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Provisional Peer Reviewed Toxicity Values for

sec-Butyl alcohol
(CASRN 78-92-2)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose

PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR sec-BUTYL ALCOHOL (2-BUTANOL, CASRN 78-92-2)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and

circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

sec-butyl alcohol is a high production volume (HPV) chemical also listed in the Toxic Release Inventory (TRI). No RfD, RfC, or carcinogenicity assessment for sec-butyl alcohol (sec-butanol, 2-butanol) is available on IRIS (U.S. EPA, 2008a), in the Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997), or in the Drinking Water Standards and Health Advisory list (U.S. EPA, 2006). The IRIS RfD (consensus date 09/10/2003) for methyl ethyl ketone (2-butanone), however, is based on a reproduction study of sec-butyl alcohol in rats (FDRL, 1975). The Chemical Assessments and Related Activities (CARA) lists (U.S. EPA, 1991a, 1994a) show no U.S. EPA documents for sec-butyl alcohol. The Agency for Toxic Substances and Disease Registry (ATSDR, 2008) has not produced a Toxicological Profile for sec-butyl alcohol. A World Health Organization (WHO, 1987) Environmental Health Criteria document that includes sec-butyl alcohol is available, but data are inadequate to derive an assessment. The International Agency for Research on Cancer (IARC, 2008) has not evaluated sec-butyl alcohol for carcinogenicity. The National Toxicology Program (NTP) has not tested the carcinogenicity of sec-butyl alcohol or included it in its 11th Report on Carcinogens (NTP, 2005, 2008). The California Environmental Protection Agency (CalEPA, 2002, 2005a, 2005b) has not derived a recommended exposure limit (REL) or cancer potency factor for sec-butyl alcohol. Occupational exposure limits are available for sec-butyl alcohol based on acute respiratory tract and eye irritation and CNS effects; these are time-weighted-average (TWA) limits that include an Occupational Safety and Health Administration (OSHA, 2008) permissible exposure limit (PEL) of 150 ppm, a National Institute of Occupational Safety and Health (NIOSH, 2005) REL of 100 ppm, and an American Conference of Governmental Industrial Hygienists (ACGIH, 2001, 2007) threshold limit value (TLV) of 100 ppm.

We conducted literature searches from 1960's through December 2007 for studies relevant to the derivation of provisional toxicity values for sec-butyl alcohol. Databases searched include MEDLINE (including cancer subset), TOXLINE (Special), BIOSIS, TSCATS 1/TSCATS 2, CCRIS, DART/ETIC, GENETOX, HSDB, RTECS, and Current Contents. A recent review for the Joint Assessment of Commodity Chemicals (JACC) Programme of the European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC, 2003) was also evaluated for pertinent information. An updated literature search (through November 2008) was conducted using PubMed.

REVIEW OF PERTINENT DATA

Pertinent data on sec-butyl alcohol are limited to an oral multigeneration reproductive and developmental toxicity study in rats (Cox et al., 1975) and an inhalation developmental toxicity study in rats (Nelson et al., 1989). Information on the health effects of methyl ethyl ketone (MEK) are relevant to sec-butyl alcohol because sec-butyl alcohol is rapidly and almost completely metabolized to MEK in orally exposed rats (see toxicokinetics section below) and the effects of oral and inhalation exposure to sec-butyl alcohol and MEK are similar. We included selected studies of MEK in this PPRTV document as supporting data for sec-butanol because it is likely that effects produced by sec-butanol are caused by MEK or a subsequent metabolite common to both chemicals. We took summaries of these selected studies from the IRIS Summary and Toxicological Review for MEK (U.S. EPA, 2003, 2008b). The MEK studies were not independently re-evaluated for this review.

Human Studies

Oral Exposure

No pertinent information was located regarding the effects of oral exposure to sec-butyl alcohol or MEK in humans.

Inhalation Exposure

sec-Butanol Studies—No information was located regarding the effects of inhalation exposure to sec-butyl alcohol in humans.

MEK Studies—Data on the effects of inhaled MEK in humans summarized here were taken from the IRIS Summary and Toxicological Review for MEK (U.S. EPA, 2003, 2008b)**.** As with other small molecular weight, aliphatic, or aromatic organic chemicals used as solvents (e.g., acetone or toluene), acute inhalation exposure to MEK vapors is expected to cause reversible CNS depression; however, evidence for such effects in humans is limited to a single case report (Welch et al., 1991). Data from a series of NIOSH-sponsored studies involving acute, 4-hour exposures of volunteers (Dick et al., 1984, 1988, 1989, 1992) found no exposure related changes in performance of psychomotor and mood tests or incidences of irritation. Evidence that MEK may induce general solvent-like neurotoxic effects such as peripheral or central nerve fiber degeneration in humans repeatedly exposed to MEK by inhalation consists of a few case reports of neurological impairment in exposed workers (Seaton et al., 1992;

Callender, 1995; Orti-Pareja et al., 1996), and one study of problematic design reporting increased incidence of subjectively reported neurological symptoms in exposed workers (Mitran et al., 1997; Graham, 2000). The available data provide limited and equivocal evidence that repeated exposure to MEK in the workplace increases the hazard for persistent neurological impairment (U.S. EPA, 2003).

Epidemiological studies of MEK-exposed workers provide no clear evidence of a cancer hazard (Alderson and Rattan, 1980; Wen et al., 1985; Spirtas et al., 1991; Blair et al., 1998), but the studies are generally inadequate to discern an association between MEK exposure and an increased incidence of cancer (U.S. EPA, 2003, 2008b). These retrospective cohort studies provide limited epidemiological evidence for bone, prostate, and certain other cancers based on a small number of site-specific deaths and exposures that are confounded by multiple chemicals. A case-control study examining the association between paternal exposures to several solvents (including MEK) and childhood leukemia (Lowengart et al., 1987) is exploratory in scope and cannot be used to reliably support the existence of any such association. Overall, the epidemiologic evidence from which to draw conclusions about carcinogenic risks in the human population is inconclusive. There is no clear evidence for a relationship between these cancers and MEK exposure alone. Studies on the cancer risk of exposures to multiple solvents, including MEK, suggest an increased cancer risk (U.S. EPA, 2003, 2008b), however, it is not possible to attribute the increased risk to MEK.

Animal Studies

Oral Exposure

sec-Butanol Studies—The only repeat-exposure oral study of sec-butyl alcohol is a single study, encompassing both multigenerational reproduction and developmental toxicity, by Cox et al. (1975). In the oral RfD summary for methyl ethyl ketone (MEK) on IRIS (U.S. EPA, 2008b) and the Toxicological Review of MEK (U.S. EPA, 2003), the U.S. EPA summarized the Cox et al. (1975) study; a U.S. EPA-sponsored peer review of this study was conducted in 2003 (U.S. EPA, 2003, Appendix A). The Cox et al. (1975) study was used as the basis of the RfD for MEK on IRIS due to a lack of appropriate oral toxicity data for MEK and the availability of pharmacokinetic and toxicological data supporting the use of sec-butyl alcohol as an appropriate surrogate for MEK. A summary of the Cox et al. (1975) study, taken from the Toxicological Review of MEK (U.S. EPA, 2003), is presented below (editorial changes added). The study does not include statistical analyses of the results, although all collected data are fully reported.

