of some Inorganic Borates
No. 12	1,3-Butadiene OEL Criteria Document (Second Edition) (CAS No. 106-99-0)
No. 13	Occupational Exposure Limits for Hydrocarbon Solvents
No. 14	n-Butyl Methacrylate and Isobutyl Methacrylate OEL Criteria Document
No. 15	Examination of a Proposed Skin Notation Strategy
No. 16	GREAT-ER User Manual
No. 17	Risk Assessment Report for Existing Substances Methyl tertiary-Butyl Ether

Documents

No.	Title
No. 32	Environmental Oestrogens: Male Reproduction and Reproductive Development
No. 33	Environmental Oestrogens: A Compendium of Test Methods
No. 34	The Challenge Posed by Endocrine-disrupting Chemicals
No. 35	Exposure Assessment in the Context of the EU Technical Guidance Documents on Risk Assessment of Substances
No. 36	Comments on OECD Draft Detailed Review Paper: Appraisal of Test Methods for Sex-Hormone Disrupting Chemicals
No. 37	EC Classification of Eye Irritancy
No. 38	Wildlife and Endocrine Disrupters: Requirements for Hazard Identification
No. 39	Screening and Testing Methods for Ecotoxicological Effects of Potential Endocrine Disrupters: Response to the EDSTAC Recommendations and a Proposed Alternative Approach
No. 40	Comments on Recommendation from Scientific Committee on Occupational Exposure Limits for 1,3-Butadiene
No. 41	Persistent Organic Pollutants (POPs) Response to UNEP/INC/CEG-I Annex 1
No. 42	Genomics, Transcript Profiling, Proteomics and Metabonomics (GTPM). An Introduction
No. 43	Contact Sensitisation: Classification According to Potency, A Commentary