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**HIGH PRODUCTION VOLUME (HPV)
CHEMICAL CHALLENGE PROGRAM**

TEST PLAN

For

sec-Butyl Ether

CAS No. 6863-58-7

Prepared by:

ExxonMobil Chemical Company

November 28, 2006

EXECUTIVE SUMMARY

Under the U.S. Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program (Program), ExxonMobil Chemical Company committed to voluntarily compile data that can be used in an initial assessment to characterize the hazard of sec-butyl ether (sBE; CAS No. 6863-58-7). The data for this assessment include selected physicochemical, environmental fate, and human and environmental toxicity endpoints identified by the U.S. HPV Program.

A search for studies and their review identified limited data for sBE to characterize the mammalian and environmental toxicity endpoints for the HPV Program. However, the mammalian endpoints can be characterized with data for sec-butyl alcohol (sBA; 2-butanol) and methyl ethyl ketone (MEK; 2-butanone) which are metabolites of sBE, while the environmental endpoints can be characterized with data for an analog ether and calculated toxicity data.

Results of Mackay Level I distribution modeling show, at steady state, that sBE will partition primarily to the air compartment (99.1%), with a negligible amount partitioning to water (0.5%) and soil (0.4%). Level III modeling indicates, at steady state, that water and soil are the primary compartments on a percentage basis when the default emission to each of these compartments is included in the calculations. However, Level III modeling may not be representative of the ultimate disposition of sBE because default emissions, which use 1000 kg/h/compartment, are not representative of chemical discharge.

sBE is volatile, and in the atmosphere it can be quickly degraded by indirect photolysis. The sBE half-life from hydroxyl radical attack is calculated as approximately 4 hours. Aqueous photolysis and hydrolysis will not contribute to the transformation of sBE in aquatic environments because it is either poorly or not susceptible to these reactions.

sBE has a potential to biodegrade slowly based on results of biodegradation modeling. However, a number of published studies in which non-standard guideline methods were used have demonstrated that alkyl ethers can be degraded by pure strains and mixed cultures of bacteria when incubated under aerobic conditions. The rate of biodegradation for these substances, however, is slow. Despite its potential to biodegrade at a slow rate, sBE is not expected to bioaccumulate, based on a low bioconcentration factor (BCF = 32).

Results of Quantitative Structure Activity Relationship (QSAR) modeling suggest that sBE will exhibit moderate aquatic toxicity. Estimates include a 96-hour LC₅₀ value of 14.7 mg/l for a freshwater fish; a 48-hour EC₅₀ value of 16.7 mg/l for a freshwater invertebrate; and a 96-hour EC₅₀ value of 11.0 mg/l for a green alga. Experimental results for an analog substance, n-butyl ether (nBE), support the use of the modeled data to assess the aquatic hazard of sBE. The 48-hour LC₅₀ value for nBE was 30.7 mg/l.

Based on data for sBA and MEK, the degradation products of sBE, sBE is expected to present a low order of hazard for human health. sBE presents a moderate order of hazard for environmental health. In the environment, sBE is calculated to partition primarily to the soil, water, and air phases, where biological and physical processes

mediate its degradation. Given the available data for sBE and its metabolites, no additional testing is proposed.

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sec-Butyl Ether

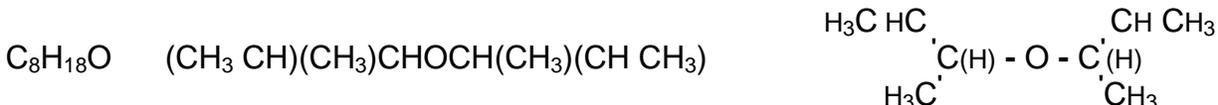
I. INTRODUCTION

Under the U.S. Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program (Program), ExxonMobil Chemical Company committed to voluntarily compile data that can be used in an initial assessment to characterize the hazard of sec-butyl ether (sBE; CAS No. 6863-58-7). This substance is supported by selected screening data needed for an initial assessment of physicochemical properties, environmental fate, and human and environmental effects endpoints identified by the U.S. HPV Program.

Procedures to assess the reliability of selected data for inclusion in this test plan were based on guidelines described by Klimisch *et al.* (1997) and identified within the U.S. EPA (1999a) document titled Determining the Adequacy of Existing Data.

II. CHEMICAL DESCRIPTION

sBE is a small molecular weight ether represented by the following chemical formula and structures:



III. TEST PLAN RATIONALE

Data used to characterize the physicochemical, mammalian and environmental toxicity, and environmental fate endpoints in the HPV Program are described below.

A literature and company search for mammalian and environmental toxicity data for sBE did not identify measured data. However, analog and metabolite data were identified that can be used to characterize the hazard of sBE for the mammalian endpoints, while adequate calculated data were developed to characterize the acute and chronic aquatic toxicity of sBE.

This assessment considered that mammalian exposure to sBE would result in potential exposures to 2-butanol (sec-butyl alcohol or sBA; CAS No. 78-92-2) and 2-butanone (methyl ethyl ketone or MEK; CAS No. 78-93-3) as metabolites of sBE. sBE has the potential to hydrolyze, resulting in two molecules of sBA. In mammalian systems sBA is either conjugated and excreted, or fairly rapidly metabolized by alcohol dehydrogenase to MEK. MEK is further metabolized to 3-hydroxy-2-butanone and 2,3-butanediol, which can also be conjugated and excreted. Data from the analog, diisopropyl ether (DIPE; CAS No. 108-20-3), are also provided as read-across data to characterize the toxicity of the parent molecule, sBE.

Data to characterize the aquatic toxicity endpoints were developed using the ECOSAR computer model (ECOSAR, 2004) provided within EPI Suite™ (2000). This model applies an equation for neutral organics to estimate aquatic toxicity and is therefore considered appropriate to estimate aquatic toxicity for sBE. As further justification, calculated data from this model for the fish effect endpoint is consistent with measured

data for an analog ether, supporting the model's use to provide adequate aquatic toxicity data for sBE.

A. Physicochemical Data

Physicochemical data (Table 1) include both calculated and measured data provided by the EPI Suite™ model (EPI Suite, 2000), as discussed in the EPA document titled The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program (US EPA, 1999b). The measured values were supplied by the database of experimental values contained within the EPI Suite model.

Table 1. Selected Physicochemical Properties for sBE.

Data Source	Melting Point (°C)	Boiling Point (°C)	Vapor Pressure (hPa @ 25°C)	Water Solubility (mg/L @ 25°C)	Log K_{ow} (25°C)
Calculated	-73	116	29.7	327	2.87
Measured	-100*	na	21.7*	330**	3.35**

* Measured value for sBE from the experimental values database contained within EPI Suite

** Measured value for the analog n-butyl ether

na Data not available for this endpoint

B. Mammalian Toxicity Data

Metabolite and Analog Justification

As discussed in the Test Plan Rationale, data are available for sBA on the following endpoints: acute toxicity (oral, inhalation, dermal), irritation (skin, eye, respiratory tract), reproductive toxicity, developmental toxicity, and genotoxicity. MEK is a major metabolite of sBA and based on its structural similarity with sBA, it's data will be used to address the repeated dose toxicity and supplement the genotoxicity endpoints for sBE. Additionally, diisopropyl ether (DIPE) is a small molecular weight ether similar to sBE and the mammalian toxicity data identified for DIPE can be used as an analog to characterize the mammalian toxicity of sBE, as their inherent toxicities are expected to be similar.