> Weanling FDRL-Wistar stock rats (30/sex/group) were given sec-butyl alcohol in drinking water at 0, 0.3, 1 or 3% solutions and a standard laboratory ration *ad libitum* (Cox et al., 1975). Weekly food consumption, fluid intakes and body weights were examined to determine the efficiency of food utilization and to calculate the average daily intake of sec-butyl alcohol, which was reported by the authors for the initial 8 weeks of the study (intake was not reported for subsequent weeks) as 0, 538, 1644, and, 5089 mg/kg-day (males) and 0, 594, 1771 and, 4571 mg/kg-day (females) for the 0, 0.3, 1, and, 3% solutions, respectively. After 8 weeks of initial exposure, F_0 males and females from each exposure group were mated to produce F_{1A} litters, which were delivered naturally and nursed through

21 days of lactation. F_{1A} litters with more than eight pups were randomly culled to eight pups per litter on day 4 after birth. Pup and dam weights were recorded on days 4 and 21 after birth. Various indices of reproductive performance were recorded (e.g., number of successful pregnancies, litter size, number of live pups at birth and end of lactation). Because increased mortality and decreased body weight occurred in the F_{1A} litters at the 3% dose level (see below), all high-dose parents and F_{1A} offspring were given drinking water without sec-butanol between days 10 and 21 of lactation and then 2% sec-butyl alcohol for the remainder of the experimental protocol. The average daily intake in mg/kg-day at the 2% (initially 3%) exposure level was not reported by the study investigators; therefore, average daily intakes of 3384 mg/kg-day in males and 3122 mg/kg-day in females were estimated based on a linear regression analysis of the reported average intakes for males and females at drinking water concentrations of 0, 0.3, 1 and 3%.

After a 2-week post-lactation period, the F_0 females were remated with males of their respective exposure groups to produce F_{1B} litters. The F_{1B} pregnancies of 20 pregnant rats per group were terminated on gestation day (GD) 20. Data recorded included numbers of corpora lutea, implant sites and resorptions, number of live and dead fetuses and the sex and weight of live fetuses. F_{1B} fetuses were also examined for skeletal and visceral malformations and variations.

Selected male and female F_{1A} rats (30 of each sex per exposure group) continued on their respective treatment protocols (0, 0.3, 1 or 2% sec-butyl alcohol) and mated at 12 weeks of age to produce F_2 litters that were delivered and nursed through day 21 of lactation. Indices of second generation reproductive performance were assessed, as were F_2 pup weights at days 4 and 21. At day 21 of lactation, F_{1A} adults were sacrificed. Limited hematology (six indices), blood biochemistry (six indices) and urinary (five indices) evaluations were performed on terminal blood and urine samples from the F_{1A} adults. Major organs and tissues (35 in all) from 10 male and 10 female F_{1A} rats per exposure group were examined histopathologically and the liver and kidneys from all 30 F_{1A} rats/sex/group were examined histopathologically.

At the highest exposure level (3%), net parental (F_0) body-weight gain was reduced compared with controls both in males (15%) and females (16%) during the 8 weeks of initial exposure. No differences were found in the efficiency of food utilization. Following birth of the first litter (F_{1A}) of the parental generation, various reproduction and lactation responses were measured. The study authors reported no effects on reproductive parameters. Analysis of F_0 male rat copulatory success suggests a possible impact of 3% sec-butyl alcohol on male reproductive performance. The incidence of male F_0 rats that did not successfully copulate with F_0 females was 0% (1/30), 0.3% (2/30), 1% (0/30), and, 3% (6/30). Data from which to determine copulatory failure were not provided for other generations. In addition, reduced body weight gain in this high-dose group could have contributed to copulatory success. For these reasons, the biological significance of these data for the F0 generation males is uncertain.

When compared to the control group, marked litter effects on pup survival and body weight occurred in the F_{1A} litters from the high-dose group (3%); these included reductions in the mean number of pups/litter born alive (8.46 vs. 10.3), the mean number of pups/litter alive before culling at 4 days (8.12 vs. 10.3), the mean number of pups/litter alive at 21 days (6.85 vs. 7.68), the mean body weight/pup after culling at 4 days and the mean body weight/pup at 21 days. The high-dose mean F_{1A} body weights at 4 and 21 days represent 22 and 39% decreases, respectively, when compared to control values (see Table 3 on p. 15). At the lower dose levels, the litter mean body weights were decreased relative to control at postnatal days 4 and 21 (5 and 4% for the 0.3% group and 7 and 10% for the 1% group, respectively), but only the change in body weight at day 21 in the 1% group is considered to be biologically significant.

During the second pregnancy, the high-dose F_0 dams receiving 2% sec-butyl alcohol exhibited reduced weight gain (94 g) compared to control, 0.3% and 1% dams (gains of 113, 111 and 120 g, respectively). The F_{1B} fetuses of high-exposure (2%) dams showed a 10% reduction in average fetal weight compared with controls (see Table 3 on p. 15). No differences in average fetal weight were observed at 0.3% and 1%. The difference in the mean fetal weights of the adjusted high-dose (2%) and control groups was not statistically significant ($p > 0.05$) using a t-test, but when the F_{1B} fetal weight data were fit by linear dose-response models, log-likelihood ratio tests indicated that mean body weights significantly decreased with increasing dose levels.

The incidences of nidation, early fetal death and late fetal death did not appear to be affected in the F_{1B} litters of any exposure group compared with controls (Cox et al., 1975). The F_{1B} fetuses in the 2% group showed increases in skeletal variations (missing sternebrae, wavy ribs and incomplete vertebrae ossification) when compared with the 1% dose group. When compared with control incidences, however, no differences were apparent. The investigators provided no explanation for the consistently lower responses observed in the 1% (mid-dose) group.

F_2 pups from the high-dose group (2%) showed reductions in mean pup body weight at postnatal day 4 and day 21 (see Table 3 on p. 15). Mean body weights of F_2 pups in the 0.3 and 1% groups were similar to controls at day 4 and day 21. Although body weight reductions in the high-dose F_2 pups were not as great as those observed in the high-dose F_{1A} pups, a continued decrease in body weight occurred in the high-dose pups at days 4 and 21 (reductions of 5% at day 4 and 13% at day 21 when compared with F_2 controls).

No exposure-related changes in hematology, blood biochemistry, urinalysis, organ weights or increased incidence of lesions were found in the adult F_{1A} rats sacrificed 21 days after the F_2 birth, with the exception of specific histopathologic changes in the kidneys that were most prominent in males (Cox et al., 1975). Microcysts in the tip of the renal papilla were reported for rats receiving 2% sec-butanol alcohol, but not in control rats; however, the incidence was not

reported. Slight-to-mild hydropelvis (hydronephrosis) was also observed among control and sec-butyl alcohol-exposed rats, although no dose-related effect was observed. Other changes included tubular cast formation and foci of tubular degeneration and regeneration. Incidences of male F_{1A} rats with these types of kidney changes were 0/30, 1/30, 1/30, and, 8/30 for the control through high-dose groups, respectively. A similar increased incidence was not observed in females. The findings are consistent with the pattern for [several aspects] of α_{2u}-globulin-associated rat nephrotoxicity as described by the Risk Assessment Forum (U.S. U.S. EPA, 1991b). Testing was not conducted, however, to demonstrate the presence of the α_{2u}-globulin protein.

In summary, the results of the Cox et al. (1975) study demonstrate that the administration of sec-butyl alcohol in drinking water at concentrations as high as 3% did not affect reproductive performance in rats (with the possible exception of male rat copulatory success), but produced maternal toxicity accompanied by developmental effects at the highest exposure level. Decreased maternal weight gain, decreased F_{1A} pup survival and decreased F_{1A} pup weights at days 4 and 21 were observed in the groups exposed to 3% sec-butyl alcohol in drinking water. At the next lower dose (1%) in this same generation, only reductions in F_{1A} pup weights (7 to 10% at days 4 and 21) were observed; however, no similar reductions in body weight were observed in subsequent generations at the 1% dose level. The following effects were noted at the 2% level (the adjusted high-dose level administered following F_{1A} postnatal day 21): decreased maternal body-weight gain during the second pregnancy of the F_0 dams, decreased F_{1B} fetal weights when pregnancy was terminated at gestation day 20, and decreased F_2 pup weights at postnatal days 4 and 21. Developmental endpoints were not affected at the 0.3% sec-butyl alcohol exposure levels in any of the generations. sec-butanol treatment produced an increase in the incidence of kidney lesions in high-dose male rats (F_{1A} generation) that were exposed from gestation through 12 weeks after birth, mating and gestation and lactation of the F_2 generation; no other treatment-related histopathologic lesions were observed in adult rats. Thus, Cox et al. (1975) identified a LOAEL of 3122 mg/kg-day (2% solution) and a NOAEL of 1771 mg/kg-day (1% solution) based on decreased F_{1B} fetal weights and decreased F_{1A} and F_2 pup body weights. The maternal LOAEL in this study was 3122 mg/kg-day (2% solution) based on decreased weight gain and the NOAEL was 1771 mg/kg-day (1% solution. (p. 35-39).

