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Provisional Peer Reviewed Toxicity Values for

Butyl benzyl phthalate
(CASRN 85-68-7)

Derivation of a Carcinogenicity Assessment

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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
i.v.	intravenous
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
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 BUTYL BENZYL PHTHALATE (CASRN 85-68-7)
Derivation of a Carcinogenicity Assessment

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 science and available information evolve, PPRTVs are initially derived with a three-year life-cycle. However, EPA Regions or the EPA Headquarters Superfund Program sometimes request that a frequently used PPRTV be reassessed. 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

A carcinogenicity assessment for butyl benzyl phthalate is available on IRIS (U.S. EPA, 2002). This assessment, verified on 8/26/87, assigned butyl benzyl phthalate to cancer weight-of-evidence group C, possible human carcinogen. This classification was based on a 1982 NTP study wherein a statistically significant increase in mononuclear cell leukemia in female rats following 2 years of exposure to butyl benzyl phthalate was reported. Tumor incidence was 7/49 (14%) in controls, 7/49 (14%) in the low-dose group, and 19/50 (38%) in the high-dose group; historical data indicate that mononuclear cell leukemia occurs in control rats at a frequency in the 12-24% range (NTP, 1982). NTP concluded that the results were positive for female rats. The response in male rats was inconclusive due to excessive toxicity (they died or were sacrificed *in extremis* within 30 weeks of treatment), and there was no response in mice (NTP, 1982). A quantitative estimate of carcinogenic risk from oral exposure was not included on IRIS due to the qualitative weakness of the response, including similarity of the pathology in the control and treated groups and lack of reduction in time to first tumor (U.S. EPA, 2002). The assessment

presented on IRIS was based on a draft Drinking Water Criteria Document (DWCD) for Phthalic Acid Esters that was finalized in 1991 (U.S. EPA, 1991a). This assessment is reflected in the HEAST (U.S. EPA, 1997) and in the Drinking Water Standards and Health Advisories list (U.S. EPA, 2000).

In addition to the DWCD, other relevant documents included in the CARA list (U.S. EPA, 1991b, 1994) include a Health Effects Assessment (HEA) for Selected Phthalic Acid Esters (U.S. EPA, 1987a), a Health and Environmental Effects Profile (HEEP) for Phthalic Acid Alkyl, Aryl and Alkyl/Aryl Esters (U.S. EPA, 1987b), and a Health and Environmental Effects Document (HEED) for Butyl Benzyl Phthalate (U.S. EPA, 1989). These documents all concluded that the available data support the Group C cancer weight-of-evidence classification. ATSDR has not produced a Toxicological Profile for butyl benzyl phthalate (ATSDR, 2001). The NTP (2001) status report showed that subsequent to the 1982 study NTP published two additional studies in 1997 concerning the carcinogenicity of butyl benzyl phthalate. The International Agency for Research on Cancer (IARC) published a review of the carcinogenicity of butyl benzyl phthalate wherein butyl benzyl phthalate was determined to be not classifiable as to its carcinogenicity to humans (Group 3) based on inadequate evidence in humans and limited evidence in experimental animals from the 1982 and 1997 NTP studies (IARC, 2001). In 1999, WHO prepared a Concise International Chemical Assessment Document on butyl benzyl phthalate, wherein the literature on the carcinogenicity of butyl benzyl phthalate were reviewed, including the latest NTP studies from 1997 (WHO, 1999, 2001). WHO found that the data from experimental mammals demonstrate some evidence of carcinogenicity, based on an increased incidence of pancreatic and bladder tumors. In that report, WHO found the weight of evidence for genotoxicity of butyl benzyl phthalate to be clearly negative. In the absence of carcinogenicity data from humans, the WHO report concluded that butyl benzyl phthalate can be considered, at most, possibly carcinogenic to humans and, on this basis, declined to quantify the cancer risk associated with exposure to butyl benzyl phthalate (WHO, 1999). Update literature searches for cancer data were conducted from 1987 to May 2001. The databases searched were: TOXLINE, MEDLINE, CANCERLIT, CCRIS, TSCATS, HSDB, RTECS, GENETOX, DART/ETICBACK, and EMIC/EMICBACK.

