*FINAL*
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# Provisional Peer-Reviewed Toxicity Values for

# Perfluorobutane Sulfonate
(CASRN 375-73-5)
# and Related Compound
# Potassium Perfluorobutane Sulfonate
(CASRN 29420-49-3)

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Questions regarding the contents of this document may be directed to the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

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## COMMONLY USED ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| α2u-g | alpha 2u-globulin |
| ACGIH | American Conference of Governmental Industrial Hygienists |
| AIC | Akaike's information criterion |
| ALD | approximate lethal dosage |
| ALT | alanine aminotransferase |
| AST | aspartate aminotransferase |
| atm | atmosphere |
| ATSDR | Agency for Toxic Substances and Disease Registry |
| BMD | benchmark dose |
| BMDL | benchmark dose lower confidence limit |
| BMDS | Benchmark Dose Software |
| BMR | benchmark response |
| BUN | blood urea nitrogen |
| BW | body weight |
| CA | chromosomal aberration |
| CAS | Chemical Abstracts Service |
| CASRN | Chemical Abstracts Service Registry Number |
| CBI | covalent binding index |
| CHO | Chinese hamster ovary (cell line cells) |
| CL | confidence limit |
| CNS | central nervous system |
| CPN | chronic progressive nephropathy |
| CYP450 | cytochrome P450 |
| DAF | dosimetric adjustment factor |
| DEN | diethylnitrosamine |
| DMSO | dimethylsulfoxide |
| DNA | deoxyribonucleic acid |
| EPA | Environmental Protection Agency |
| FDA | Food and Drug Administration |
| FEV1 | forced expiratory volume of 1 second |
| GD | gestation day |
| GDH | glutamate dehydrogenase |
| GGT | γ-glutamyl transferase |
| GSH | glutathione |
| GST | glutathione-S-transferase |
| Hb/g-A | animal blood-gas partition coefficient |
| Hb/g-H | human blood-gas partition coefficient |
| HEC | human equivalent concentration |
| HED | human equivalent dose |
| i.p. | intraperitoneal |
| IRIS | Integrated Risk Information System |
| IVF | in vitro fertilization |
| $LC_{50}$ | median lethal concentration |
| $LD_{50}$ | median lethal dose |
| LOAEL | lowest-observed-adverse-effect level |
| MN | micronuclei |
| MNPCE | micronucleated polychromatic erythrocyte |
| MOA | mode-of-action |
| MTD | maximum tolerated dose |
| NAG | N-acetyl-β-D-glucosaminidase |
| NCEA | National Center for Environmental Assessment |
| NCI | National Cancer Institute |
| NOAEL | no-observed-adverse-effect level |
| NTP | National Toxicology Program |
| NZW | New Zealand White (rabbit breed) |
| OCT | ornithine carbamoyl transferase |
| ORD | Office of Research and Development |
| PBPK | physiologically based pharmacokinetic |
| PCNA | proliferating cell nuclear antigen |
| PND | postnatal day |
| POD | point of departure |
| $POD_{[ADJ]}$ | duration-adjusted POD |
| QSAR | quantitative structure-activity relationship |
| RBC | red blood cell |
| RDS | replicative DNA synthesis |
| RfC | inhalation reference concentration |
| RfD | oral reference dose |
| RGDR | regional gas dose ratio |
| RNA | ribonucleic acid |
| SAR | structure activity relationship |
| SCE | sister chromatid exchange |
| SD | standard deviation |
| SDH | sorbitol dehydrogenase |
| SE | standard error |
| SGOT | glutamic oxaloacetic transaminase, also known as AST |
| SGPT | glutamic pyruvic transaminase, also known as ALT |
| SSD | systemic scleroderma |
| TCA | trichloroacetic acid |
| TCE | trichloroethylene |
| TWA | time-weighted average |
| UF | uncertainty factor |
| $UF_A$ | interspecies uncertainty factor |
| $UF_H$ | intraspecies uncertainty factor |
| $UF_S$ | subchronic-to-chronic uncertainty factor |
| $UF_D$ | database uncertainty factor |
| U.S. | United States of America |
| WBC | white blood cell |

# PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR PERFLUOROBUTANE SULFONATE (CASRN 375-73-5) AND RELATED COMPOUND POTASSIUM PERFLUOROBUTANE SULFONATE (CASRN 29420-49-3)

## BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (http://www.epa.gov/iris), the respective PPRTVs are removed from the database.

## DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

## QUESTIONS REGARDING PPRTVs

Questions regarding the contents and appropriate use of this PPRTV assessment should 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).

## INTRODUCTION

Perfluorobutane sulfonate (PFBS) (CASRN 375-73-5) and its related salt called potassium perfluorobutane sulfonate ($K^+$PFBS) (CASRN 29420-49-3) are polyfluorinated compounds (PFCs) manufactured for use in paints, cleaning agents, and water-impermeable products (Rosal et al., 2010). Concerns about PFBS and other PFCs stem from the resistance of these compounds to hydrolysis, photolysis, and biodegradation, which leads to their persistence in the environment (Sundström et al., 2012). The chemical formula of PFBS is $C_4HF_9O_3S$ and the chemical formula of $K^+$PFBS is $C_4F_9KO_3S$. Their respective chemical structures are presented in Figure 1. $K^+$PFBS differs from PFBS by having a potassium atom. A table of physicochemical properties for PFBS and $K^+$PFBS is provided below (see Table 1).

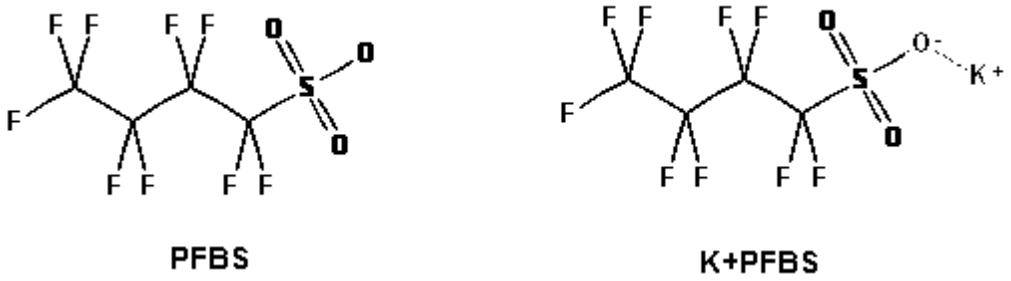



**Figure 1. Chemical Structures of PFBS and $K^+$PFBS**

**Table 1. Physicochemical Properties of PFBS (CASRN 375-73-5) and Related Compound $K^+$PFBS (CASRN 29420-49-3)[a]**

| Property (unit) | Value | |
|---|---|---|
| | PFBS (free acid) | $K^+$PFBS (potassium salt) |
| Boiling point (°C) | 200 | 76−84 |
| Density (g/cm$^3$ at 71°C) | ND | ND |
| Vapor pressure (mm Hg at 20°C) | ND | $9.15 \times 10^{-8}$ |
| pH (unitless) | ND | ND |
| Solubility in water (mg/L) | 56.6 at 24°C | 46.2 at 20°C |
| Molecular weight (g/mol) | 300.10 | 338.19 |
| Dissociation constant | NA | Fully dissociated in water over the pH range of 4−9 |

[a]NICNAS (2005b).

ND = no data; NA = not applicable.

A summary of available toxicity values for PFBS and related compound $K^+$PFBS from U.S. EPA and other agencies/organizations is provided in Table 2.