MEK Studies—Studies of repeat-dose oral exposures to MEK that might be relevant to sec-butanol have not been conducted (U.S. EPA 2003, 2008b).

Inhalation Exposure

sec-Butyl Alcohol Studies—Developmental toxicity was evaluated in groups of 15-16 female Sprague-Dawley rats that were exposed to sec-butyl alcohol at target concentrations of 0, 3500, 5000, or 7000 ppm for 7 hours/day on GDs 1-19 (Nelson et al., 1989). Continuous infrared monitoring showed that mean measured concentrations were essentially the same as the target concentrations. The maternal animals were evaluated for clinical signs

(presumed daily), food and water intake (weekly), and body weight (GDs 0-7, 14, and 20); the animals were sacrificed on GD 20 for uterine and fetal examinations. Developmental endpoints included numbers of *corpora lutea*, resorptions and live fetuses, fetal body weight and sex, and external (all fetuses), skeletal (one-half of fetuses), and visceral (the other half of fetuses) malformations and variations. An exposure of 7000 ppm produced narcosis in all maternal animals and the animals did not recover completely between exposures. At 5000 ppm, the animals were partially narcotized with impaired locomotor activity. At 3500 ppm the animals were not visibly affected. Maternal body weights were not reported, but maternal body-weight gain and food consumption were statistically significantly reduced at ≥ 3500 ppm. At 3500, 5000, and 7000 ppm, body-weight gain at the end of the study was approximately 27, 23, and, 77% lower than controls (as estimated from graphed data), and overall mean food consumption was approximately 11, 14, and, 29% lower than controls. Fetal body weight was significantly reduced at ≥ 5000 ppm; at 3500, 5000, and, 7000 ppm, mean weight was 6.5, 16.1, and, 54.8% lower than controls in male fetuses and 6.1, 18.2, and, 54.5% lower than controls in female fetuses (see Table 1). Other developmental toxicity only occurred at 7000 ppm; these effects consisted of significantly increased resorptions/litter, decreased live fetuses/litter, and increased number of fetuses with skeletal variations. The skeletal variations were described as typical of fetotoxicity, particularly reduced ossification (additional details not reported). This study identifies a LOAEL of 3500 ppm and no NOAEL for maternal toxicity based on reduced body-weight gain and food consumption. A NOAEL of 3500 ppm and LOAEL of 5000 ppm were identified for developmental toxicity based on reduced fetal body weight.

Table 1. Key Maternal and Fetal Effects in Rats Exposed to sec-Butyl Alcohol by Inhalation for 7 hours/day on Gestation Days 1-19[a]

Endpoint	0 ppm	3500 ppm	5000 ppm	7000 ppm
Resorptions/litter	1.5 ± 1.3[b]	1.6 ± 1.4	1.5 ± 0.9	3.8 ± 2.2[c]
Live fetuses/litter	14 ± 2	15 ± 2	14 ± 3	10 ± 3[c]
Fetal weight, female (g)[d]	3.1 ± 0.22	2.9 ± 0.20	2.6 ± 0.23[c]	1.4 ± 0.18[c]
Fetal weight, male (g)[d]	3.3 ± 0.23	3.1 ± 0.22	2.7 ± 0.25[c]	1.5 ± 0.12[c]

[a]Nelson et al., 1989
[b]Mean values ± standard deviations
[c]Significantly different from control ($p < 0.05$)
[d]Not reported whether based on individual or litter weights

MEK Studies—Developmental toxicity, subchronic toxicity, and neurotoxicity studies showed that developmental toxicity is the most sensitive toxicologically relevant effect of inhalation exposure to MEK. Summaries of these studies, taken from the IRIS RfC summary for MEK (U.S. EPA, 2008b), are presented below (editorial changes added).

> Deacon et al. (1981) exposed groups of 26, 19, 19 and 18 Sprague-Dawley dams to nominal MEK concentrations of 0, 400, 1000 or 3000 ppm, respectively (7 hours/day on GD 6-15). Results from the study were also reported by Dow Chemical Corporation (1979). Average measured MEK concentrations were 412,

1002 and, 3005 ppm. Dams exposed to 3005 ppm MEK exhibited maternal toxicity that was demonstrated by a slight decrease in weight gain (326 g for 3005 ppm group vs. 351 g for control; $p < 0.05$ at GD 16) and increased water consumption on days 15-17 (82 mL/day for 3005 ppm group vs. 69 mL/day for control; $p < 0.05$ at GD 16) (Dow Chemical Corporation, 1979). None of the exposure levels produced statistically significant effects on the incidence of pregnancy or resorptions, the average number of implantations or live fetuses per dam, or fetal weight and length. No statistically significant differences in the incidences of external or soft-tissue alterations were observed in the exposed groups when compared with the control. A statistically significant difference in the incidence of litters with extra ribs was observed in the 3005 ppm exposure group when compared with the controls. The incidence of extra ribs was 2/26 for control litters versus 0/19, 0/19, and, 6/18 for 412, 1002, and, 3005 ppm litters, respectively. Thus, this study found maternal toxicity (decreased weight gain) and fetal toxicity (increased incidence of skeletal variations) at 3005 ppm (LOAEL) but not at 412 or 1002 ppm (NOAEL).

Schwetz et al. (1991) exposed groups of 10 virgin Swiss CD-1 mice and 33 sperm plug-positive (GD 0) females to mean MEK concentrations of 0, 398 ± 9, 1010 ± 28 or 3020 ± 79 ppm by inhalation for 7 hours/day on GD 6-15. Dams were then sacrificed on GD 18. Results from this study were also reported by Mast et al. (1989) and NTP (1990). At these exposure concentrations (0, 398, 1010 or 3020 ppm), the number of gravid/mated mice were 26/33, 23/33, 26/33, and, 28/33, respectively. A slight concentration-related increase in liver-to-body-weight ratio (approximately 7% over control at 3020 ppm) was observed in the dams. Only two statistically significant developmental effects were observed: (1) a decrease in mean fetal weight (per litter) at 3020 ppm for males (5% decrease compared with controls) and for male and female fetuses combined (4% decrease compared with controls) and (2) a positive trend for increasing incidence of fetuses (total) with misaligned sternebrae with increasing exposure level (incidences were 31/310, 27/260, 49/291, and, 58/323 for the control through 3020 ppm exposure groups). No increase in the incidence of intrauterine death was observed in any of the exposed groups and no statistically significant increases in the incidence of malformations occurred. Developmental and maternal effect levels were established at 3020 ppm for a small, but statistically significant, decrease in fetal weight among males, increased incidence of misaligned sternebrae and an increase in maternal liver-to-body-weight ratio.

Cavender et al. (1983) exposed male and female Fischer 344 rats (15/sex/group) in a whole body dynamic airflow chamber to MEK 6 hours/day, 5 days/week, for 90 days. The reported TWA exposure concentrations (by gas-liquid chromatography) of MEK were 0, 1254, 2518, or, 5041 ppm. Results of the study are also reported in Toxigenics (1981). At the study termination, 10 animals/sex/group were subject to routine gross pathology and histopathology. Special neurohistopathological studies were conducted on the medulla and the

sciatic and tibial nerves of the remaining five male and female rats from each group.