REVIEW OF THE PERTINENT LITERATURE

Human Studies

The existing review documents and update literature search identified no relevant studies regarding the carcinogenicity of butyl benzyl phthalate in humans following oral exposure.

Animal Studies

As reported on IRIS (U.S. EPA, 2002), butyl benzyl phthalate has been tested by NTP in male and female F344 rats and B6C3F$_1$ mice by oral administration (NTP, 1982; also published

as Kluwe, 1986). This carcinogenicity assay employed estimated maximum tolerated doses (based on a 13-week range finding study) administered in the feed for 2 years to groups of 50 animals per species per sex per dose: the low dose was 6000 ppm and the high dose was 12,000 ppm. At the conclusion of the experiment, animals were sacrificed for complete necropsy and histopathological examination of major organs. Male rats did not tolerate either low or high dose, and all were sacrificed by 30 weeks. Among female rats, a statistically significant increase in the incidence of monocytic leukemia was observed: 14% among controls and low dose rats, and 38% among high dose rats (NTP, 1982). (A later publication of the data by one of the authors (Kluwe, 1986) reported the incidence for high-dose rats as 36%). Islet cell adenomas of the pancreas in female rats were observed in three animals at the low dose but not at the high dose or in the controls. The incidence for the low-dose group was not statistically significant by the Fisher exact test ($p>0.05$), but the linear trend was ($p=0.013$). The authors and reviewers of the report concluded that these lesions were unrelated to treatment with the test compound. In mice, no increased incidence of any tumor type was observed in either sex (NTP, 1982). Based on the increased incidence of monocytic leukemia among female rats, butyl benzyl phthalate was assigned to U.S. EPA cancer weight-of-evidence group C, possible human carcinogen (U.S. EPA, 2002).

Subsequently, NTP conducted additional long-term feeding studies with butyl benzyl phthalate in F344 rats (NTP, 1997a,b). Groups of 60 male and female F344/N rats were given butyl benzyl phthalate (at least 97% pure) *ad libitum* in feed for 2 years (NTP, 1997a). Male rats were fed concentrations of 0, 3000, 6000, or 12,000 ppm in feed; these concentrations were reported to deliver average doses of approximately 120, 240 or 500 mg butyl benzyl phthalate/kg-day, respectively. Females were fed 0, 6000, 12,000 or 24,000 ppm of butyl benzyl phthalate, reportedly delivering average doses of approximately 300, 600 or 1200 mg/kg-day, respectively. Ten males and 10 females from each dose group were sacrificed at 15 months for interim evaluation. Survival of all exposed rats was similar to that of controls. Only the mean body weight of the high-dose groups of male and female rats were lower than controls. Mean weight of high-dose males was 4-10% less than controls for most of the study. Mean weight of high-dose females was reduced after week 15 of the study, with the difference from controls increasing from 7% to 27% over the course of the study. Tumor incidence data from this study are shown in Table 1.

In conjunction with the aforementioned experiment, another control group, weight-matched to the high-dose group, was run (NTP, 1997b). The weight-matched control group comprised 60 males and 60 females, with 10 from each sex sacrificed for interim evaluation. Restricted feed experiments were also conducted in which groups of male and female rats were provided food in amounts that restricted mean body weights to 85% of the *ad libitum* controls (NTP, 1997b). The food contained either 0, 12,000 (male) or 24,000 (female) ppm of butyl benzyl phthalate. Two such restricted feed experiments were conducted: one for 2 years using groups of 60 rats per sex with 10 from each group used for interim sacrifice, and one for 30 (males) or 32 (females) months using groups of 50 rats per sex with no interim sacrifice. Food concentrations of 12,000 and 24,000 ppm in this study correspond to average daily doses shown

in Table 1, as calculated from consumption and body weight data presented in the paper. Tumor incidence data are shown in Table 1.