Toxicokinetics and Metabolism

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

Saito (1975) administered 2 ml/kg sBA (approximately 1.6 g/kg) orally to rabbits and blood samples were collected and analyzed by gas chromatography. Approximately 1 mg/ml sBA was found in blood after 1 hour, with 0.7 mg/ml present after 7 hours, and only trace amounts after 10 hours. sBA was metabolized via alcohol dehydrogenase to MEK, which was detected in the blood, reaching its maximum level in the blood after 6 hours. sBA was excreted via exhalation (3.3% of the original dose) and urine (2.6%), but more of the original sBA was excreted as its metabolite MEK. MEK excretion via exhalation and urine were 22.3% and 4.1% of the original dose, respectively. In another

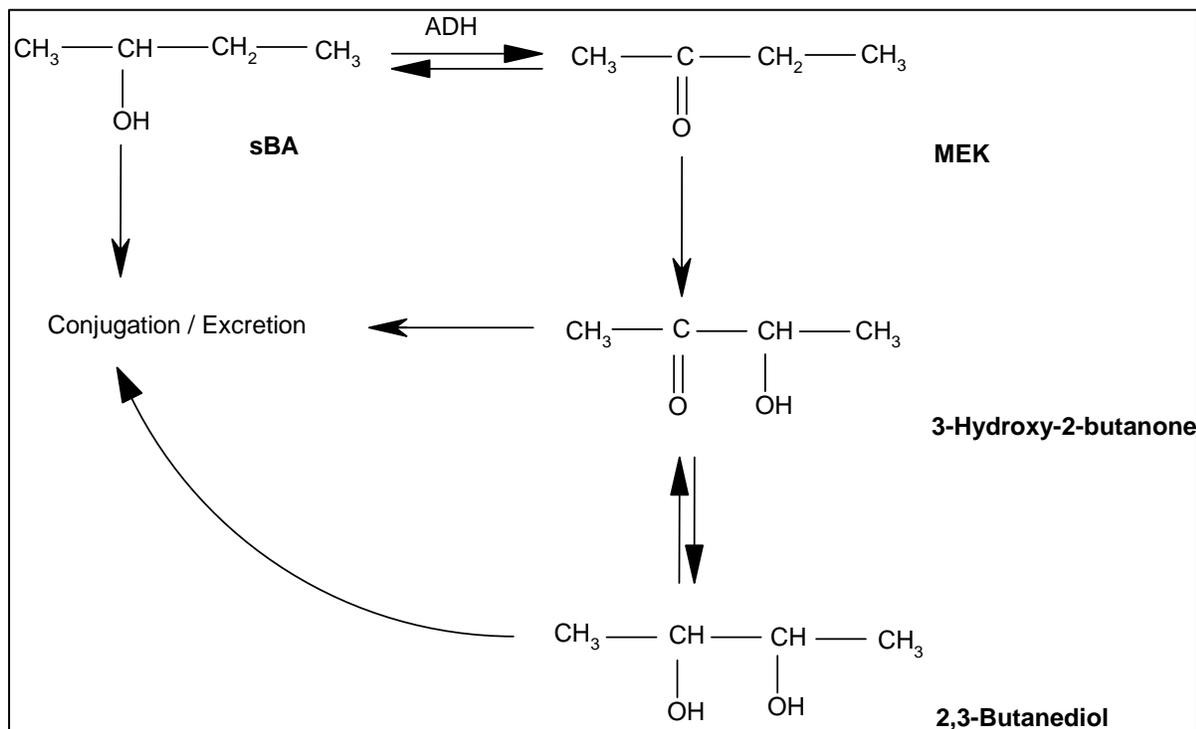
study, 14% of an 8 mmol/kg [approximately 600 mg/kg] oral dose of sBA in rabbits was excreted in the urine as a glucuronic acid conjugate (Kamil, 1952 as cited by Williams, 1959). Majority of the remaining dose was metabolized to MEK.

In rats, Traiger and Bruckner (1976) found a blood elimination half-life of 2.5 hours (after an oral dose of 2.2 ml/kg). One hour after administration, a maximum blood sBA level of 800 mg/l was found; the MEK level at that time point was 430 mg/l and rose to a maximum of 1050 mg/l 4 hours after the sBA administration.

DiVincenzo *et al.* (1976) examined the metabolism and clearance of MEK, the primary sBA metabolite, in serum of male guinea pigs following a single i.p. dose 450 mg/kg MEK as a 25% solution in corn oil. Metabolites were identified in serum by gas chromatography-mass spectrometry. The serum half-life of MEK was determined to be 270 minutes, and the clearance time was 12 hours. sBA, 3-hydroxy-2-butanone and 2,3-butanediol were identified as the serum metabolites of MEK. Reduction at the carbonyl group led to the formation of sBA from MEK. The sBA is then likely eliminated in urine as *o*-sulfates or *o*-glucuronide or may enter the intermediary metabolism to be eliminated as CO₂ or incorporated into tissues. Oxidation of MEK appeared to proceed by hydroxylation of the ω-1 carbon to form 3-hydroxy-2-butanone, which is further reduced to 2,3-butanediol (DiVincenzo *et al.*, 1976).

The following metabolic scheme is proposed (Figure 1):

Figure 1. Metabolic Pathways of sBA.



Dietz *et al.* (1981) developed a physiologically based pharmacokinetic 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 the 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 observed data. The authors reported that that 97% of sBA administered orally at 1,776 mg/kgbw to rats was oxidized via alcohol dehydrogenase to MEK. Equimolar doses (1,776 mg/kg/bw) of sBA and MEK produced very similar maximum blood concentrations (C_{max}) and areas under the concentration curve (AUC) for both MEK and 2,3-butanediol (Table 2).

Table 2. Blood Parent and Metabolite Concentrations after Administration of sBA and MEK to Rats.

	Parent and Metabolite Concentrations Following Oral sBA Dose ^a			
	sBA	MEK	3-Hydroxy-2-butanone	2,3-Butanediol
PEAK at time after dosing (mg/ml)	0.59 (2 hr)	0.78 (8 hr)	0.04 (12 hr)	0.21 (18 hr)
AUC (mg hr/L)	3254	9868	443	3167
	Parent and Metabolite Concentrations Following Oral MEK Dose ^b			
	MEK	sBA	3-Hydroxy-2-butanone	2,3-Butanediol
PEAK at time after dosing (mg/ml)	0.95 (4 hr)	0.033 (6 hr)	0.027 (8 hr)	0.26 (18 hr)
AUC (mg hr/L)	10, 899	414	382	3863

^a 1,776 mg sBA/kg, or 2.2 ml/kg of a 22% aqueous solution

^b 1,690 mg MEK/kg, or 2.1 ml/kg of a 21% aqueous solution

PEAK Maximum concentration measured

AUC Area under the concentration curve

In addition, human study data are available. The kinetics of inhaled MEK has been studied in human volunteers exposed in an exposure chamber (Liira *et al.*, 1988). Nine healthy males were exposed to 200 ppm MEK for 4 hours on two separate occasions, one with only sedentary activity and one that included three 10-minute periods of exercise. Relative pulmonary uptake of about 53% was found throughout a 4-hour inhalation exposure period. Blood MEK concentrations rose steadily throughout the exposure period without achieving a steady state. Exercise increased the overall blood MEK level markedly in comparison to sedentary activity. Only 2-3% of the absorbed dose was excreted unchanged by exhalation. This value is much lower than the pulmonary excretion observed after an oral dose of MEK (30%) by Munies and Wurster (1965).