**Table 2. Summary of Available Toxicity Values for PFBS (CASRN 375-73-5) and Related Compound $K^+$PFBS (CASRN 29420-49-3)[a]**

| Source/Parameter[a] | Value (Applicability) | Notes | Reference | Date Accessed |
|---|---|---|---|---|
| **Noncancer** | | | | |
| ACGIH | NV | NR | ACGIH (2013) | NA |
| ATSDR | NV | NR | ATSDR (2013) | NA |
| Cal/EPA | NV | NR | Cal/EPA (2014a), 2014b) | 4-29-2014[b] |
| NIOSH | NV | NR | NIOSH (2010) | NA |
| OSHA | NV | NR | OSHA (2011), 2006) | NA |
| IRIS | NV | NR | U.S. EPA | 4-29-2014 |
| Drinking water | NV | NR | U.S. EPA (2012a) | NA |
| HEAST | NV | NR | U.S. EPA (2011a) | NA |
| CARA HEEP | NV | NR | U.S. EPA (1994) | NA |
| WHO | NV | NR | WHO | 4-29-2014 |
| **Cancer** | | | | |
| IRIS | NV | NR | U.S. EPA | 4-29-2014 |
| HEAST | NV | NR | U.S. EPA (2011a) | NA |
| IARC | NV | NR | IARC (2013) | NA |
| NTP | NV | NR | NTP (2011) | NA |
| Cal/EPA | NV | NR | Cal/EPA (2014b, (2011) | 4-29-2014[b] |

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; Cal/EPA = California Environmental Protection Agency; CARA = Chemical Assessments and Related Activities; HEAST = Health Effects Assessment Summary Tables; HEEP = Health and Environmental Effects Profile; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; WHO = World Health Organization.

[b]The Cal/EPA Office of Environmental Health Hazard Assessment (OEHHA) Toxicity Criteria Database (http://oehha.ca.gov/tcdb/index.asp) was also reviewed and found to contain no information on PFBS.

NA = not applicable; NV = not available; NR = not relevant.

Literature searches were conducted on sources published from 1900 through April 2014 for studies relevant to the derivation of provisional toxicity values for PFBS and related compound $K^+$PFBS. The following databases were searched by chemical name, synonyms, or CASRN: ACGIH, ANEUPL, ATSDR, BIOSIS, Cal/EPA, CCRIS, CDAT, ChemIDplus, CIS, CRISP, DART, EMIC, EPIDEM, ETICBACK, FEDRIP, GENE-TOX, HAPAB, HERO, HMTC, HSDB, IARC, INCHEM IPCS, IPA, ITER, IUCLID, LactMed, NIOSH, NTIS, NTP, OSHA, OPP/RED, PESTAB, PPBIB, PPRTV, PubMed (toxicology subset), RISKLINE, RTECS, TOXLINE, TRI, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, and U.S. EPA TSCATS/TSCATS2. The following databases were searched for toxicity values or exposure limits: ACGIH, ATSDR, Cal/EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA HEEP, U.S. EPA OW, U.S. EPA TSCATS/TSCATS2, NIOSH, NTP, OSHA, and RTECS.

## REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide an overview of the relevant database for PFBS and related compound $K^+$PFBS and include all potentially relevant repeated-dose, short-term-, subchronic-, and chronic-duration studies. Principal studies are identified in bold. The phrase "statistical significance," used throughout the document, indicates a $p$-value $<0.05$, unless otherwise noted.

**Table 3A. Summary of Potentially Relevant Noncancer Data for PFBS (CASRN 375-73-5) and the Related Compound $K^+$PFBS (CASRN 29420-49-3)**

| Category | Number of Male/Female, Strain, Species, Study Type, Study Duration | Dosimetry[a] | Critical Effects | NOAEL[a] | BMDL/ BMCL[a] | LOAEL[a] | Reference (Comments) | Notes[b] |
|---|---|---|---|---|---|---|---|---|
| **Human** | | | | | | | | |
| **1. Oral (mg/kg-day)[a]** | | | | | | | | |
| ND | | | | | | | | |
| **2. Inhalation (mg/m$^3$)[a]** | | | | | | | | |
| ND | | | | | | | | |
| **Animal** | | | | | | | | |
| **1. Oral (mg/kg-day)[a]** | | | | | | | | |
| **Subchronic[c]** | **10/10, S-D rat, $K^+$PFBS administered by gavage, 7 days/week, 90 days** | **0, 60, 200, 600** | **Increased incidence of renal hyperplasia in males and females** | **200** | **78.7** | **600** | **Lieder et al. (2009a)** | **PR, PS** |
| Chronic[d] | ND | | | | | | | |
| Developmental | ND | | | | | | | |
| Reproductive | 30/30, S-D rat, $K^+$PFBS administered by gavage, two-generation reproductive study | F0 adults: 0, 30, 100, 300, 1,000<br>F1 adults: 0, 30, 100, 300, 1,000 | F0 and F1 adults: increased incidence of hyperplasia and focal papillary edema in the kidneys of males and females.<br>F2 pups: no dose-related effects at the highest dose tested (1,000 mg/kg-day) | 100 | 26.6 (based on increased incidence of kidney hyperplasia in F0 females) | 300 | Lieder et al. (2009b) | PR |
| **2. Inhalation (mg/m$^3$)[a]** | | | | | | | | |
| ND | | | | | | | | |