Cavender et al. (1983) reported no deaths during the 90-day study. Transient, statistically significant depressions in body weight gain compared to the control were seen in high dose (5041 ppm) male and female rats early in the study. There were no treatment-related effects on food consumption or in the ophthalmological studies in any MEK-exposed rats. The evaluation of neurological function (i.e., assessments of posture, gait, facial muscular tone or symmetry and four neuromuscular reflexes) revealed no abnormalities (Toxigenics, 1981). At all exposure concentrations, female rats exhibited statistically significant ($p < 0.05$) dose-dependent increases in absolute liver weight when compared to controls, which were unaccompanied by any histopathology. Other statistically significant differences in organ weights included decreased brain weights (absolute and relative) and spleen weights (absolute) in 5041 ppm females and increased relative kidney weights in 5041 ppm males and females. Differences in the serum chemistry values for female rats in the 5041 ppm exposure group included significant increases in serum potassium, alkaline phosphatase and glucose and a significant decrease in SGPT (ALT) activity when compared to controls. No differences in serum chemistry between MEK-exposed males and control animals were observed. The only statistically significant differences in hematology parameters were higher mean corpuscular hemoglobin in 5041 ppm male and female rats and higher mean corpuscular hemoglobin concentration in 5041 ppm females. The findings corresponded to a slight, but not significant, decrease in the number of red blood cells. With the exception of larger urine quantity in 5041 ppm males, no urinalysis parameters were significantly different in MEK-exposed rats when compared with controls. (None of these changes are considered toxicologically significant).

Routine gross and histopathological examinations and the special neuropathology studies revealed no lesions that could be attributed to MEK exposure (Cavender et al., 1983). Thus, while the increase in absolute liver weights and mildly altered serum enzyme activities in high-dose female rats indicated possible liver damage, no histopathological lesions in the liver were observed. The authors stated that the response may have been the result of a physiological adaptation mechanism. While the decrease in brain weight in the 5041 ppm females (9% compared to controls) indicated possible effects of MEK on brain tissue, no histopathological lesions of the brain were observed.

Minimal-to-mild lesions in the upper or lower respiratory tract were noted in all control and MEK-exposed rats and were coded as chronic respiratory disease consisting of "multifocal accumulation of lymphoid cells in the bronchial wall and peribronchial tissues with occasional polymorphonuclear cells (eosinophils) in the perivascular areas of small veins" (Toxigenics, 1981). Because the bronchial epithelium remained intact and exudates were not present in bronchial lumens, the lesions were considered insignificant pathologically. In addition, the

authors reported an increased prevalence of nasal inflammation (including submucosal lymphocytic infiltration and luminal exudate) across control and all exposure groups. There was no difference in the character or severity of lesions among the control and three treatment groups. While the authors suggested that the pulmonary lesions were secondary to mycoplasma infection, no infectious agent was cultured to verify this etiology. Since there is no indication that respiratory lesions are related to MEK exposure, the results confound the outcome of the study with regard to lesions of the upper respiratory tract.

In summary, review of the Cavender et al. (1983) findings reveals effects remote to the respiratory tract in the 5041 ppm animals that are of uncertain biological significance, including: reduced body-weight gain, statistically significant increases in relative liver weight (males and females) and altered serum liver enzymes (females) and decreased brain weight (females). As noted previously, reported liver effects are more likely indicative of a physiological adaptive response than toxicity. The finding of decreased brain weight observed in female rats raises concerns, but is difficult to interpret. Generally, with a brain weight reduction of 5%, one might expect evidence of corresponding pathology; however, no treatment-related brain pathology was observed in this study. The reduction in brain weight relative to controls observed in only one sex also raises questions about the relevance of the finding. Thus, while the reduction in brain weight at 5041 ppm is noteworthy, its biological significance is uncertain.

Animal studies provide no convincing evidence that exposure to MEK alone causes persistent neurotoxic effects (U.S. EPA, 2003, 2008b). Saida et al. (1976) found no evidence of peripheral neuropathy (as indicated by paralysis) following continuous exposure of 12 Sprague-Dawley rats to 1125 ppm MEK for 16-55 days. Cavender et al. (1983) found no neurological effects in special neuropathological studies of the medulla and sciatic and tibial nerves of rats exposed to MEK at concentrations up to 5041 ppm for 90 days. Takeuchi et al. (1983) exposed male Wistar rats (8 per group) to 200 ppm MEK 12 hours/day for 24 weeks and found no evidence of a persistent effect on motor or mixed nerve conduction velocity, distal motor nerve latency or histopathological lesions of tail nerves. Couri et al. (1974) exposed four cats, four rats, five mice and an unknown number of chickens to 1500 ppm MEK 24 hours/day, 7 days/week, for 7-9 weeks with no apparent adverse neurologic effects.

The range of toxic effects in animals resulting from inhalation exposure to MEK indicates that developmental effects are the most sensitive, toxicologically relevant endpoint. Inhalation exposure of experimental animals to approximately 3000 ppm MEK (7 hours/day) during gestation resulted in developmental effects (Schwetz et al., 1991; Deacon et al., 1981). (p. 41)

Other Studies

Toxicokinetics

The IRIS document for MEK summarizes the toxicokinetics of sec-butyl alcohol. In brief, Traiger and Bruckner (1976) reported the determination of a half-life of 2.5 hours for the elimination of sec-butanol from blood of rats administered an oral dose of 2.2 ml/kg (equivalent to 1.77 g/kg). One hour after administration, a maximal blood level of 800 mg sec-butanol/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 administration of the alcohol. Based on this and other data, Dietz et al. (1981) established that approximately 96% of an administered oral dose of 2-butanol is oxidized *in vivo* to MEK within 16 hours of oral administration. A physiologically based pharmacokinetic model (PBPK model) reported by Dietz et al. (1981) reported that no significant difference in the area under the curve (AUC) of MEK blood concentration was observed after oral dosing of rats with either 1776 mg/kg sec-butanol or 1,690 mg/kg MEK (10,899 ± 842 or 9868 ± 566 mg-hour/liter, respectively). Peak concentrations of MEK and its downstream metabolites were similar whether MEK or sec-butanol were administered (Dietz et al., 1981), with a shift of approximately 4 hours to reach peak concentrations when MEK was administered:

Table 2. Peak Blood Concentrations Following sec-Butanol or MEK

Administration of	Administration of
1776 mg/kg sec-butanol	1690 mg/kg MEK
MEK 0.78 mg/ml at 8 hr	0.95 mg/ml at 4 hr
3H-2B 0.04 mg/ml at 12 hr	0.027 mg/ml at 8 hr
2,3-BD 0.21 mg/ml at 18 hr	0.26 mg/ml at 18 hr

The Dietz et al. (1981) paper provides further support for the rapid conversion of orally administered 2-butanol to MEK as ultimately, sec-butanol and MEK are metabolized to the same intermediates (3H-2B and 2,3-BD).

Mutagenicity

sec-Butanol Studies—The mutagenicity of sec-butyl alcohol has been tested in bacteria, yeast and mammalian cells with negative results. In bacteria, sec-butyl alcohol does not induce reverse mutation in *Salmonella typhimurium* TA 1535, TA 1537, TA1538, TA98, or, TA100, or *Escherichia coli* WP_2 *uvr A* pKM 101 in the presence or absence of metabolic activation (rat liver S9 fraction) (Brooks et al., 1988; Shell Oil Company, 1986). In yeast, sec-butanol does not induce mitotic gene conversions in *Saccharomyces cerevisiae* JD1 in the presence or absence of rat liver S9 metabolic activation (Brooks et al., 1988; Shell Oil Company, 1986). In mammalian cells, sec-butyl alcohol does not cause chromosome damage in cultured Chinese hamster ovary cells in the presence or absence of rat liver S9 metabolic activation (Brooks et al., 1988; Shell Oil Company, 1986).