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 metabolized via pathways of the intermediary metabolism, e.g. converted to acetate or acetoacetate via the 3-hydroxy-2-butanone intermediate metabolite.

Health

The data on metabolism and pharmacokinetics of sBA in animals indicate that this chemical is rapidly absorbed, partly excreted as conjugates, but mostly metabolized to MEK. The MEK is subsequently converted to metabolites that are exhaled, excreted in the urine, or incorporated into endogenous metabolism. Based on this metabolic relationship, the toxicities of sBA and MEK in animals are considered to be very similar. It is assumed that the metabolic relationship between sBA and MEK in humans will be similar to that in rats.

sBA has a low order of acute toxicity to mammals. Oral LD₅₀ values in laboratory animals range from approximately 2.2 to 6.5 g/kg body weight. The dermal LD₅₀ value for sBA in rats was greater than 2 g/kg body weight. The inhalation LC₅₀ for sBA is between 8,000 and 16,000 ppm for a 4-hr exposure. sBA liquid is practically non-irritating to the skin, but corrosive to the rabbit eye. It is a weak irritant to the respiratory tract of mice. sBA is not a skin sensitizer in animal studies.

In the Aarstad (1985) study, inductions of cytochrome P-450 concentrations were found in the livers (33% increase) and kidneys (47% increase) of rats that inhaled, 2,000 ppm sBA vapors for 3 days and 500 ppm vapors for 5 days, respectively. Information on repeated-dose toxicity of sBA can be deduced from a two-generation reproductive toxicity study (Cox *et al.*, 1975; Gallo *et al.*, 1977). sBA was initially administered to the F0 generation at concentrations of 0, 0.3, 1.0, and 3.0% in the drinking water. Due to toxicity at the 3%, the highest dose level; was reduced to 2.0% for the second-generation (F1 30/sex/group) that was reared to maturity (up to week 12), mated to produce a F2 generation, then sacrificed for organ weights, and gross and microscopic pathological evaluations. Ten F1 animals/sex/group were evaluated for hematological, biochemical, and urinary parameters at termination. A series of mild changes in the kidney (non-reactive tubular degeneration, tubular casts, foci of tubular regeneration, microcysts) were observed in animals treated with 2.0% sBA. The authors concluded that these findings were non-specific effects due to increased renal workload, possibly from an increased urine volume and pressure at the high dose of sBA. These effects were not considered to be a result of direct toxicity and did not have clear pathologic significance. No significant findings were seen. The no-effect level for the study was 1.0% (estimated to be approximately 1500 mg/kg/day by the authors and 1771 mg/kg/day by EPA/IRIS). The most comprehensive repeated-dose toxicity study available for MEK was conducted in rats by Cavender *et al.* (1983). None of the exposure concentrations (1,250, 2,500, or 5,000 ppm MEK vapor for 6 hours per day, 5 days per week, for 90 days) were lethal or even significantly harmful. There were no adverse effects on the clinical health or growth of male or female rats except a depression of mean body weight in the 5,000 ppm group. The female rats exposed to 5,000 ppm for 90 days showed only slightly increased liver weight, slightly decreased brain and spleen weights, and slightly altered blood chemistry in comparison with

controls. Male rats that received this exposure exhibited only a slightly increased liver weight. At the lower concentrations (1,250 and 2,500 ppm), there was only slightly increased liver weight for female rats and no significant differences for males. The pathological examination did not reveal any lesions that could be attributed to MEK exposure. The liver changes found in the study, an increase in liver weights and altered serum enzyme activities, indicate a MEK treatment-related effects; however, since histopathological lesions were not observed, these responses may have been the result of a physiologic adaptation mechanism. There were no findings of respiratory tract irritation in this study.

Additional information on repeated-dose effects by inhalation may be gained from a modified developmental study by Nelson *et al.* (1989). Rats were exposed by inhalation to 0, 3,500, 5,000 or 7,000 ppm sBA, 7 hours/day on days 1-19 of gestation and at 7,000 ppm, narcosis was observed in all animals. At 5000 ppm, the dams were partially narcotized with locomotion activity impaired. Maternal weight gain and food consumption was significantly reduced in all dose groups. The number of live fetuses was significantly reduced and resorptions were increased in the high exposure group only. Fetal body weights were significantly reduced in the mid- and high dose groups. There was no evidence of teratogenic effects in this study, and there was also no evidence of selective developmental toxicity. The no-effect levels were < 3,500 ppm for maternal toxicity and 3,500 ppm for developmental toxicity. In a two-generation reproductive toxicity study (Cox *et al.*, 1975; Gallo *et al.*, 1977), all findings at 0.3 and 1.0% were negative in both generations with respect to signs of toxicity in terms of growth and reproduction efficiency. In the group exposed to 3.0%, there were reductions in body weight gain during the 8-week pre-mating period, in number of pups born, and in pup body weight, but fertility was not affected. Due to toxicity, the high level was reduced to 2.0% for the second generation. In the second generation, the high level caused a slight but not significant depression in growth of weanling rats. The no-effect level for reproduction parameters was 1.0% (estimated to be 1500 mg/kg/day by the authors, and 1771 mg/kg/day by EPA/IRIS). Overall the weight of evidence indicates that sBA does not produce reproductive or teratogenic toxic effects in the developing embryo/fetus of laboratory animals.

sBA was inactive in *in vitro* tests for mutagenicity in both bacteria and yeast in either the presence or absence of metabolic activation (Brooks *et al.*, 1988; Elf Atochem, 1989). There was no structural damage to chromosomes observed in cultured mammalian cells (Chinese hamster ovary) treated with sBA (Brooks *et al.*, 1988). An evaluation of MEK in *in vivo* genotoxicity provides additional information on the potential for genotoxicity of sBA *in vivo*. MEK did not cause an increase in micronucleated polychromatic erythrocytes in two *in vivo* assays. MEK was also negative in the mouse lymphoma test, the chromosome aberration assay, and liver hepatocyte unscheduled DNA synthesis assay, MEK produces minimal or no systemic effects in laboratory animals following repeated exposure to high doses.

Acute Oral Toxicity

sBA has a low order of acute toxicity to mammals. The available data are reviewed below (Table 3). Clinical signs observed with acute intoxication following exposure to high levels of sBA in laboratory animals include variable expressions of central nervous system depression. Among the clinical effects reported were restlessness, ataxia,

prostration, decreased respiratory rate, narcosis and death. (Price, 1986; Hansen and Nielsen, 1994).

Table 3. Oral LD₅₀ values for sBA.

Species and Exposure Condition	Result	Clinical Signs	Reference	CoR*
Rat, male Carworth-Wistar; diluted, 20%	LD ₅₀ = 6480 (5730-7320) mg/kg	Not reported	Mellon, 1951; Smyth <i>et al.</i> , 1954	2
Rat, male and female Fischer 344; undiluted sBA (99.5%); gavage dose - key study	LD ₅₀ = 2193 (1608-4146) mg/kg	Gait and/or posture abnormalities, coma, prostration	Price, 1986	1

* Criteria of reliability; see Appendix A

Acute Inhalation Toxicity

Studies by Mellon (1951) and Smyth *et al.* (1954) suggest that the LC₅₀ for sBA is between 8,000 and 16,000 ppm for a 4-h inhalation exposure (Table 4). A vapor concentration of 10,000 ppm administered for 7 hours was lethal to rats (Nelson *et al.*, 1989).