The data show a statistically significant increase in the incidence of pancreatic acinar cell adenoma and acinar cell adenoma or carcinoma (combined) among male F344/N rats following ingestion of butyl benzyl phthalate in their diet (animals fed *ad libitum*). Incidence for the combined tumors was 6% in controls, 4% in the low-dose group, 6% in the mid-dose group, and 22% in the high-dose group. Incidence in weight-matched controls was 2%. In addition to the pancreatic neoplasia, preneoplastic acinar focal hyperplasia was noted among these rats with an incidence of 8, 14, 18, and 24% in the control, low-, mid-, and high-dose groups, respectively. The incidence of acinar hyperplasia in weight-matched controls was 4%. The restricted feeding studies showed 6% incidence of acinar hyperplasia and no tumors in the treated group in the 2-year study (no response in untreated group) and 4% incidence of acinar hyperplasia and 6% incidence of acinar tumors in the treated group in the 30-month study (no response in untreated group). Pancreatic lesions in female rats were limited to acinar hyperplasia in 2% of controls, 8% of the low-dose group, and 4% of the mid-dose group (*ad libitum* groups), with acinar adenomas appearing only in the high-dose group (4% incidence).

Female rats showed a statistically significant increase in incidence of hyperplasia in the transitional epithelium of the urinary bladder in the high-dose group (incidence of 8, 0, 2 and 20% in the control, low-, mid- and high-dose *ad libitum* feeding groups, respectively). This lesion was also significantly elevated in the treated female groups in the restricted feeding studies (28% incidence in the 2-year study and 32% incidence in the 32-month study versus 0% in controls for both studies). Papillomas of the transitional epithelium were found in 2% of control females, 0% of low- and mid-dose females, and 4% of high-dose females in the *ad libitum* study. Treated females in the restricted feeding studies had 2 papillomas in the 2-year study (versus none in controls) and 2 papillomas and 4 carcinomas in the 32-month study (versus 1 papilloma in controls). The difference from controls in the 32-month study approached statistical significance ($p=0.08$). Observations in the transitional epithelium of the urinary bladder in males were limited to 2 cases of hyperplasia in the high-dose group in the *ad libitum* feeding study and a few cases of hyperplasia, papilloma and carcinoma in the restricted feeding studies (2 hyperplasia and 1 papilloma in the treated group in the 2-year study versus 1 hyperplasia in controls, and 1 hyperplasia, 1 papilloma and 1 carcinoma in the 30-month study versus no findings in controls).

The incidence of mononuclear cell leukemia was similar in treated groups (males and females) and controls fed *ad libitum*. In both males and females, the incidence of this neoplasm was reduced in the weight-matched controls so that there was a statistically significant difference between the high-dose group and the corresponding weight-matched control. There were no significant differences with treatment in the restricted feed studies. NTP (1997b) concluded that the difference between the high-dose group (NTP, 1997a) and weight-matched controls (NTP, 1997b) was due to a significant decrease in the incidence of mononuclear cell leukemia in the weight-matched control group, and that mononuclear cell leukemia was an incidental finding.

TABLE 1

Data Summary Table from NTP (1997a,b)

	Ad libitum feeding (2 years)				Weight-matched control (2 years)	Restricted feed (2 years)		Restricted feed (lifetime[b])	
Male rats									
Dose (mg/kg-day)	0	120	240	500	0	0	485[a]	0	466[a]
Pancreas:									
acinar focal hyperplasia	4/50	7/49	9/50	12/50	2/50	0/50	3/50	0/50	2/49
acinar adenoma	3/50[c]	2/49[c]	3/50[c]	10/50[c,d,e]	0/50	0/50	0/50	0/50	3/49
acinar carcinoma	0/50	0/49	0/50	1/50	1/50	0/50	0/50	0/50	0/49
acinar adenoma or carcinoma	3/50[c]	2/49[c]	3/50[c]	11/50[c,d,e]	1/50	0/50	0/50	0/50	3/49
Urinary bladder:									
transitional epithelium hyperplasia	0/50	0/50	0/50	2/50	0/50	1/50	2/50	0/50	1/50
transitional epithelial papilloma	0/50	0/50	0/50	0/50	0/50	0/50	1/50	0/50	1/50
transitional epithelial carcinoma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/50	1/50
Mononuclear cell leukemia	31/50	28/50	34/50	30/50[e]	15/50	21/50	27/50	39/50	36/50
Female rats									
Dose (mg/kg-day)	0	300	600	1200	0	0	1180[a]	0	1176[a]
Pancreas:									
acinar focal hyperplasia	1/50	4/50	2/50	0/50	0/50	0/50	0/50	0/50	0/50
acinar adenoma	0/50	0/50	0/50	2/50	0/50	0/50	0/50	0/50	0/50