MEK Studies—As reported in the IRIS summary for MEK (U.S. EPA, 2008b):

> MEK has not exhibited mutagenic activity in a number of conventional short-term test systems. In vitro tests showed that MEK is not genotoxic in the Salmonella (Ames) assay (with or without metabolic activation), the L5178/$TK^{+/-}$ mouse lymphoma assay, or the BALB/3T3 cell transformation assay and did not induce unscheduled DNA synthesis in rat primary hepatocytes or chromosome aberrations or sister chromatid exchange (Florin et al., 1980; Douglas et al., 1980; O'Donoghue et al., 1988; NTP, undated; Zeiger et al., 1992). No induction of micronuclei was found in the erythrocytes of mice (O'Donoghue et al., 1988) or hamsters (WHO, 1992) after intraperitoneal injection with MEK. The only evidence of mutagenicity was mitotic chromosome loss at a high concentration in a study on aneuploidy in the diploid D61, M strain of the yeast Saccharomyces cerevisiae (Zimmerman et al., 1985); the relevance of this positive result to humans is unknown. In general, studies of MEK yielded little or no evidence of mutagenicity. Structure Activity Relationships (SAR) analysis suggests that MEK is unlikely to be carcinogenic based on the absence of any structural alerts indicative of carcinogenic potential (Woo et al., 2002).
>
> No cancer bioassay is available from which to assess the carcinogenic potential of MEK in experimental animals by the oral or inhalation routes. In a skin carcinogenesis study, groups of 10-15 male C3H/He mice received dermal applications of 50 mg of a solution containing 17, 25, or, 29% MEK and one or more other solvents (dodecylbenzene, benzyl disulfide, phenylbenzothiophene and/or decalin) twice a week for 1 year (Horton et al., 1965). A single skin tumor developed in 1/10 mice treated for 27 weeks with the solution containing 29% MEK, and in 1/15 mice treated with the solution containing 17% MEK. This study is an inadequate test of MEK carcinogenicity because of concomitant exposure to chemicals that are expected to accelerate the rate of skin tumor formation. (p. 47).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL p-RfD VALUES FOR sec-BUTYL ALCOHOL

Studies of MEK are relevant to derivation of toxicity values for sec-butyl alcohol because pharmacokinetic and toxicological data indicate that effects produced by sec-butyl alcohol are likely caused by MEK or a subsequent metabolite common to both chemicals. As summarized in the Toxicological Review of MEK (U.S. EPA, 2003), supporting pharmacokinetic findings in rats include

> (1) orally administered sec-butyl alcohol was almost completely (96%) converted to MEK and its metabolites within 16 hours, (2) peak MEK blood concentrations occurred at similar times after the administration of 1776 mg/kg (0.024 mol/kg) sec-butyl alcohol (7-8 hours) and 1690 mg/kg (0.023 mol/kg) MEK (4-5 hours), and (3) common metabolites (3-hydroxy-2-butanone and 2,3-butanediol) were formed and eliminated with similar kinetics after the administration of sec-butyl

> alcohol or MEK (Traiger and Bruckner, 1976; Dietz et al., 1981). Comparable pharmacokinetic data for sec-butyl alcohol and MEK in humans are not available; however, evidence for conversion of sec-butyl alcohol to MEK in humans supports the assumption that rats and humans metabolize sec-butyl alcohol similarly. (p. 10).

Toxicological findings supporting the relevance of MEK to sec-butyl alcohol include

> (1) fetal weight deficits were critical effects in studies of rats (Schwetz et al., 1974; Deacon et al., 1981) and mice (Schwetz et al., 1991) exposed to MEK by inhalation during gestation, in the two-generation reproductive and developmental toxicity study in rats exposed to sec-butyl alcohol in drinking water (Cox et al., 1975), and in the study of rats exposed to sec-butyl alcohol by inhalation during gestation (Nelson et al., 1989) and (2) the relationships between air concentrations and the degree of fetal weight changes were consistent for MEK and sec-butyl alcohol. (p. 60).

Oral RfD

The oral toxicity database for sec-butyl alcohol consists of a two-generation reproductive and developmental toxicity study in rats (Cox et al., 1975). No relevant oral MEK studies are available. Effects identified in the two-generation study include decreased pup survival and decreased neonatal body weight in F_{1A} pups whose parents were exposed to 3% sec-butyl alcohol in drinking water before mating through day 10 of lactation. Decreased body weights, with no effect on survival, were observed in F_{1B} fetuses and F_{1A} and F_2 pups that were exposed to 2% sec-butyl alcohol in drinking water. In adult rats, exposure to 3% sec-butyl alcohol in drinking water for 8 weeks caused reduced weight gain in F_0 males and females. F_1 animals exposed to sec-butyl alcohol in drinking water at concentrations up to 2% for 12 weeks after birth and through mating, gestation, and lactation of F_2 litters were subject to hematology, blood biochemistry, urinalysis, organ weight, gross pathology, and histopathology evaluations. No exposure-related changes were found with the exception of specific histopathologic changes of the kidney in male rats exposed to 2% sec-butyl alcohol. Changes were consistent with the pattern of several aspects of α_{2u}-globulin-associated rat nephrotoxicity; however, testing needed to demonstrate the presence of α_{2u}-globulin was not conducted. Therefore, the relevance of this finding to humans is uncertain. This study (Cox et al., 1975) identifies a LOAEL of 3122 mg/kg-day (2% solution) and a NOAEL of 1771 mg/kg-day (1% solution) based on the decreases in fetal weight and pup body weight. The finding of developmental toxicity as the most sensitive toxicologically relevant endpoint in rats exposed orally to sec-butyl alcohol is consistent with similar findings in inhalation developmental toxicity studies of sec-butyl alcohol (Nelson et al., 1989) and MEK (Schwetz et al., 1974, 1991; Deacon et al., 1981) (U.S. EPA 2003, 2008b).

The Cox et al. (1975) study of sec-butyl alcohol is the principal study used to derive the RfD for MEK that is on IRIS (U.S. EPA, 2008b). The derivation of the MEK RfD used benchmark dose (BMD) analysis of the fetal and pup body weight data to obtain an LED_{05} value for sec-butyl alcohol that was molar adjusted to account for differences in the molecular weights

of sec-butyl alcohol and MEK. The unadjusted LED_{05} value can be used to derive subchronic and chronic RfDs for sec-butyl alcohol. Calculation of the unadjusted LED_{05} value for sec-butyl alcohol, as reported in the IRIS summary for MEK (editorial changes added), is presented below.

> Fetal body weight data from the F_{1B} generation and day 4 and 21 pup weights from the F_{1A} and F_2 generations (Table 3) were analyzed by benchmark dose modeling. Decreased F_{1A} pup survival observed in the highest dose group (i.e., 3% solution) is likely to have confounded the effects on body weight. Therefore, these data were not included in the modeling. Models for continuous data (linear, polynomial or power), either with a constant variance or with variance as a power function of the mean value (using an additional model parameter), were fit to the data using U.S. EPA's Benchmark Dose Software (BMDS version 1.3.1). The software was used to calculate potential points of departure for deriving the RfD by estimating the effective dose at a specified level of response (ED_x) and its 95% lower bound (LED_x). In the case of pup or fetal body weight, there is no specific decrement that is generally regarded as indicative of an adverse response. Consequently, for each generation, a 5% decrease in the mean pup or fetus body weight per litter (compared with the control mean) was selected as the benchmark response because it was a response rate that fell within the range of experimental dose levels used in the Cox et al. (1975) study. (p. 64).

Additionally, Kavlock et al. (1995) determined that the 5% benchmark response level for fetal weight was essentially comparable to the no-statistical-significance-of-trend dose (a surrogate for the NOAEL) for a series of developmental toxicity studies conducted by the National Toxicology Program.