Table 4. sBA Inhalation Toxicity Data.

Species and Exposure Condition	Result	Clinical Signs	Reference	CoR*
Rat, male and female Carworth-Wistar; 4-h exposure	16,000 ppm killed 5/6 rats	Not reported	Smyth <i>et al.</i> , 1954	2
Rat, male and female Carworth-Wistar; 4-h exposure	8000 ppm killed 1/6 rats	Not reported	Mellon, 1951	2
Rat, female Sprague-Dawley; 7-h exposure	10,000 ppm killed 5/5 rats	Not reported	Nelson <i>et al.</i> , 1989	2

* Criteria of reliability; see Appendix A

Acute Dermal Toxicity

In an acute dermal toxicity study (Price, 1986), ten male and female Fischer 344 rats had sBA applied to the skin under an occlusive patch. Results of the study indicated no mortality at 2000 mg/kg and no clinical signs were observed.

Corrosiveness and Irritation

Skin Irritation

Using an OECD 404-test method, the skin irritation of sBA in white New Zealand rabbits was observed at 24, 48 and 72 hours and 7 days after dosing. Results indicate that sBA did not cause a skin reaction and is not considered a skin irritant in rabbits (Price, 1986).

Eye Irritation

Studies with rabbits using undiluted sBA liquid found moderate to severe irritation of the eyes (Table 5).

Table 5. sBA Eye Irritation Data.

Test Method	Test Conditions	Result	Reference	CoR*
OECD 405	0.1 ml of undiluted sBA (99.5%) instilled into the conjunctival sac of the eye	Moderate conjunctival inflammation in all six 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	1
None	0.02 and 0.1 ml of undiluted sBA instilled into the conjunctival sac of the eye	Irritating Severe injury from 0.1 ml, minor from 0.02 ml	Mellon, 1952; Smyth <i>et al.</i> , 1954	2

* Criteria of reliability; see Appendix A

In the study of Price (1986), sBA was reported to be corrosive to the eye based on the progressive corneal opacity in one of six rabbits which was sacrificed at day 7. All other rabbits had mild effects but recovered completely by day 7.

Respiratory Tract Irritation

An Alarie test conducted in mice determined a RD₅₀ value (concentration expected to cause a 50% decrease in respiratory rate over a 10-min exposure period) of 11,800 ppm for sBA vapor (Hansen and Nielsen, 1994).

Sensitization

sBA was not a skin sensitizer when tested in guinea pigs in Magnusson-Kligman maximization tests performed according to OECD guidelines (Price, 1986; Elf Atochem, 1997).

Repeated Dose Toxicity

There are several studies available that contribute to the weight of evidence regarding the repeated-dose toxicity of sBA. Many of the studies are limited in duration or

toxicological evaluation parameters. As a result, this endpoint is supplemented with data using an analog, methyl ethyl ketone (MEK).

Oral Toxicity

A two-generation reproductive toxicity study (Cox *et al.*, 1975) and a developmental toxicity study (Cox *et al.*, 1975) were conducted on sBA, which can also be considered relevant for repeat dose toxicity (Table 6).

Information on repeated-dose toxicity of sBA can be deduced from a two-generation reproductive toxicity study (Cox *et al.*, 1975; Gallo *et al.*, 1977). sBA was initially administered to the F0 generation at concentrations of 0, 0.3, 1.0, and 3.0% in the drinking water. Due to toxicity at the 3%, the highest dose level; was reduced to 2.0% for the second-generation (F1 30/sex/group) that was reared to maturity (up to week 12), mated to produce a F2 generation, then sacrificed for organ weights, and gross and microscopic pathological evaluations. Ten F1 animals/sex/group were evaluated for hematological, biochemical, and urinary parameters at termination. A series of mild changes in the kidney (non-reactive tubular degeneration, tubular casts, foci of tubular regeneration, microcysts) were observed in animals treated with 2.0% sBA. The authors concluded that these findings were non-specific effects due to increased renal workload, possibly from an increased urine volume and pressure at the high dose of sBA. These effects were not considered to be a result of direct toxicity and did not have clear pathologic significance. No significant findings were seen. The no-effect level for the study was 1.0% (estimated to be approximately 1500 mg/kg/day by the authors and 1771 mg/kg/day by EPA/IRIS).

Table 6. sBA Oral Repeated Dose Toxicity Data.

Species and Exposure Condition	Result	Clinical Signs	Reference	CoR*
Rat, male and female Wistar; 8-wks exposure	NOAEL F1 offspring = 1% (estimated 1500 mg/kg/day by authors and 1771 mg/kg/day in EPA IRIS)	Mild changes in kidney, but not specific and due to increased renal workload	Cox <i>et al.</i> , 1975; Gallo <i>et al.</i> , 1977	2
Rat, female Wistar; 8-wks exposure pre-mating and during gestation	NOAEL maternal and pup = 1% (1771 mg/kg/day)	Fetotoxic at 2% (3122 mg/kg/day) showing decreased pup weights. Increase in missing sternbrae, wavy ribs, and incomplete vertebra ossification at 2%, but consistent in type and frequency with the controls and the spontaneous incidences in the colony. Effects were not determined to be compound-related.	Cox <i>et al.</i> , 1975; Gallo <i>et al.</i> , 1977	2

* Criteria of reliability; see Appendix A

Inhalation Toxicity

There is one inhalation repeated-dose (Aarstad *et al.*, 1985) and one developmental toxicity study (Nelson *et al.*, 1989) available on sBA. These studies are limited due to their short duration and limited evaluation of toxicological parameters. Further supportive data are available from a 90-day inhalation toxicity study conducted on MEK, the major initial metabolite of sBA (Table 7).

Studies were conducted primarily to assess narcosis, liver and kidney mixed function oxidases, and developmental toxicity. In the Aarstad study, inductions of cytochrome P-450 concentrations were found in the livers (33% increase) and kidneys (47% increase) of rats that inhaled, 2,000 ppm sBA vapors for 3 days and 500 ppm vapors for 5 days, respectively. The most comprehensive subchronic toxicity study available for MEK was conducted in rats by Cavender *et al.* (1983). In this study, male and female rats were exposed to 0, 1,250, 2,500, or 5,000 ppm MEK vapors for 6 hours per day, 5 days per week, for 90 days. The animals were examined for clinical signs of toxicity and changes on body weight, clinical pathology parameters (hematology and serum chemistry), gross pathology and histopathology, and neuropathology. The results of this study indicated that none of the MEK exposure concentrations were lethal or even significantly harmful. There were no adverse effects on the clinical health or growth of male or female rats except a depression of mean body weight in the 5,000 ppm group. The female rats

exposed to 5,000 ppm for 90 days showed only slightly increased liver weight, slightly decreased brain and spleen weights, and slightly altered blood chemistry in comparison with controls. Male rats that received this exposure exhibited only a slightly increased liver weight. At the lower concentrations (1,250 and 2,500 ppm), there was only slightly increased liver weight for female rats and no significant differences for males. The pathological examination did not reveal any lesions that could be attributed to MEK exposure. The liver changes found in the study, an increase in liver weights and altered serum enzyme activities, indicate a MEK treatment-related effect; however, since histopathological lesions were not observed, these responses may have been the result of a physiologic adaptation mechanism. There were no findings of respiratory tract irritation in this study. MEK produces minimal or no systemic effects in laboratory animals following repeated exposure to high doses. This finding 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 NOAEL is 5000 ppm.