TABLE 1 cont.

	Ad libitum feeding (2 years)				Weight-matched control (2 years)	Restricted feed (2 years)		Restricted feed (lifetime[b])	
Urinary bladder:									
transitional epithelium hyperplasia	4/50	0/50	1/50	10/50[d]	0/50	0/50	14/50[d]	0/49	16/50[d]
transitional epithelial papilloma	1/50	0/50	0/50	2/50	0/50	0/50	2/50	1/49	2/50
transitional epithelial carcinoma	0/50	0/50	0/50	0/50	0/50	0/50	0/50	0/49	4/50
transitional epithelial papilloma or carcinoma	1/50	0/50	0/50	2/50	0/50	0/50	2/50	1/49	6/50
Mononuclear cell leukemia	21/50	20/50	21/50	19/50[e]	13/50	16/50	18/50	29/50	39/50

[a]Dose calculated from data presented in NTP (1997b)

[b]Defined as time when survival fell to 20% , which was at 30 months for males and 32 months for females

[c]Statistically significant trend

[d]Statistically significant in pairwise test versus like-tested control

[e]Statistically significant in pairwise test versus weight-matched control

Under the conditions of the 2-year feeding studies, NTP concluded that there was some evidence of carcinogenic activity of butyl benzyl phthalate in male F344/N rats based on the increased incidences of pancreatic acinar cell adenoma and acinar cell adenoma or carcinoma (combined). There was equivocal evidence of carcinogenic activity of butyl benzyl phthalate in female 344/N rats based on the marginally increased incidences of pancreatic acinar cell adenoma and of transitional epithelial papilloma of the urinary bladder (NTP, 1997a).

In contrast to *ad libitum*-feeding regimens which produced pancreatic lesions in male rats, consumption of restricted diets containing butyl benzyl phthalate did not result in these cancerous lesions in male rats after 2 years of exposure (NTP, 1997b). However, acinar cell adenomas were observed in three exposed, feed-restricted males at 30 months (6% incidence) (NTP, 1997b). NTP (1997b) states that feed restriction is known to influence the incidence of pancreatic acinar cell neoplasms (Roebuck, 1986; Roebuck et al., 1981, 1993) and may have prevented the full expression of this chemical-induced effect.

Other Studies

No data were available concerning the genotoxicity of butyl benzyl phthalate in humans. Studies indicate that butyl benzyl phthalate is not a direct acting mutagen in the reverse mutation assay in *Salmonella typhimurium* (Rubin et al., 1979; Kozumbo et al., 1982; Zeiger et al., 1982; NTP, 1982) or in *E. coli* (NTP, 1982). Butyl benzyl phthalate was not mutagenic in *Drosophila melanogaster* (NTP, 1997a). Testing in mammalian cells also suggests that butyl benzyl phthalate is not genotoxic; it did not induce mutations at the thymidine kinase locus of L5178Y mouse lymphoma cells (Myhr and Caspary, 1991; Barber et al., 2000). Butyl benzyl phthalate did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells (Galloway et al., 1987; NTP, 1982). Butyl benzyl phthalate was not active in the Balb/3T3 cell transformation assay with or without metabolic activation (Barber et al., 2000).