Table 3. Body Weight (Litter Means and Standard Deviation) for F_{1A} and F_2 Neonatal Rats and F_{1B} Fetuses Exposed to sec-Butyl Alcohol[a]

Endpoint (generation)	Control	0.3% (594 mg/kg-day[b])	1% (1771 mg/kg-day[b])	2% (3122 mg/kg-day[c])
F_{1A} pup body weight, day 4	10.7 ± 1.1 (n = 29)	10.2 ± 1.3 (n = 27)	10.0 ± 1.3 (n = 30)	NA[d]
F_{1A} pup body weight, day 21	49.0 ± 3.8 (n = 28)	47.0 ± 3.9 (n = 27)	44.0 ± 4.8 (n = 30)	NA[d]
F_{1B} fetal weight, GD 20	4.1 ± 1.5 (n = 29)	4.2 ± 0.7 (n = 27)	4.4 ± 1.0 (n = 30)	3.7 ± 1.0 (n = 29)
F_2 pup body weight, day 4	10.0 ± 1.4 (n = 28)	9.7 ± 1.6 (n = 28)	9.6 ± 2.3 (n = 27)	9.5 ± 1.6 (n = 24)
F_2 pup body weight, day 21	40.0 ± 6.1 (n = 27)	39.0 ± 7.8 (n = 28)	39.0 ± 9.4 (n = 25)	35.0 ± 4.7 (n = 23)

[a]Mean body weights and associated standard deviations were calculated from individual litter means in Appendix II of the Cox et al. (1975) report.
[b]Average daily intake of sec-butyl alcohol as reported by the authors.
[c]Calculated based on a linear regression analysis of the reported average intakes and drinking water concentrations of sec-butyl alcohol.
[d]High-dose F_{1A} pups were exposed to 3% sec-butyl alcohol (4571 mg/kg-day). These were not included in the modeling due to possibly confounding mortality.

Table 4 summarizes the ED_{05} and LED_{05} values calculated from the various data sets from the study.

Table 4. Benchmark Doses for Developmental Effects in Various Generations of Rats Exposed to sec-Butyl Alcohol and Potential Points of Departure for the RfD[a]

Endpoint	ED_{05}[b] (mg/kg-day)	LED_{05}[b] (mg/kg-day)
F_{1A} pup body weight, day 4[c]	1387	803
F_{1A} pup body weight, day 21[c]	878	657
F_{1B} fetal weight, GD 20	2198	1046
F_2 pup body weight, day 4	3471	1347
F_2 pup body weight, day 21	2056	901

[a]U.S. EPA, 2003; 2008b
[b]ED_{05} = Benchmark dose associated with a 5% decrease in litter mean pup or fetus body weight (compared with control mean).
LED_{05} = 95% lower confidence limit on the ED_{05}.
[c]The data for the high-dose group (3%) were not included in the modeling due to possibly confounding mortality.

LED_{05} values from the data sets are within 2-fold of each other, suggesting that all of the modeling results are equally plausible. The lowest point of departure, based on the decreased pup body weight at postnatal day 21 in the F_{1A} generation (LED_{05} = 657 mg/kg-day), was selected for deriving the RfD as the most health protective value."

Subchronic p-RfD

Derivation of the subchronic RfD for sec-butyl alcohol involves dividing the LED_{05} of 657 mg/kg-day by an UF of 300. The **subchronic p-RfD of 2E+0 mg/kg-day** is calculated as follows:

Subchronic p-RfD = LED_{05} ÷ UF
= 657 mg/kg-day ÷ 300
= **2 or 2E+0 mg/kg-day**

The composite UF of 300 includes component UFs of 10 for extrapolation from rats to humans, 10 for human variability, and 3 for database insufficiencies, as explained below.

- A 10-fold UF is used to account for laboratory animal-to-human interspecies differences. No information is available on the toxicity of sec-butyl alcohol or MEK in humans exposed by the oral route. No other information is available to assess possible differences between animals and humans in pharmacokinetic and pharmacodynamic responses to sec-butyl alcohol. Rat and human PBPK models for oral exposure to sec-butyl alcohol could potentially be used to decrease pharmacokinetic uncertainty in extrapolating from rats to humans, but such models are not currently available.
- A 10-fold UF for intraspecies differences is used to account for potentially susceptible human subpopulations because information on the variability in response of humans to sec-butyl alcohol exposure is not available.
- A partial uncertainty factor of 3 ($10^{0.5}$) is used to account for deficiencies in the available sec-butyl alcohol database. The oral database comprises a two-generation reproductive and developmental toxicity study (Cox et al., 1975) wherein rats were exposed to sec-butyl alcohol for 14-18 weeks. The study includes evaluations of food and water intake, body weight, hematology, clinical chemistry, urinalysis, and gross and microscopic pathology in the parental animals. However, supporting data from a second study or species are not available, and, as noted in the Toxicological Review of MEK (U.S. EPA, 2003),

The Cox et al. (1975) study protocol, although consistent with U.S. Food and Drug Administration (FDA) guidelines available at the time that the study was conducted, did not include the evaluation of certain parameters routinely measured in studies of more current design. Deficiencies included: lack of measurements of estrous cyclicity, sperm parameters, weights of uterus, epididymides, seminal vesicles and brain and less than complete clinical chemistry/hematology and histopathology. Water consumption was recorded in F_0 and F_{1A} rats prior to mating, but not during gestation and lactation.

> Consequently, more accurate measures of offspring exposure could not be developed. Statistical analyses were not performed by study investigators. In addition, changes in the drinking water concentration of high-dose animals during the last 2 weeks of F_0 lactation of F_{1A} litters from 3% to 0% and then to 2% sec-butyl alcohol introduces some uncertainty in the exposure of high-dose animals.
>
> As stated in the IRIS summary for MEK (U.S. EPA, 2008b),
>
> An uncertainty factor for extrapolation from a LOAEL to a NOAEL was not necessary because BMD modeling was used to determine the point of departure. The dose corresponding to a 5% decrease in pup weight, relative to control, was selected as the point of departure. There is no specific decrement in fetal/pup weight that is generally recognized as indicative of an adverse effect. Further, there were no other effects in the range of the LED_{05} of 657 mg/kg-day. Therefore, no further adjustments were considered for identifying a level of oral exposure to sec-butyl alcohol associated with a minimal level of risk.
>
> Consistent with U.S. EPA practice (U.S. EPA, 1991c), an UF was not used to account for extrapolation from less-than-subchronic results because developmental toxicity (decreased pup body weight following in utero and neonatal exposure) was used as the critical effect. The developmental period is recognized as a susceptible lifestage where exposure during certain time windows of development are more relevant to the induction of developmental effects than lifetime exposure.

The overall confidence in this RfD assessment is medium-to-low. As stated in the IRIS summary for MEK (U.S. EPA, 2008b):

> Confidence in the principal study is medium-to-low. The multigeneration reproduction and developmental drinking water toxicity study of sec-butyl alcohol defined a critical effect that is corroborated by inhalation exposure developmental toxicity studies for sec-butyl alcohol and MEK. The principal study examined appropriate reproductive, developmental and systemic toxicity endpoints in an adequate number of rats exposed to control conditions or three dose levels and identified NOAELs and LOAELs for maternal and developmental toxicity and a NOAEL for reproductive toxicity. Lowering the drinking water concentration of sec-butyl alcohol in the high-dose group from 3% to 2%, however, confounds the ability to discern the dose level responsible for the observed developmental effects. Furthermore, certain parameters routinely evaluated in studies of more current design (e.g., estrous cyclicity, sperm parameters and uterine weight) were not measured in Cox et al. (1975).