Table 7. sBA Inhalation Repeated Dose Toxicity Data.

Species and Exposure Condition	Result	Clinical Signs	Reference	CoR*
Rat, male Sprague-Dawley; 3-d (2000 ppm), 5-d (500 ppm) exposure	47% and 33% increase in cytochrome P-450 at 500 and 2000 ppm, respectively		Aarstad <i>et al.</i> , 1985	2
Rat, female Sprague-Dawley; 19-d exposure	NOAEL maternal = 3500 ppm, NOAEL teratogen > 7000 ppm (highest dose tested)	Number of live fetuses significantly reduced and resorptions increased at 7000 ppm; fetal body weights significantly reduced at 3500 and 7000 ppm	Nelson <i>et al.</i> , 1989	2
Rat, male and female Fischer 344, 90-d exposure to MEK	NOAEL > 5000 ppm (highest dose tested)	Slight decreased brain and spleen weights, increased liver weight, and altered blood chemistry in females and slight increased liver weight in males. Since histopathological lesions were not observed, these responses may have been the result of a physiologic adaptation mechanism.	Cavender <i>et al.</i> , 1983	1

* Criteria of reliability; see Appendix A

Mutagenicity

Sufficient data are available for sBA to adequately characterize its *in vitro* genotoxicity. MEK data are used as an analog to address the endpoint for *in vivo* genotoxicity and supplement existing data on sBA data for *in vitro* genotoxicity.

In Vitro Genotoxicity

Screening level mutagenic studies conducted for sBA indicate that this material is not genotoxic (Table 8). sBA was inactive in vitro tests for mutagenicity in both bacteria and yeast in either the presence or absence of metabolic activation (Brooks *et al.*, 1988; Elf Atochem, 1989). There was also no structural damage to chromosomes observed in cultured mammalian cells (Chinese hamster ovary) treated with sBA (Brooks *et al.*, 1988) (Table 8).

Available data on MEK indicate that MEK is negative in the mouse lymphoma assay, chromosomal aberration and cytotoxicity study, an unscheduled DNA synthesis and a morphologic transformation assay (Clone A31-1); (Table 9). These results are consistent with those determined using sBA.

Table 8. sBA Genotoxicity Data.

Endpoint and Test System	Test Conditions	Result / Toxicity	Geno-toxicity	Reference	CoR*
Gene mutation assay with <i>Salmonella typhimurium</i> TA98, TA100, TA1535, TA1537, and TA1538	Up to 10 mg/plate \pm rat S9. Pre-incubation assay	Toxic at 10 mg/plate on TA100 without S9	No mutagenic activity	Elf Atochem, 1989	1
Gene mutation assay with <i>Salmonella typhimurium</i> TA98, TA100, TA1535, TA1537, and TA1538	Up to 4 mg/plate \pm rat S9. Plate incorporation assay	No toxicity	No mutagenic activity	Brooks <i>et al.</i> , 1988	1
Gene mutation assay with <i>Escherichia coli</i> WP2 uvrA pKM101	Up to 4 mg/plate \pm rat S9. Plate incorporation assay	No toxicity	No mutagenic activity	Brooks <i>et al.</i> , 1988	1
Gene conversion assay with <i>Saccharomyces cerevisiae</i> JD1	Up to 5 mg/ml \pm rat S9	No toxicity	No mutagenic activity	Brooks <i>et al.</i> , 1988	1
Chromosomal aberration assay with cultured Chinese hamster ovary (CHO) cells	Up to 5 mg/ml \pm rat S9	No toxicity	No clastogenic activity	Brooks <i>et al.</i> , 1988	1

* Criteria of reliability; see Appendix A

In Vivo Genotoxicity

Data on sBA for in vivo mammalian genetic toxicity were not available and as a result, MEK data were used as an analog (O'Donoghue, 1988; Basler, 1986). MEK did not cause an increase in micronucleated polychromatic erythrocytes in two in vivo assays as shown below in Table 9. Based on similarities between sBA and MEK, it is concluded that sBA will also be considered negative in these assay systems.

Table 9. MEK Mammalian Genetic Toxicity Data.

Test	Species	Study Design	Results	References
<i>In Vitro</i> Test	Mouse lymphoma assay	L5178Y/TK +/-	Negative with and without activation	O'Donoghue <i>et al.</i> , 1988
	Rat liver cells	RL4 Chromosomal aberration and cytotoxicity	Negative with and without activation	Brooks <i>et al.</i> , 1988
	Rat hepatocyte	Unscheduled DNA synthesis	Negative with and without activation	O'Donoghue <i>et al.</i> , 1988
	Mouse BALB 3T3 cells	Morphologic transformation (Clone A31-1)	Negative with and without activation	O'Donoghue <i>et al.</i> , 1988
<i>In Vivo</i>	Mouse	Micronucleus Assay i.p. injection	Negative	O'Donoghue <i>et al.</i> , 1988
<i>In Vivo</i>	Hamster	Micronucleus Assay i.p. injection	Negative	Basler, 1986

Reproductive Toxicity

In a two-generation reproductive toxicity study (Cox *et al.*, 1975; Gallo *et al.*, 1977), sBA was initially administered via drinking water at concentrations of 0, 0.3, 1.0, and 3.0% to male and female rats (Table 10). All findings at 0.3 and 1.0% were negative in both generations with respect to signs of toxicity in terms of growth and reproduction efficiency. In the group exposed to 3.0%, there were reductions in body weight gain during the 8-week pre-mating period, in number of pups born, and in pup body weight, but fertility was not affected. Due to toxicity, the high dose level was reduced to 2.0% for the second generation. In the second generation, the high dose level caused a slight but not statistically significant depression in growth of weanling rats. The maternal and pup no-effect levels for reproduction parameters were 1.0% (estimated to be 1500 mg/kg/day by the authors, and 1771 mg/kg/day by EPA/IRIS). Overall, the weight of evidence indicates that sBA does not produce reproductive effects.

Table 10. sBA Oral Reproductive Toxicity Data.

Species and Exposure Condition	Result	Clinical Signs	Reference	CoR*
Rat, male and female Wistar; 8-wks exposure	NOAEL F1 offspring = 1% (estimated 1500 mg/kg/day by authors and 1771 mg/kg/day in EPA IRIS)	Mild changes in kidney, but not specific and due to increased renal workload	Cox <i>et al.</i> , 1975; Gallo <i>et al.</i> , 1977	2

* Criteria of reliability; see Appendix A

Developmental Toxicity

Developmental effects, such as delayed development, have been produced in laboratory animals with sBA, but only at doses that were maternally toxic. Overall the weight of evidence indicates that sBA does not produce teratogenic (developmental) toxic effects in the developing embryo/fetus of laboratory animals (Table 11).

Oral Route

During the two-generation reproductive toxicity (see section 3.6) a teratogenic phase was incorporated in which the parents (28-30/group) were rebred to produce a second litter. The females were subjected to Caesarean section on day 20 of gestation (Cox *et al.*, 1975; Gallo *et al.*, 1977). At 2.0%, sBA caused a significant depression in fetal weight, with evidence of delayed skeletal maturation, but no skeletal and visceral malformations. The authors concluded that these changes represented mild toxicity and were reminiscent of stress lesions. All findings at 0.3 and 1.0% were negative. The no-effect level for developmental toxicity was 1.0% (estimated to be 1500 mg/kg/day by the authors and 1771 mg/kg/day by EPA/IRIS].