[a]Dosimetry: Values expressed in mg/kg-day for oral noncancer effects.
[b]Notes: PS = principal study; PR = peer reviewed.
[c]Subchronic = repeated exposure for >90 days ≤ 10% lifespan (based on 70-year typical lifespan).
[d]Chronic = repeated exposure for >10% lifespan.

ND = no data; S-D = Sprague-Dawley.

**Table 3B. Summary of Potentially Relevant Cancer Data for PFBS (CASRN 375-73-5) and the Related Compound $K^+$PFBS (CASRN 29420-49-3)**

| Category | Number of Male/Female, Strain, Species, Study Type, Study Duration | Dosimetry[a] | Critical Effects | NOAEL | BMDL/ BMCL[a] | LOAEL[a] | Reference (Comments) | Notes |
|---|---|---|---|---|---|---|---|---|
| **Human** | | | | | | | | |
| **1. Oral (mg/kg-day)** | | | | | | | | |
| ND | | | | | | | | |
| **2. Inhalation (mg/m$^3$)** | | | | | | | | |
| ND | | | | | | | | |
| **Animal** | | | | | | | | |
| **1. Oral (mg/kg-day)** | | | | | | | | |
| ND | | | | | | | | |
| **2. Inhalation (mg/m$^3$)** | | | | | | | | |
| ND | | | | | | | | |

ND = no data.

## HUMAN STUDIES

### Oral Exposures

No studies have been identified for either PFBS or $K^+$PFBS.

### Inhalation Exposures

No studies have been identified for either PFBS or $K^+$PFBS.

## ANIMAL STUDIES

### Oral Exposures

The effects of oral exposure of animals to $K^+$PFBS were evaluated in one subchronic-duration and one two-generation reproductive toxicity study. No oral studies in animals have been identified for PFBS.

#### *Subchronic-duration Studies*

*Lieder et al. (2009a)*

In a peer-reviewed subchronic-duration toxicity study performed by Lieder et al. (2009a), 10 Sprague-Dawley rats/sex/dose were administered $K^+$PFBS daily via gavage for approximately 90 days (90−93 days). Doses of 0, 60, 200, or 600 mg/kg-day $K^+$PFBS were given to rats at approximately the same time each day. Animals were housed individually in steel, wire-bottomed cages and fed with Certified Rodent Diet R #5002 (PMI Nutrition International, Inc, St. Louis, MO) ad libitum throughout the study. $K^+$PFBS (Lot #120k0252, 98.2% pure) was provided by 3M Company (Maplewood, MN). Dose formulations were prepared by dissolving $K^+$PFBS in the dosing vehicle, aqueous carboxymethyl cellulose (0.1% CMC, medium viscosity). The study authors reported using Good Laboratory Practice (GLP) principles as well as adherence to test guidelines OECD 408 and OPPTS 870.3100.