In contrast with the *in vitro* results, recent *in vivo* testing of butyl benzyl phthalate reported weak, but statistically significant, positive responses in two tests: a mouse bone marrow sister chromatid exchange test was positive at sample times of 23 and 42 hours (no confirmatory test was conducted), and chromosomal aberrations were induced in bone marrow cells of male mice 17 hours after intraperitoneal injection of 5000 mg/kg butyl benzyl phthalate (NTP, 1997a). Taken together, these data indicate that butyl benzyl phthalate is not strongly genotoxic.

ORAL CARCINOGENICITY ASSESSMENT

Butyl benzyl phthalate has been tested for carcinogenicity following oral administration to F344 rats (NTP, 1982, 1997a,b) and B6C3F1 mice (NTP, 1982). No increase in the incidence of tumors of any type was observed in B6C3F1 mice (NTP, 1982). In F344 rats, butyl benzyl phthalate was reported to cause an increase in the incidence of monocytic leukemia among females (NTP, 1982). Subsequent NTP testing did not support the finding of mononuclear cell

leukemia, but demonstrated an increase in the incidence of pancreatic acinar cell tumors in males and a marginal increase in the incidences of pancreatic acinar cell adenoma and transitional epithelial papilloma of the urinary bladder in females (NTP, 1997a); and a marginal increase in the incidence of bladder tumors in female rats exposed for 32 months via a restricted-diet protocol (NTP, 1997b).

NTP (1982) reported a statistically significant increase in the incidence of monocytic leukemia among female F344 rats: 14% among controls and low dose, and 38% among high dose. Based on these results, NTP indicated that butyl benzyl phthalate was "probably" carcinogenic in female rats. U.S. EPA (2002) concluded that given the similarity of the pathology of monocytic leukemia in the control and the dosed female rats, as well as the absence of a reduction in time to first tumor, the response likely represented an acceleration of a tumor whose incidence increases with advancing age in the F344 rats. This weakens somewhat the interpretive value of the response, although EPA considered the data sufficient to classify butyl benzyl phthalate as a possible human carcinogen; Group C (U.S. EPA, 2002). More recent testing by NTP (1997a,b) found no increase in the incidence of monocytic leukemia at the same or higher doses. NTP (1997a,b) concluded that monocytic leukemia was incidental in this study. Other researchers have suggested that monocytic leukemia is unique to rats (without a histologically comparable tumor in humans) and is common among the F344 inbred strain (Caldwell, 1999).

The biological significance of the marginal increase in the incidence of transitional epithelial papilloma in the urinary bladder of female rats is uncertain (NTP, 1997a). While this neoplasm was only observed in one of the control females (2% incidence), the presence of this neoplasm in two of the 1200 mg/kg-day females (4%) exceeded the incidence of historical controls, but did not achieve statistical significance (NTP, 1997a). Nevertheless, the appearance of this neoplasm in the exposed groups was also associated with increases in the incidence and severity of transitional epithelial hyperplasia (incidence rate: 8% control, 0% 300 mg/kg-day, 2% 600 mg/kg-day, and 20% 1200 mg/kg-day). The incidence of transitional epithelial hyperplasia at 1200 mg/kg-day was statistically different from controls. This suggests that these lesions are probably associated with exposure to butyl benzyl phthalate (NTP, 1997a). In addition, this was the only effect reported by NTP that was not reduced by dietary restriction; an increase in the incidence of transitional epithelial hyperplasia (incidence: 28% after 2 years at 485 mg/kg-day and 32% after 32 months at 466 mg/kg-day) and modest increase (that did not achieve statistical significance) in papilloma or carcinoma in the bladder of female rats (incidence: 4% after 2 years and 12% after 32 months) were observed in the restricted feed studies (NTP, 1997b).