Inhalation Route

In a developmental toxicity study (Nelson *et al.*, 1989) groups of 15-16 pregnant rats were exposed via inhalation to 0, 3,500, 5,000 or 7,000 ppm sBA, 7 hours/day on days 1-19 of gestation; the dams were sacrificed on day 20. At 7,000 ppm, narcosis was observed in all animals. At 5000 ppm, the dams were partially narcotized with locomotion activity impaired. Maternal weight gain and food consumption was significantly reduced in all dose groups. The number of live fetuses was significantly reduced and resorptions were increased in the high exposure group only. Fetal body weights were significantly reduced in the mid- and high dose groups. There was no evidence of teratogenic effects in this study, and there was also no evidence of selective developmental toxicity. For maternal toxicity the NOEL was < 3,500 ppm (10,593 mg/m³) with a NOAEL of 3,500 ppm. For developmental toxicity, the NOEL was 3500 ppm with a NOAEL of >7000 ppm (21,186 mg/m³).

Table 11. sBA Developmental Toxicity Data.

Species and Exposure Condition	Result	Clinical Signs	Reference	CoR*
Rat, female Wistar; 8-wks exposure pre mating and during gestation; oral	NOAEL maternal and pup = 1% (1771 mg/kg/day)	Fetotoxic at 2% (3122 mg/kg/day) showing decreased pup weights. Increase in missing sternbrae, wavy ribs, and incomplete vertebra ossification at 2%, but consistent in type and frequency with the controls and the spontaneous incidences in the colony. Effects were not determined to be compound-related.	Cox <i>et al.</i> , 1975 ; Gallo <i>et al.</i> , 1977	2
Rat, female Sprague-Dawley; 19-d exposure; inhalation	NOAEL maternal = 3500 ppm, NOAEL teratogen > 7000 ppm (highest dose tested)	Number of live fetuses significantly reduced and resorptions increased at 7000 ppm; fetal body weights significantly reduced at 3500 and 7000 ppm	Nelson <i>et al.</i> , 1989	2

* Criteria of reliability; see Appendix A

Other Toxicological Endpoints

Neurotoxicity

sBA, like many other organic solvents, produces reversible depression of central nervous system (CNS) activity in laboratory animals at high exposure doses (Snyder and Andrews 1996). 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. One limited acute neurotoxicity study in laboratory animals is reported for sBA. In a simple functional test, the tilted plane test was used to evaluate rats that received a single oral dose of sBA and the results were compared with analogous doses of ethanol, propanols, and other butanols (Wallgren, 1960). An sBA dose of 0.0163 mole/kg (approximately 1.2 g/kg) is found to produce a greater intoxication effect than ethanol (relative molar intoxicating effect values of 4.4 and 1 for sBA and ethanol, respectively) and a slower recovery to normal behavior than ethanol.

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

The potential for neurotoxicity associated with repeated exposure to sBA has not been specifically evaluated. sBA caused partial narcosis at 5,000 ppm in pregnant rats in the developmental toxicity study by Nelson *et al.* (1989) discussed above. The few repeated exposure studies that have been conducted for sBA did not indicate enduring adverse effects on the nervous system of laboratory animals; however, the experimental designs of these studies do not permit definitive assessment.

Other Effects

sBA has demonstrated activity in a number of physiology and interaction studies. sBA inhibited the contraction of the depolarized 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), enhanced microsomal enzymes and metabolism (Aarstad *et al.*, 1985; Traiger *et al.*, 1989; Page and Carlson, 1993; Gadberry and Carlson, 1994) and 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.

Toxicity Data for Diisopropyl Ether

A test plan and dossier for diisopropyl ether (DIPE) have been submitted to the U.S. EPA by the Isopropanol Panel of the American Chemistry Council (2006). DIPE is a small molecular weight ether similar in structure to sBE and the mammalian toxicity data identified for DIPE can be used as an analog to support the characterization of mammalian toxicity for sBE, as their inherent toxicities are expected to be similar. The complete dossier for DIPE is provided with this test plan. The HPV endpoints for DIPE are characterized in Table 12 and the study summaries can be found in the dossier, which is provided with this test plan.

Table 12. Mammalian Toxicity Data for DIPE.

Toxicity Endpoint		Results	Reference
Acute	Inhalation	Low toxicity	Kimura <i>et al.</i> , 1971 Machle <i>et al.</i> , 1939
	Oral	Low toxicity	Kimura <i>et al.</i> , 1971 Machle <i>et al.</i> , 1939
	Dermal	Low toxicity	Kimura <i>et al.</i> , 1971 Machle <i>et al.</i> , 1939
Irritation	Skin	Minimal irritant	Machle <i>et al.</i> , 1939
	Eye	Minimal irritant	Machle <i>et al.</i> , 1939
	Respiratory	Sensory irritant	Hine <i>et al.</i> , 1955 Silverman <i>et al.</i> , 1946
Sensitization		Negative <i>in vitro</i> sensitizer	Wass and Belin, 1990
Repeated Dose		Liver and kidney effects	Dalbey and Feuston, 1996
Reproductive		No effects on reproductive organ structure or sperm/spermatid number	Dalbey and Feuston, 1996
Developmental		Equivocal developmental effect at maternal effect level	Dalbey and Feuston, 1996
Neurotoxicity		Minor reversible effect on CNS	Rodriguez and Dalbey, 1997
Geno-toxicity	<i>In vitro</i> mutation	Negative	Brooks <i>et al.</i> , 1988
	<i>In vitro</i> chromosome aberration	Negative	Brooks <i>et al.</i> , 1988

C. Aquatic Toxicity Data

Although experimental data were not available to characterize the acute aquatic toxicity of sBE to fish, invertebrates, and green algae, a Quantitative Structure Activity Relationship (QSAR) model that applies an equation for neutral organics to estimate aquatic toxicity is appropriate for sBE. Modeling was performed using the ECOSAR computer model (Cash and Nabholz, 1990). ECOSAR is a subroutine of the EPI Suite™ computer model. Results of modeling show that sBE is expected to exhibit a 96-hour LC₅₀ value of 14.7 mg/l for a freshwater fish, a 48-hour EC₅₀ value of 16.7 mg/l for a daphnid (freshwater invertebrate), and a 96-hour EC₅₀ value of 11.0 mg/l for a green alga (Table 13). Based on these model values, sBE presents a moderate order of acute toxicity to aquatic species. Table 13 also shows modeled chronic data for a fish, invertebrates, and green algae. The values for both sBE and nBE range from approximately 1 to 2 mg/L for the three trophic levels.

There are measured and calculated data for an analog ether, n-butyl ether (nBE; CAS No. 142-96-1), that support using the calculated data for sBE. A study that evaluated nBE acute toxicity to fish was reported by the Ministry of International Trade and

Industry of Japan (CITI, 1992). The study reported a 48-hour LC₅₀ value of 30.7 mg/l for the Orange Killifish (*Oryzias latipes*). The modeled 96-hour LC₅₀ value for nBE was 10.8 mg/l for a freshwater fish. The difference in exposure periods can explain some of the difference between the two values. However, a comparison of the two values supports the use of the ECOSAR model to estimate aquatic toxicity for these chemicals and suggest that the modeled data may be conservative.