The rats were observed twice daily during the study: once before dosing and approximately 1 hour after each dose administration. Detailed clinical observations were conducted for all rats once before the first dose and at least once weekly thereafter. The eyes of all rats were examined by a veterinary ophthalmologist prior to the first dose and at termination of the study. Body weights were recorded prior to treatment, weekly during treatment, and at sacrifice. Food consumption was determined prior to treatment and weekly during treatment. Blood was collected on the day following the last administration of the test substance (Days 91−94 of the study), and the following hematological parameters were evaluated: erythrocyte count (RBC), hematocrit (HCT), hemoglobin (HGB), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), total leukocyte count (WBC), differential leukocyte count, platelet count (PLAT), mean platelet volume (MPV), cell morphology, prothrombin time (PT), and activated partial thromboplastin time (APTT). Two milliliters of blood were processed to obtain serum and analyze the following clinical chemistry parameters: total protein (TP), triglycerides (TRI), albumin (A), globulin (G), albumin/globulin ratio (A/G), glucose (GLU), cholesterol (CHOL), total bilirubin (TBILI), blood urea nitrogen (BUN), creatinine (CREAT), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALK), calcium (Ca), phosphorus (PHOS), sodium (Na), potassium (K), and chloride (Cl). At the scheduled termination, a gross necropsy of the thoracic, abdominal, and pelvic viscera was performed. The liver, kidney, spleen, thymus, adrenals, gonads, heart, and brain were weighed. All tissues from rats in the 0 and 600 mg/kg-day dose groups were histologically examined. In

addition, the nasal cavities, nasal turbinates, stomachs, and kidneys of rats in the 60 and 200 mg/kg-day groups were evaluated microscopically.

No treatment-related effects were noted on food consumption, mortality, or behavior. One male rat in the high-dose group died on Day 85 of the study. However, the study authors deemed this death to be unrelated to the administration of $K^+$PFBS because the sudden onset of clinical observations such as urine-stained abdominal fur, decreased motor activity, and dehydration indicated a possible injury. Body weights for both male and female rats were similar for all four dose groups throughout the treatment period (see Table B-1). As shown in Table B-2, males in the 60, 200, and 600 mg/kg-day dose groups showed statistically significantly decreased (5−17%) absolute and relative spleen weights (spleen-to-body weight ratio) compared to controls. However, these reductions were not dose dependent and did not occur in female rats treated with $K^+$PFBS (see Table B-3). No other treatment-related organ weight effects were observed (see Tables B-2 and B-3). Chloride levels were statistically significantly increased (3%) in male rats, but not in females, in the 600 mg/kg-day group (see Table B-4). Also, average total protein and albumin were statistically significantly decreased (7 and 10%, respectively) in female rats, but not in males, in the 600 mg/kg-day group (see Table B-4). No other changes in clinical chemistry measurements were reported in male or female rats. Dose-dependent and statistically significant decreases (5−7.5%) in HGB as well as HCT levels were observed in males, but not females, in the 200 and 600 mg/kg-day groups (see Table B-5). There was also a statistically significant decrease (7.3%) in RBCs in males in the 600 mg/kg-day group (see Table B-5). No other treatment-related changes in hematological parameters (e.g., MCV, MCH, and MCHC) were reported in males or females; thus, the biological significance of these small changes in HGB, HCT, and RBC levels is unclear. Statistically significant histopathological findings included increased incidence of hyperplasia in the medullary and papillary tubules of the kidneys of both sexes in the 600 mg/kg-day group (see Table B-6). Hyperplasia and necrosis were also observed in the stomachs of males and females in the 600 mg/kg-day group (see Table B-6), but the study authors considered this effect to be the result of repeated gavage dosing. No other biologically significant histopathological findings were reported. Based on histopathological findings in the kidneys, the high dose of 600 mg/kg-day is considered the lowest-observed-adverse-effect level (LOAEL) and the mid dose of 200 mg/kg-day is identified as the corresponding no-observed-adverse-effect level (NOAEL) for both male and female rats.

***Chronic-duration Studies***

No studies have been identified.