Confidence in the database is medium-to-low. The Cox et al. (1975) study includes investigation of systemic toxicity endpoints, as well as reproductive and developmental toxicity. Developmental effects were identified as the most sensitive endpoints. Similar developmental effects were reported following inhalation exposure to both sec-butyl alcohol and MEK,

providing support for the Cox et al. (1975) findings. However, the absence of oral data in a second study or species precludes any higher level of database confidence. Reflecting the medium-to-low confidence in the principal study and medium-to-low confidence in the database, confidence in the subchronic p-RfD is medium-to-low.

Chronic p-RfD

Chronic toxicity testing of sec-butyl alcohol has not been conducted, indicating that the subchronic RfD of 2 mg/kg-day provides the only basis for deriving a chronic RfD. No UF is applied to the subchronic p-RfD to extrapolate from subchronic-to-chronic duration because developmental toxicity is the critical effect. Consistent with U.S. EPA practice, the developmental period is recognized as a susceptible lifestage where exposure during certain time windows of development are more relevant to the induction of developmental effects than lifetime exposure. Therefore, the **chronic p-RfD is 2E+0 mg/kg-day**, the same value as the subchronic p-RfD.

Confidence in the subchronic toxicity study used to derive the chronic p-RfD is medium-to-low as discussed in the subchronic p-RfD derivation. Confidence in the database is low due to the lack of chronic data and for the reasons discussed in the subchronic p-RfD derivation. Low confidence in the chronic p-RfD results.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION p-RfC VALUES FOR sec-BUTYL ALCOHOL

Inhalation RfC

The inhalation toxicity database for sec-butyl alcohol is limited to a single developmental toxicity study in rats (Nelson et al., 1989). In this study, rats were exposed to sec-butyl alcohol at concentrations of 0, 3500, 5000, or 7000 ppm for 7 hours/day on GDs 1-19. Maternal effects include reduced food consumption and body-weight gain at ≥ 3500 ppm and narcosis at ≥ 5000 ppm. Developmental effects include reduced fetal body weight at ≥ 5000 ppm and increased resorptions, decreased live fetuses, and increased skeletal variations at 7000 ppm. No NOAEL and a LOAEL of 3500 ppm were identified for maternal toxicity based on reduced body-weight gain. A NOAEL of 3500 ppm and LOAEL of 5000 ppm were identified for developmental toxicity based on reduced fetal body weight.

The reduced fetal body weight provides an adequate basis for RfC derivation because supporting MEK data indicate that developmental toxicity is likely to be a critical effect of sec-butyl alcohol. As discussed previously, data from rats suggest that almost all of an oral dose of sec-butyl alcohol is rapidly converted to MEK, indicating the plausibility that effects produced by sec-butyl alcohol and MEK are caused by MEK or a subsequent metabolite common to both chemicals. This plausibility is supported by the consistency of the finding of developmental toxicity in rats exposed to sec-butyl alcohol by inhalation (Nelson et al., 1989) with similar findings in inhalation developmental toxicity studies of MEK in rats and mice (Deacon et al., 1981; Schwetz et al., 1974, 1991) and in the oral 2-generation reproductive and developmental toxicity study of sec-butyl alcohol in rats (Cox et al., 1975). Critical effects in all of these

studies include fetal weight deficits, and the relationships between air concentrations and the degree of fetal weight changes are consistent for sec-butyl alcohol and MEK (U.S. EPA, 2003).

There is no clear evidence for other systemic effects resulting from inhalation exposure to MEK (U.S. EPA, 2003). A subchronic inhalation study of MEK found no persistent body-weight changes, gross behavioral changes, or histological changes in major tissues and organs in rats exposed 6 hours/day, 5 days/week, for 90 days to concentrations as high as 5041 ppm (Cavender et al., 1983). Some changes in organ weight (including increased liver weight and decreased brain weight) and clinical pathology parameters were observed; however, these were not supported by histological changes. No central or peripheral neural histopathology occurred in this study and other studies of shorter duration provide no convincing evidence that repeated exposure to MEK, by itself, is capable of producing nerve degeneration or other persistent neurological effects (Couri et al., 1974; Saida et al., 1976; Takeuchi et al., 1983). The inhalation developmental toxicity studies found that repeated exposure of rats and mice to MEK at approximately 3000 ppm (highest tested levels) produced no overt neurological effects in the dams (Schwetz et al., 1974, 1991; Deacon et al., 1981) and narcosis only occurred at ≥ 5000 ppm in the maternal rats exposed to sec-butyl alcohol (Nelson et al., 1989). The available data also provide no evidence for upper respiratory tract irritation or other portal-of-entry effects following inhalation exposure to MEK at concentrations up to 6000 ppm (U.S. EPA, 2003).

As summarized above, developmental toxicity is a likely critical effect of inhaled sec-butanol because (1) effects produced by sec-butyl alcohol and MEK are probably caused by MEK or a subsequent metabolite common to both and (2) developmental toxicity is a documented critical effect of inhaled MEK as well as ingested sec-butyl alcohol.

Subchronic p-RfC

The NOAEL of 3500 ppm (10,605 mg/m^3) for reduced fetal body weight in rats (Nelson et al., 1989) is used to derive the subchronic p-RfC. The lack of specificity regarding sample size precludes BMD analysis of the fetal body-weight data.

The RfC is intended to apply to continuous lifetime exposures to humans (U.S. EPA, 1994b). Because the RfC values are often derived from studies using intermittent and less-than-lifetime exposures, U.S. EPA has established guidance (U.S. EPA, 1994b) for adjusting the exposures to an appropriate human equivalent via a simple concentration (C) × time (t) relationship (e.g., 8 hours @ 300 ppm = 24 hours @ 100 ppm). For developmental studies, the *Guidelines for Developmental Toxicity Risk Assessment* (U.S. EPA, 1991c) and the *Reproductive Toxicity Risk Assessment Guidelines* (U.S. EPA, 1996) note that peak exposure may be a more relevant exposure metric for short half-life compounds because the toxic effects may be due to absolute concentration at a specific critical period during fetal development. Some more recent studies suggest that area under the curve (AUC), the assumption underlying the C × t relationship, may be a more appropriate metric for some developmental toxicants than peak exposure. The latter has been demonstrated for certain agents with a short half-life in the body (U.S. EPA, 2002). In consideration of this information, U.S. EPA recommends that adjusted continuous exposures be used for inhalation developmental toxicity studies as for other health effects from inhalation exposure (U.S. EPA, 2002).

Duration adjustment is appropriate as the more health-protective procedure, unless there are pharmacokinetic data suggesting that the adjustment to a continuous exposure equivalent is inappropriate, or mode of action information suggests that a susceptible period of development is specifically targeted (which would suggest that the peak dose may represent the effective dose). In applying these considerations to sec-butyl alcohol, the critical effect is nonspecific developmental toxicity (reduced fetal body weight), which suggests that duration adjustment may be appropriate. Alternatively, the available pharmacokinetic data (oral) indicate that sec-butanol is rapidly absorbed and metabolized, suggesting that duration adjustment may be less appropriate than peak exposure. Overall, the available pharmacokinetic and mechanism of action data for sec-butyl alcohol do not provide sufficient evidence to support the use of either peak exposure level or AUC as the most appropriate metric for internal effective dose. Thus, it is appropriate to apply a health-protective duration adjustment to time-weight the intermittent exposures used in the principal study. The NOAEL of 3500 ppm (10,605 mg/m³) for reduced fetal body weight in rats exposed to sec-butyl alcohol for 7 hours/day on days 1–19 of gestation (Nelson et al., 1989) is adjusted from intermittent to continuous exposure as follows:

$$\begin{aligned} NOAEL_{ADJ} &= 10{,}605\ mg/m^3 \times 7\ hours/24\ hours \\ &= 3093\ mg/m^3 \end{aligned}$$

Derivation of the p-RfC next involves converting the duration-adjusted rat NOAEL to a human equivalent concentration (HEC). The U.S. EPA (1994b) procedure for calculating a HEC for an extrarespiratory effect from a vapor is to multiply the duration-adjusted NOAEL by the ratio of animal-to-human blood:air partition coefficients, as follows:

$$\begin{aligned} NOAEL_{HEC} &= NOAEL_{ADJ} \times (H_{b/g})_A/(H_{b/g})_H \\ &= 3093\ mg/m^3 \times 1 \\ &= 3093\ mg/m^3 \end{aligned}$$

where,

$(H_{b/g})_A/(H_{b/g})_H$ = rat-to-human blood:air partition coefficient ratio
= default ratio of 1 because $H_{b/g}$ values for sec-butyl alcohol were not located.