NTP (1997a) concluded that there was some evidence of carcinogenic activity of butyl benzyl phthalate in high-dose (500 mg/kg-day) male F344 rats based on the increased incidences of pancreatic acinar cell adenoma (20% as compared to 6% for controls) and of acinar cell adenoma or carcinoma (combined) (22% as compared to 6% for controls). In addition, the NTP study reports that these cancerous lesions were accompanied by a concomitant increase in the incidence of preneoplastic lesions (pancreatic acinar cell hyperplasia) that exhibited a dose-

dependent increase (incidence rate: 8, 14, 18, and 24% for control, 120, 240, and 500 mg/kg-day, respectively). These effects suggest that the pancreatic lesions were related to chemical administration; pancreatic lesions in the F344 rat are generally characterized by a clear morphological continuum from focal acinar cell hyperplasia to adenoma to carcinoma (NTP, 1997a). Furthermore, the authors stated that there was equivocal evidence of carcinogenic activity of butyl benzyl phthalate in female 344 rats based on a marginal increase in the incidence of pancreatic acinar cell adenoma at high dose (incidence rate: 0% for control, 300, and 600 mg/kg-day and 4% at 1200 mg/kg-day) (NTP, 1997a).

Under the dietary restriction paradigm (NTP, 1997b), the increased incidence of pancreatic tumors in male rats from the *ad libitum* group (NTP, 1997a) did not occur, despite extension of the exposure period to 30 months in males and 32 months in females (NTP, 1997b). These data suggest that lower body weights are associated with a decrease in the incidence of pancreatic acinar cell adenoma in rats. In general, the low incidence of proliferative lesions in the dosed rats fed restricted diets for up to 30 months suggests that the effects of feed restriction may have delayed the development of spontaneous and treatment-related lesions of the pancreas (NTP, 1997b). Regarding the decreased incidence of pancreatic neoplasia among rats consuming a restricted diet containing butyl benzyl phthalate as compared to *ad libitum* feeding regimens, NTP concluded that feed restriction may have prevented the full expression of this chemical-induced effect (NTP, 1997b). Thus, the available data suggest that chronic oral exposure to butyl benzyl phthalate increases the incidence of pancreatic precancerous and cancerous lesions in male F344 rats.

PROVISIONAL WEIGHT OF EVIDENCE CLASSIFICATION

Under the 1986 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986), butyl benzyl phthalate is provisionally classified as Group C (Possible Human Carcinogen), based on no available data on the carcinogenicity of butyl benzyl phthalate in humans and limited evidence of carcinogenicity in animals. Evidence of animal carcinogenicity is based primarily on the results of a 2-year feeding study (NTP, 1997a) that concluded there was some evidence that oral exposure to butyl benzyl phthalate produced an increase in the incidence of pancreatic cancer in male F344 rats. The occurrence of these lesions was supported by a dose-dependent increase in preneoplastic lesions (NTP, 1997a). This study also reported equivocal evidence of carcinogenic activity of butyl benzyl phthalate in female 344 rats based on the marginally increased incidences of pancreatic acinar cell adenoma and precancerous and cancerous lesions in the bladder (NTP, 1997a). A previous study had found that dietary exposure to butyl benzyl phthalate resulted in a statistically significant increase in the incidence of monocytic leukemia in female F344 rats (NTP, 1982), but that finding was not supported by the more recent study. Under the proposed guidelines (U.S. EPA, 1996a, 1999), butyl benzyl phthalate is considered likely to be carcinogenic to humans.

The majority of data from genotoxicity testing have indicated that butyl benzyl phthalate is not strongly genotoxic. Whereas the *in vitro* testing reported negative results, weak, though statistically significant, positive results were reported by NTP (1997a) for two *in vivo* studies. Thus, while it is possible that butyl benzyl phthalate may act as a carcinogen through DNA damage, an alternative mechanism for carcinogenesis is also possible.