***Reproductive Studies***

*Lieder et al. (2009b)*

In a peer-reviewed, two-generation reproductive toxicity study performed by Lieder et al. (2009b), Sprague-Dawley rats were administered doses of 0, 30, 100, 300, or 1,000 mg/kg-day $K^+$PFBS (Lot #2, 97.9% pure) via gavage using formulations that were prepared by dissolving $K^+$PFBS in aqueous carboxymethyl cellulose with highly purified water. The parental (F0) generation consisted of 30 rats/sex/group and received daily doses of $K^+$PFBS beginning at 6 weeks of age and lasting until at least 70 days prior to cohabitation. The first generation (F1) rats received the same dose as their respective sires and dams beginning at Lactation Day (LD) 22. Animals were housed individually (except during mating and lactation) in steel, wire-bottomed cages and fed with Certified Rodent Diet R #5002 (PMI Nutrition International,

Inc, St. Louis, MO) ad libitum throughout the study. The study authors reported adherence to test guidelines OECD 416 and OPPTS 870.3800.

For mating, animals were allowed to cohabitate for a maximum of 14 days. Evidence of mating was determined by the presence of spermatozoa in a vaginal smear or copulatory plug and this was considered Gestation Day (GD) 0. For the F0- and F1-generation rats, clinical observations, abortions or premature deliveries, and deaths were recorded before dosing and at 60 minutes postdosing. Body weights and food consumption for F0- and F1-generation rats were recorded weekly prior to conception; on GDs 0, 7, 10, 14, 18, 21, and 25 (if females did not give birth); and on LDs 1, 5, 8, 11, 15, and 22. Body weights and food consumption were also recorded for F1-generation rats upon attainment of sexual maturation. Second generation (F2) pup body weights were recorded on LDs 1, 5, 8, 15, and 22. The F0- and F1-generation rats were evaluated for duration of gestation, fertility and gestation indices, number and sex of offspring, number of implantation sites, condition of dams and litters, litter size, viability index, lactation index, percent survival, and sex ratio. At scheduled termination (after cohabitation for males and on LD 22 for females), F0- and F1-generation rats were euthanized by carbon dioxide ($CO_2$) asphyxiation, necropsied, and examined for gross lesions. The following organs were individually weighed: brain, kidneys, spleen, ovaries, testes, thymus, liver, adrenal glands, pituitary, uterus with oviducts and cervix, left epididymis, right epididymis, prostate, and seminal vesicles. The study authors stated that histopathological evaluations were performed on the liver and kidneys of all F0 and F1 animals in the control and treatment groups. However, data were only presented for the 300 and 1,000 mg/kg-day treatment groups. For the pituitary, adrenal glands, vagina, uterus, cervix, ovaries, right testis, seminal vesicles, right epididymis, and prostate, histological examinations were only performed on 10 randomly selected rats per sex from the control and 1,000 mg/kg-day groups. All F2-generation pups culled on LD 22 were euthanized by $CO_2$ asphyxiation and three randomly selected pups per sex per litter were examined for gross lesions. The brain, spleen, liver, thymus, and kidneys from one of the three randomly selected pups per litter were weighed. F1-generation pups were not examined for gross lesions.

No biologically significant reproductive effects were observed in F0- or F1-generation males following $K^+$PFBS treatment. At the highest dose, there were statistically significant increases in the percentage of abnormal sperm in F1 animals and decreases in testicular sperm count in F0-generation males (see Table B-7). However, these effects were not dose dependent and were observed in only one generation; thus, they were not considered biologically significant by the study authors. No statistically significant changes in estrous cycling were reported in F0- or F1-generation females treated with $K^+$PFBS. No treatment-related weight changes in the gonads were reported in F0- or F1-generation males and females. Fertility parameters and delivery outcomes for F0- and F1-generation dams remained unaffected by $K^+$PFBS treatment (see Table B-8). Litter outcomes for F1- and F2-generation pups such as the mean number of stillborn pups, mean pup weight at birth, and mean pup weight at weaning did not exhibit statistically significant changes (see Table B-9). The mean number of live born F1 pups was statistically significantly decreased in the 30 mg/kg-day group, but this change was not dose dependent. The viability index in F1 pups and the lactation index in F1 and F2 pups showed statistically significant changes at various doses but were not dose dependent (see Table B-9).