The $NOAEL_{HEC}$ of 3093 mg/m^3 is divided by a composite UF of 100 to derive a **subchronic p-RfC of 3E+1 mg/m³**, as follows:

$$\begin{aligned} \textbf{Subchronic p-RfC} &= NOAEL_{HEC} \div UF \\ &= 3093\ mg/m^3 \div 100 \\ &= \textbf{30 or 3E+1 mg/m}^3 \end{aligned}$$

The composite UF of 100 includes component factors of 3 for interspecies extrapolation, 10 for human variability, and 3 for database insufficiencies, as explained below.

- A partial UF of 3 ($10^{0.5}$) is used for interspecies extrapolation. This UF comprises two areas of uncertainty: pharmacokinetics and pharmacodynamics. In this assessment the pharmacokinetic component is addressed by the dosimetric adjustment (i.e., calculation of the HEC according to the procedures in the RfC

methodology (U.S. EPA, 1994b). Consequently, only the pharmacodynamic area of uncertainty remains as a partial factor for interspecies extrapolation.

- A 10-fold UF for intraspecies differences is used to account for potentially susceptible individuals within the human population because information on the variability in response of humans to sec-butyl alcohol or MEK exposure is not available.
- A partial UF of 3 ($10^{0.5}$) is used to account for database deficiencies. The inhalation database for sec-butyl alcohol is limited to a single developmental toxicity study in rats (Nelson et al., 1989), although supporting inhalation data on MEK provide minimum database requirements for RfC derivation. The MEK inhalation database includes a 90-day toxicity study in rats (Cavender et al., 1983) and developmental toxicity studies in rats and mice (Deacon et al., 1981; Schwetz et al., 1991). An inhalation multigeneration reproductive toxicity study of MEK is lacking, although this database deficiency is partially addressed by the oral 2-generation study of sec-butyl alcohol in rats (Cox et al., 1975). Neurotoxicity is adequately addressed by the subchronic inhalation study (Cavender et al., 1983), which includes examinations for both neurological function and for central nervous system lesions with special neuropathological procedures, but the MEK database lacks a developmental neurotoxicity study.

Consistent with U.S. EPA practice (U.S. EPA, 1991c), an UF is not used to account for extrapolation from less-than-subchronic results because developmental toxicity resulting from a narrow period of exposure (GD 1-19) is used as the critical effect. The developmental period is recognized as a susceptible lifestage where exposure during certain time windows of development are more relevant to the induction of developmental effects than lifetime exposure.

Confidence in the principal study is medium. The principal study examines appropriate developmental toxicity endpoints in an adequate number of rats exposed to control conditions or three exposure levels and identified a NOAEL and LOAEL for developmental toxicity and a LOAEL for maternal toxicity, but a NOAEL for maternal toxicity is not identified and the data for the critical effect (fetal body weight) is incompletely reported (precluding BMD analysis). Confidence in the database is medium-to-low. The inhalation developmental toxicity study of sec-butyl alcohol defined a critical effect that is corroborated by inhalation developmental toxicity studies for MEK and an oral multigeneration reproductive and developmental toxicity study for sec-butyl alcohol. Although similar developmental effects were reported following oral exposure to sec-butyl alcohol and by inhalation exposure to MEK, the absence of any subchronic inhalation data for sec-butyl alcohol precludes any higher level of database confidence. Reflecting the medium confidence in the principal study and medium-to-low confidence in the database, confidence in the subchronic p-RfC is medium-to-low.

Chronic p-RfC

Chronic toxicity testing of sec-butyl alcohol (or MEK) has not been conducted, indicating that the subchronic p-RfC of 30 mg/m^3 provides the only basis for deriving a chronic RfC. No UF is applied to the subchronic RfC to extrapolate from subchronic-to-chronic duration because developmental toxicity is the critical effect. Consistent with U.S. EPA practice, the

developmental period is recognized as a susceptible lifestage where exposure during certain time windows of development are more relevant to the induction of developmental effects than lifetime exposure. Therefore, the **chronic p-RfC is 3E+1 mg/m^3**—the same value as the subchronic RfC.

Confidence in the developmental toxicity study used to derive the chronic p-RfC is medium as discussed in the subchronic RfC derivation. Confidence in the database is low due to the lack of chronic data and for the reasons discussed in the subchronic p-RfC derivation. Low confidence in the chronic p-RfC follows.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR sec-BUTYL ALCOHOL

There are no human or animal carcinogenicity data for sec-butyl alcohol.

As stated in the Toxicological Review of MEK (U.S. EPA, 2003),

> Epidemiological studies of MEK-exposed workers provide no clear evidence of a cancer hazard (Alderson and Rattan, 1980; Wen et al., 1985; Spirtas et al., 1991; Blair et al., 1998), but the studies are generally inadequate to discern an association between MEK exposure and an increased incidence of cancer... Overall, the epidemiologic evidence from which to draw conclusions about carcinogenic risks of MEK in the human population is inconclusive. Although there is some suggestion of increased risk for certain cancers (including bone and prostate) involving multiple solvent exposures that include MEK, there is no clear evidence for a relationship between these cancers and MEK exposure alone. (p. 23)

The only information on the carcinogenicity of MEK in animals is a dermal application study that is an inadequate test of MEK's potential carcinogenicity due to concomitant exposure to chemicals that are expected to accelerate the rate of skin tumor formation (Horton et al., 1965). SAR analysis suggests that MEK is unlikely to be carcinogenic based on the absence of any structural alerts indicative of carcinogenic potential (Woo et al., 2002).

The mutagenicity of sec-butanol has been tested in bacteria, yeast, and mammalian cells with negative results. When tested *in vitro* with and without metabolic activation, sec-butyl alcohol did not induce reverse mutations in *Salmonella typhimurium* or *Escherichia coli*, mitotic gene conversions in *Saccharomyces cerevisiae* or chromosome damage in Chinese hamster ovary cells (Brooks et al., 1988; Shell Oil Company, 1986).

The preponderance of studies of MEK yielded no evidence of mutagenicity. As stated in the IRIS summary for MEK (U.S. EPA, 2008b),

> In vitro tests showed that MEK was not genotoxic in Salmonella typhimurium (with or without metabolic activation), the L5178/TK$^{+/-}$ mouse lymphoma assay or the BALB/3T3 cell transformation assay and did not induce unscheduled DNA

> synthesis in rat primary hepatocytes or chromosome aberrations or sister chromatid exchange (Florin et al., 1980; Douglas et al., 1980; O'Donoghue et al., 1988; NTP, undated; Zeiger et al., 1992). Micronuclei were not induced in the erythrocytes of mice (O'Donoghue et al., 1988) or hamsters (WHO, 1992) after intraperitoneal injection with MEK. The only evidence of genotoxicity was mitotic chromosome loss at a high concentration in a study on aneuploidy in the diploid D61, M strain of the yeast *Saccharomyces cerevisiae* (Zimmerman et al., 1985); the relevance of this positive result to humans is unknown. (p. 48)

In accordance with current U.S. EPA cancer guidelines (U.S. EPA, 2005), the available data are inadequate for an assessment of human carcinogenic potential of sec-butanol.

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