Evidence exists that phthalate diesters, including butyl benzyl phthalate are capable of inducing peroxisome proliferation (Barber et al., 1987). In collaborative studies conducted concomitantly with the 2-year NTP (1997a) study at the same laboratory, butyl benzyl phthalate was evaluated for its ability to induce hepatic peroxisomes in female F344/N rats as evidenced by the activities of two hepatic peroxisomal enzyme markers, palmitoyl CoA oxidase and carnitine acetyl transferase. When evaluated after 1 month and 1 year of exposure, butyl benzyl phthalate did not cause liver neoplasms, which would be expected because they have been observed with other peroxisome proliferators (Monsanto Company, 1994). It appears that butyl benzyl phthalate can cause a mild, yet detectable increase in peroxisome proliferation, although at a lower level than that induced by only 3 weeks of exposure to the positive control, di(2-ethylhexyl)phthalate (NTP, 1997a). Other research has reported similar results; butyl benzyl phthalate results in peroxisome proliferation, but is relatively weaker than other phthalate diesters (Barber et al., 1987).

While it is only speculative, this mechanism, peroxisome proliferation, may be the cellular change that results in pancreatic neoplasia. This hypothesis is supported in the literature, as other peroxisome proliferators (such as clofibrate and nafenopin) have caused pancreatic acinar cell neoplasms in male rats (Reddy and Qureshi, 1979). Research has also revealed that the peroxisome proliferation induced by butyl benzyl phthalate is more pronounced in male rats than in female rats (Barber et al., 1987). This difference in susceptibility between males and females has also been reported for other peroxisome proliferating agents, such as hydrochlorofluorocarbon 123 (Malley et al., 1995). While the sexual difference in susceptibility of peroxisome proliferation is not clearly understood, the sexual difference parallels the incidence of pancreatic lesions that result from exposure to butyl benzyl phthalate. In addition, research suggests that testosterone is stimulatory and that estrogen is inhibitory for growth of acinar cell neoplasms in rat models (Lhoste et al., 1987a,b; Longnecker and Sumi, 1990). According to NTP (1997a), the sex-related difference in the incidence of pancreatic neoplasia was probably related to the sex-hormonal dependency of peroxisomal proliferating activity of butyl benzyl phthalate.

DERIVATION OF A PROVISIONAL ORAL SLOPE FACTOR

NTP (1997a) concluded that there was some evidence of carcinogenic activity of butyl benzyl phthalate in male F344/N rats based on the increased incidences of pancreatic acinar cell adenoma and of acinar cell adenoma or carcinoma (combined) and that there was equivocal evidence of carcinogenic activity of butyl benzyl phthalate in female F344 rats based on

marginally increased incidences of pancreatic acinar cell adenoma and transitional epithelial papilloma of the urinary bladder (NTP, 1997a).

Incidence data relating to carcinogenic effects in the pancreas can be used as the basis for a quantitative estimate of cancer potency to humans. In accordance with the 1986 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1986), these data (NTP, 1997a,b) were fit to a linearized multistage model (Global86) and used to calculate cancer slope factors. Calculations were based on extra risk. The incidence data for butyl benzyl phthalate induction of pancreatic cancer among male F344 rats and the estimated potency values are shown in Table 2.

Choice of control group had little effect on the results. The q_1* and LED_{10} based on the weight-matched control group were used in further calculations because this produced a slightly more health protective result than using those estimated based on the *ad libitum* controls or both control groups together. A provisional human oral slope factor of 1.7×10^{-3} $(mg/kg\text{-}day)^{-1}$ was calculated from the data on pancreatic tumors in male rats using the following equation:

$$p\text{-}SFO_{hum} = p\text{-}SFO_{rat} \times \sqrt[3]{Wt_{hum} / Wt_{rat}} \times (Dur / LS_{rat})^3$$
$$= 4.7 \times 10^{-4} (mg/kg\text{-}day)^{-1} \times \sqrt[3]{70kg / 0.381kg} \times (2years / 2years)^3$$
$$= 1.7 \times 10^{-3} (mg/kg\text{-}day)^{-1}$$

where:

$p\text{-}SFO_{hum}$	=	provisional human oral slope factor
$p\text{-}SFO_{rat}$	=	provisional rat oral slope factor
Wt_{hum}	=	reference human body weight (70 kg) (U.S. EPA, 1987c)
Wt_{rat}	=	time-weighted average body weight calculated from NTP, 1997a (0.381 kg)
Dur	=	duration of exposure (2 years)
LS_{rat}	=	life span of rat (2 years)