Table 13. Calculated Aquatic Toxicity Data for sBE and nBE.

Endpoint	Result (mg/l)	
	sBE	nBE
Acute		
Fish 96-hr LC ₅₀	14.7	10.8 (30.7*)
Daphnid 48-hr EC ₅₀	16.7	12.5
Alga 96-hr EC ₅₀	11.0	8.3
Chronic		
Fish 30-da ChV**	2.2	1.6
Daphnid 16-da EC ₅₀	1.3	1.0
Alga 96-hr ChV**	1.8	1.5

* Experimental 48-hour LC₅₀ (CITI, 1992)

** Chronic Value

D. Environmental Fate Data

Biodegradation

Biodegradation of an organic substance by bacteria can provide energy and carbon for microbial growth. This process results in a structural change of an organic substance and can lead to the complete degradation of that substance, producing carbon dioxide and water.

Experimental data are not available to assess the biodegradability of sBE. However, a number of published studies in which non-standard guideline methods were used have demonstrated that alkyl ethers can be degraded by pure strains and mixed cultures of bacteria when incubated under aerobic conditions (Fujiwara, *et al.*, 1984; Kim and Engesser, 2004). The rate of biodegradation for these substances is slow because it is believed the ether bond has high dissociation energy (about 360kJ mol⁻¹) (Kim and Engesser, 2004). A modified MITI test conducted on the analog substance nBE reported a 28-day percent biodegradation of 3 to 4%, based on biological oxygen demand (CITI, 1992). The BIOWIN model, a subroutine within the EPI Suite (2000) computer model, further supports this and estimates biodegradation of both sBE and nBE to occur at a slow rate.

Photodegradation – Photolysis

Direct photochemical degradation occurs through the absorbance of solar radiation by a

chemical substance in aqueous solution. If the absorbed energy is high enough, then the resultant excited state of the chemical may undergo a transformation. A prerequisite for direct photodegradation is the ability of one or more bonds within a chemical to absorb ultraviolet (UV)/visible light in the 290 to 750 nm range. Light wavelengths longer than 750 nm do not contain sufficient energy to break chemical bonds, and wavelengths below 290 nm are shielded from the earth by the stratospheric ozone layer (Harris, 1982a).

An approach to assessing the potential for a substance to undergo photochemical degradation is to assume that degradation will occur in proportion to the amount of light wavelengths >290 nm absorbed by constituent molecules (Zepp and Cline, 1977).

Saturated hydrocarbons and R-OH groups do not absorb light above 290 nm (Harris, 1982a). Therefore, these moieties are stable in regard to direct photolytic processes. Ethers are also stable as this group absorbs UV light in the far UV region, below 220 nm (Mill, 2000). Therefore, direct photolysis will not be an important transformation process for the degradation of sBE in the environment.

Photodegradation – Atmospheric Oxidation

Photodegradation can be measured (U.S. EPA, 1999a) or estimated using an atmospheric oxidation potential (AOP) model accepted by the EPA (U.S. EPA, 1999b). Atmospheric oxidation as a result of hydroxyl radical attack is not direct photochemical degradation, but rather indirect degradation.

sBE has the potential to volatilize to air, based on a vapor pressure of 21.7 hPa @ 25° C, where it is subject to atmospheric oxidation. In air, sBE can react with photosensitized oxygen in the form of hydroxyl radicals ($\cdot\text{OH}$). The computer program AOPWIN (atmospheric oxidation program for Microsoft Windows) (EPI Suite, 2000) calculates a chemical half-life for a 12-hour day based on an $\cdot\text{OH}$ reaction rate constant and a defined $\cdot\text{OH}$ concentration (the 12-hour day half-life value normalizes degradation to a standard day light period during which hydroxyl radicals needed for degradation are generated).

sBE has a calculated half-life in air of 4.0 hours or 0.33 days, based on a rate constant of $3.21\text{E-}13 \text{ cm}^3/\text{molecule}\cdot\text{sec}$ and an $\cdot\text{OH}$ concentration of $1.5\text{E}6 \cdot\text{OH} / \text{cm}^3$.

Stability in Water (Hydrolysis)

Hydrolysis of an organic chemical is the transformation process in which a water molecule or hydroxide ion reacts to form a new carbon-oxygen bond. Chemicals that have a potential to hydrolyze include alkyl halides, amides, carbamates, carboxylic acid esters and lactones, epoxides, phosphate esters, and sulfonic acid esters (Neely, 1985). The lack of a suitable leaving group renders a compound resistant to hydrolysis. sBE is expected to be resistant to hydrolysis because it lacks a functional group that is hydrolytically reactive (Harris, 1982b). Therefore, hydrolysis will not contribute to its removal from the environment.

Chemical Distribution In The Environment (Fugacity Modeling)

Fugacity-based multimedia modeling provides basic information on the relative distribution of a chemical between selected environmental compartments. Two widely used fugacity models are the EQC (Equilibrium Criterion) Level I and Level III model

(Mackay *et al.*, 1996; Mackay *et al.*, 2003). The Mackay Level I and Level III Models do not include a groundwater compartment.

The input data required to run a Level I model include basic physicochemical parameters; distribution is calculated as the percent of chemical partitioned to six compartments (air, soil, water, suspended sediment, sediment, biota) within a unit world. Level I data are basic partitioning data that allow for comparisons between chemicals and indicate the compartment(s) to which a chemical may partition, based on the selected physical parameters. The Level III model uses the same physical parameters as the Level I model, but also requires half-life degradation data for the air, soil, water, and sediment compartments, as well as emission parameters for the air, water, and soil compartments. Distribution in the Level III model is calculated as percent of chemical partitioned to 4 compartments (air, water, soil and sediment) within a unit world. As with Level I data, Level III data are basic partitioning data that allow for comparisons between chemicals and indicate the compartment(s) to which a chemical may partition.

Results of the Mackay Level I environmental distribution model (Table 14) suggest that sBE will partition primarily to the air (>99%). These results can be largely explained by its vapor pressure, 2170 Pa at 25°C, one of the physical parameters used by the model. In comparison, the Level III model suggests that the majority of sBE will partition primarily to the soil (51%) and water (45%) compartments (Table 15).

Table 14. Environmental Distribution as Calculated by the Mackay (2003) Level I Fugacity Model.

Environmental Compartment	Percent Distribution*
Air	99.1
Water	0.5
Soil	0.4
Sediment	<0.01
Suspended Sediment	<0.01
Biota	<0.01

* Distribution is based on the following model input parameters for sBE:

Molecular Weight	130.23
Temperature	25°C
Log K _{ow}	2.87
Water Solubility	327 g/m ³
Vapor Pressure	2170 Pa
Melting Point	-100°C

Table 15. Environmental Distribution as Calculated by the Mackay (2003) Level III Fugacity Model.

Environmental Compartment	Percent Distribution*
Air	3.2
Water	44.8
Soil	51.1
Sediment	0.9

* Distribution is based on the following model input parameters for sBE:

Molecular Weight	130.23	Degradation half-lives:	
Temperature	25°C	Air	4.0 hrs
Log K _{ow}	2.87	Water	320 hrs
Water Solubility	327 g/m ³	Soil	7200 hrs
Vapor Pressure	2170 Pa	Sediment	72000 hrs
Melting Point	-100°C		

Bioaccumulation Potential

A bioconcentration factor (BCF) of 32 (log BCF = 1.5) is calculated for sBE (EPI Suite, 2000) using a log K_{ow} value of 2.87. These data indicate that sBE has a low BCF and is not expected to bioaccumulate. Additionally, a 6-week BCF study, conducted by the Ministry of International Trade and Industry of Japan, reported a measured BCF in carp (*Cyprinus carpio*) of 47 to 83 for nBE (CITI, 1992). Computer model estimates for nBE indicate a BCF of 59 using a log K_{ow} value of 3.21. These data support the use of the calculated BCF value for sBE.