No significant changes in food consumption were reported in F0- or F1-generation males. The terminal body weights of F0-generation males were not affected by $K^+$PFBS treatment (see

Table B-10). However, a statistically significant decrease in terminal body weight was noted in F1-generation males in the 1,000 mg/kg-day dose group (see Table B-10). Statistically significant increases in absolute (~12%) and relative (12−21%) liver weight were observed in F0-generation males in the 300 and 1,000 mg/kg-day dose groups (see Table B-10). In contrast, F1-generation males exhibited statistically increased relative liver weight (9%), but not absolute liver weight, only at the highest dose (see Table B-10). No other statistically significant organ weight changes were noted in males. With respect to females, the study authors reported sporadic decreases in food consumption in F0-generation rats in the 300 and 1,000 mg/kg-day dose groups between GD 10 and GD 14. No changes in food consumption were noted for F1-generation females. No statistically significant reductions in body weights were observed in F0-generation females (see Table B-11). Body weight changes in F1-generation females were statistically significant but did not reach 10% and were not dose dependent. The organ weights of F0- and F1-generation females were not affected by $K^+$PFBS treatment (see Table B-11). Also, no treatment-related changes in body weight or organ weights were observed in F2-generation pups (data not shown).

There were no treatment-related gross anatomical findings in F0-, F1-, or F2-generation males and females. Increased incidences of hepatocellular hypertrophy were observed in F0- and F1-generation males in the 300 and 1,000 mg/kg-day dose groups (see Table B-12), however only incidences in the 1,000 mg/kg-day group were statistically significant. Fewer incidences of these liver effects were observed in F1-generation males when compared to F0-generation males. Also, liver effects were not observed in females; thus, the biological significance of the liver effects in males is unclear. Additional histopathological findings included statistically significant mild-to-moderate hyperplasia and focal papillary edema in the kidneys of F0- and F1-generation males and females in the 300 and 1,000 mg/kg/day dose groups (see Table B-12). The study authors did not present the incidences of histopathological findings for the 100 mg/kg-day group, although the methods section of the article states that the livers and kidneys of rats in all dose groups were histologically examined. No histopathological findings were reported in the F2 generation. Based on kidney histopathology changes observed in F0- and F1-generation males and females, 300 mg/kg-day is identified as the LOAEL, with a corresponding NOAEL of 100 mg/kg-day. No dose-related effects were observed in F1 or F2 pups, therefore the highest dose of 1,000 mg/kg-day is considered the NOAEL for reproductive toxicity. Identification of a LOAEL for reproductive toxicity is precluded.

***Developmental Studies***

No studies have been identified.

**Inhalation Exposures**

No inhalation studies have been identified on the subchronic-duration, chronic, developmental, or reproductive toxicity or on the carcinogenicity of PFBS or $K^+$PFBS in animals.

**OTHER DATA**

Other studies that utilized PFBS or $K^+$PFBS are described here. These studies are not adequate for the determination of provisional reference dose (p-RfD), provisional reference concentration (p-RfC), provisional oral slope factor (p-OSF), or provisional inhalation unit risk (p-IUR) values but provide supportive data supplementing a weight-of-evidence approach. These data may include genotoxicity, metabolism, mechanistic, and other studies (see Table 4).

**Table 4. Other Studies**

| Test | Materials and Methods | Results | Conclusions | References |
|---|---|---|---|---|
| Mutagenicity test | *Salmonella typhimurium* (strains TA98 and TA100) and *E. coli* (strain pKM101) in the presence or absence of S9. Doses of PFBS were between 0−5,000 μg/plate. | Test was negative for TA100 and pKM101 strains and equivocal for TA98 strain. | There is no in vitro evidence of PFBS mutagenicity. | NTP (2005) |
| Genotoxicity test | Human hepatoma (HepG2) cells were treated with 0.4 μM to 2 mM PFBS. Intracellular ROS production was measured by use of 2′,7′-dichlorofluorescein diacetate and DNA damage was measured with the comet assay. | The amount of ROS and DNA strand breaks remained unaffected by PFBS treatment. | PFBS did not generate ROS or DNA damage in human liver cells. | Eriksen et al. (2010) |
| Metabolism/ toxicokinetic | Blood and urine samples were collected from the following species: Sprague-Dawley rats (3M/3F) treated with a single intravenous (i.v.) or oral (gavage) dose of 30 mg $K^+$PFBS/kg body weight; cynomolgus monkeys (3M/3F) treated with a single i.v. dose of 10 mg $K^+$PFBS/kg body weight; and human workers (5M/1F) engaged in the production of $K^+$PFBS prior to study initiation but not during 6 mo of follow-up. | The mean terminal serum elimination half-life of $K^+$PFBS is 3.96−4.51 hours in rats, 83.2−95.2 hours in monkeys, and 25.8 days in humans. | $K^+$PFBS appears to be eliminated at a slower rate in humans than in monkeys or rats. | Olsen et al. (2009) |