In accordance with the proposed Guidelines for Carcinogen Risk Assessment (U.S. EPA, 1996a, 1999), the slope factor was also calculated by drawing a straight line between the LED_{10} and the origin. A nonlinear dose-response model was considered, although disregarded for the following reasons:

1. Although the putative mechanism of action suggests that peroxisome proliferation may trigger neoplastic changes in the pancreas (as opposed to direct genotoxicity), butyl benzyl phthalate is a relatively weak inducer of peroxisome proliferation.

2. Albeit weak, there is some evidence of *in vivo* genotoxicity following exposure to butyl benzyl phthalate.

Therefore, there is insufficient information to support deviation from the linear default assumption.

The LED_{10} was calculated to be 189 mg/kg-day using the polynomial model in the Global86 program and the U.S. EPA (1996b) benchmark dose methodology (see Table 2). This method results in a provisional oral slope factor for rat pancreatic carcinogenesis of 5.3×10^{-4} per (mg/kg-day), calculated as follows:

$$\begin{aligned} \text{p-SFO}_{rat} &= \text{Incidence / Dose} \\ &= 10\% \div LED_{10} \\ &= 0.1 \div 189 \text{ mg/kg-day} \\ &= 5.3 \times 10^{-4} \text{ (mg/kg-day)}^{-1} \end{aligned}$$

A human provisional oral slope factor of 1.9×10^{-3} $(mg/kg\text{-}day)^{-1}$ was calculated from the rat value using the following equation:

$$\begin{aligned} p\text{-}SFO_{hum} &= p\text{-}SFO_{rat} \times \sqrt[4]{Wt_{hum} / Wt_{rat}} \times (Dur / LS_{rat})^3 \\ &= 5.3 \times 10^{-4} (mg/kg\text{-}day)^{-1} \times \sqrt[4]{70kg / 0.381kg} \times (2years / 2years)^3 \\ &= 1.9 \times 10^{-3} (mg/kg\text{-}day)^{-1} \end{aligned}$$

The principal studies (NTP, 1997a,b) on which the provisional slope factor derivation is based were well-conducted and demonstrated a clear carcinogenic dose-response relationship for butyl benzyl phthalate in the rat pancreas. There was also a suggestion that butyl benzyl phthalate may be associated with bladder tumors in the same studies. However, there are no other studies assessing the carcinogenic potential of butyl benzyl phthalate. There is some evidence that butyl benzyl phthalate could be carcinogenic by a mechanism other than genotoxicity, suggesting that a threshold might exist. However, the evidence is very weak and does not warrant departure from the linear non-threshold approach. There is also some uncertainty as to which incidence rate to use for the control group, but the quantitative impact is minimal.

In summary, a provisional oral slope factor of 1.9×10^{-3} $(mg/kg\text{-}day)^{-1}$ was derived for butyl benzyl phthalate based on increased incidence of pancreatic cancer in male F334 rats. This slope factor, derived using the proposed guidelines (U.S. EPA, 1996a, 1999), was slightly more conservative than the value derived using the 1986 guidelines (U.S. EPA, 1986).

TABLE 2

Oral Slope Factor and LED_{10} Values Based on Tumor Incidence Data from Male Rats

Sex/Strain/ Species/ (Duration)	Tumor Location	Incidence (0 mg/kg-day)	Incidence (120 mg/kg-day)	Incidence (240 mg/kg-day)	Incidence (500 mg/kg-day)	q_1* $(mg/kg\text{-}day)^{-1}$	LED_{10} (mg/kg-day)
Male F344 Rat (2 years)	pancreas[a]	3/50[b]	2/49	3/50	11/50	3.1E-4	212
		1/50[c]				4.7E-4	189
		4/100[d]				2.7E-4	207

[a]Acinar cell adenoma or carcinoma (combined)

[b]*Ad libitum* control group

[c]Weight-matched control group

[d]Combined control groups

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