IV. TEST PLAN AND DATA SUMMARY FOR sBE

A search for existing studies/information and their review identified good quality data to characterize the hazard of sBE for all endpoints in the U.S. HPV Program. Where there were good quality data for selected endpoints beyond those included in the HPV Program, they were added to their respective dossiers.

Three dossiers are forwarded with this test plan. They include sBE, DIPE, and sBA. Data for MEK are included in the sBA dossier. No further testing is planned. Data to characterize the endpoints discussed in this test plan for sBE are summarized in Table 16.

Table 16. Data Characterizing Endpoints for sBE.

Endpoint	Characterization / Value	Source
Physicochemical		
Melting Point (°C)	-100 (m)	EPI Suite, 2000
Boiling Point (°C)	116 (c)	EPI Suite, 2000
Vapor Pressure (hPa @ 25°C)	21.7 (m)	EPI Suite, 2000
Water Solubility (mg/L@ 25°C)	327 (c)	EPI Suite, 2000
Log K _{ow} (25°C)	2.87 (c)	EPI Suite, 2000
Environmental Fate		
Biodegradation	Slow (m, c)	EPI Suite, 2000 Fujiwara, <i>et al.</i> , 1984 Kim and Engesser, 2004
Direct Photolysis	Direct photolysis will not contribute to degradation	Harris, 1982a Mill, 2000 Zepp and Cline, 1977
Indirect Photolysis (half- life; da)	0.33 (c)	EPI Suite, 2000
Hydrolysis	Hydrolysis will not contribute to degradation	Harris, 1982b Neely, 1985
Fugacity - Level I (Distribution to compartment)	Partitions primarily to: air (>99%) (c)	Mackay <i>et al.</i> , 1996 Mackay <i>et al.</i> , 2003
Fugacity - Level III (Distribution to compartment)	Partitions primarily to: soil (51%); water (45%) (c)	Mackay <i>et al.</i> , 1996 Mackay <i>et al.</i> , 2003
Aquatic Toxicity		
Freshwater Fish 96-hr LC ₅₀ (mg/L)	14.7 (c)	Cash and Nabholz, 1990
Freshwater Fish 30-da ChV* (mg/L)	2.2 (c)	Cash and Nabholz, 1990
Freshwater Invert. 48-hr EC ₅₀ (mg/L)	16.7 (c)	Cash and Nabholz, 1990
Freshwater Invert. 16-da EC ₅₀ (mg/L)	1.3 (c)	Cash and Nabholz, 1990
Freshwater Alga 96-hr EC ₅₀ (mg/L)	11.0 (c)	Cash and Nabholz, 1990
Freshwater Alga 96-hr ChV* (mg/L)	1.8 (c)	Cash and Nabholz, 1990

Table 16 (continued). Data Characterizing Endpoints for sBE.

Endpoint		Characterization / Value	Source
Mammalian Toxicity			
Acute	Inhalation	Low toxicity LD ₅₀ = >8,000 ppm (4 hr) LD ₅₀ = <16,000 ppm (4 hr) (ra from sBA) (m)	Mellon, 1951 Smyth <i>et al.</i> , 1954
	Oral	Low toxicity LD ₅₀ = 2.2 to 6.5 g/kg bw (ra from sBA) (m)	Mellon, 1951 Smyth <i>et al.</i> , 1954 Price, 1986
	Dermal	Low toxicity LD ₅₀ = >2 g/kgbw (ra from sBA) (m)	Price, 1986
Irritation	Skin	Minimal irritant PII = 0 (ra from sBA) (m)	Price, 1986
	Eye	Moderate – Severe irritant (ra from sBA) (m)	Mellon, 1952 Smyth <i>et al.</i> , 1954 Price, 1986
	Respiratory	640 ppm RD ₀ Threshold at 2 Min, 11800 ppm RD ₅₀ at 10 Min (ra from sBA) (m)	Hansen and Nielsen, 1994
Sensitization		Negative sensitizer (ra from sBA) (m)	Price, 1986 Elf Atochem, 1997
Repeated Dose		Oral sBA NOEL = 1.0% (1771 mg/kg/day); Inhalation MEK NOAEL = 5000 mg/kg/day (ra from sBA and MEK) (m)	Cox <i>et al.</i> , 1975 Cavender <i>et al.</i> , 1983
Reproductive		Not a Reproductive Hazard NOAEL = 1771 mg/kg/day (ra from sBA) (m)	Cox <i>et al.</i> , 1975 Gallo <i>et al.</i> , 1977
Developmental		Oral NOEL (maternal) = 1771 mg/kg/day NOEL (pup) = 1771 mg/kg/day Inhalation NOEL (maternal) = <3,500 ppm NOAEL (maternal) = 3,500 ppm NOEL (pup) = 3,500 ppm NOAEL (pup) = >7,000 ppm (ra from sBA) (m)	Cox <i>et al.</i> , 1975 Gallo <i>et al.</i> , 1977 Nelson <i>et al.</i> , 1989

Table 16 (continued). Data Characterizing Endpoints for sBE.

Endpoint		Characterization / Value	Source
Mammalian Toxicity			
Neurotoxicity		Minor reversible narcosis at 5,000 ppm in pregnant rats in the developmental toxicity study (ra from sBA) (m)	Nelson <i>et al.</i> , 1989
Geno- toxicity <i>In vitro</i>	Mutation	<i>S. typhimurium</i> Negative <i>E. coli</i> Negative (ra from sBA) (m)	Brooks <i>et al.</i> , 1988
	Chromosome aberration	Chinese hamster ovary Negative (ra from sBA) (m)	Brooks <i>et al.</i> , 1988
	Gene conversion assay	<i>S. cerevisiae</i> Negative (ra from sBA) (m)	Brooks <i>et al.</i> , 1988
	Mouse lymphoma	L5178Y/TK +/- Negative with and without activation (ra from MEK) (m)	O'Donoghue <i>et al.</i> , 1988
	Rat liver cells chromosomal aberration and cytotoxicity	RL4 Negative with and without activation (ra from MEK) (m)	Brooks <i>et al.</i> , 1988
	Rat hepatocyte unscheduled DNA synthesis	Negative with and without activation (ra from MEK) (m)	O'Donoghue <i>et al.</i> , 1988
	Morphologic transformation (Clone A31-1)	Mouse BALB 3T3 cells Negative with and without activation (ra from MEK) (m)	O'Donoghue <i>et al.</i> , 1988
Geno- toxicity <i>In vivo</i>	Mouse Micronucleus Assay i.p. injection	Negative (ra from MEK) (m)	O'Donoghue <i>et al.</i> , 1988
	Hamster Micronucleus Assay i.p. injection	Negative (ra from MEK) (m)	Basler, 1986

m Measured for sBE

c Calculated for sBE

ra Read-across data from analog and/or metabolite as indicated

* Chronic value

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APPENDIX A: RELIABILITY CRITERIAAdapted 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