**Tests Evaluating Genotoxicity and Mutagenicity**

PFBS was negative for mutagenicity in *E. Coli* strain pKM101 and *Salmonella typhimurium* strain TA100 (NTP, 2005). Mutagenicity test results were equivocal in *S. typhimurium* strain TA98. PFBS did not generate reactive oxygen species (ROS) or oxidative DNA damage in HepG2 cells (Eriksen et al., 2010) (see Table 4).

**Metabolism/Toxicokinetic Studies**

Olsen et al. (2009) evaluated the toxicokinetics of $K^+$PFBS in Sprague-Dawley rats, cynomolgus monkeys, and humans. The following parameters were evaluated: (1) elimination of $K^+$PFBS after intravenous (i.v.) dosing in rats and monkeys; (2) oral uptake and elimination of $K^+$PFBS in rats; and (3) human serum $K^+$PFBS elimination in a group of workers with occupational exposure. In rats, the mean terminal serum $K^+$PFBS elimination half-lives, after i.v. administration of 30 mg/kg $K^+$PFBS, were 4.51 ± 2.22 hours for males and 3.96 ± 0.21 hours for females. Although there was no statistical difference between the terminal serum half-lives in male and female rats, clearance was statistically significantly greater in female rats (469 ± 40 mL/hour) than in male rats (119 ± 34 mL/hour). These differences were not observed between male and female monkeys. For rats receiving an oral dose, terminal serum $K^+$PFBS elimination half-lives were 4.68 ± 0.43 hours for males and 7.42 ± 0.79 hours for females. In monkeys, the mean terminal serum elimination half-lives, after i.v. administration of 10 mg/kg $K^+$PFBS, were 95.2 ± 27.1 hours in males and 83.2 ± 41.9 hours in females. Based on estimates obtained for the volume of distribution in rats and monkeys, $K^+$PFBS appears to be primarily distributed in the extracellular space. Among 6 human subjects (5 male, 1 female) followed up to 180 days after cessation of further $K^+$PFBS work-related activity, the geometric mean serum elimination half-life for $K^+$PFBS was 25.8 days (95% confidence interval = 16.6−40.2). These findings indicate that $K^+$PFBS is eliminated at a slower rate from human serum than from that of rats or monkeys. Urine appeared to be a major route of elimination in all three species tested.

## DERIVATION OF PROVISIONAL VALUES

Tables 5 and 6 present summaries of noncancer and cancer reference values, respectively.

**Table 5. Summary of Noncancer Provisional Reference Values for PFBS (CASRN 375-73-5) and Related Compound $K^+$PFBS (CASRN 29420-49-3)**

| Toxicity Type (units) | Species/Sex | Critical Effect | p-Reference Value | POD Method | POD[a] | $UF_C$ | Principal Study |
|---|---|---|---|---|---|---|---|
| Subchronic p-RfD (mg/kg-day) for $K^+$PFBS (salt) | Rat/F | Increased incidence of kidney hyperplasia. | $2 \times 10^{-1}$ | $BMDL_{10}$ | 18.9 | 100 | Lieder et al. (2009a) |
| Subchronic p-RfD (mg/kg-day) for PFBS (free acid) | Rat/F | Increased incidence of kidney hyperplasia. | $2 \times 10^{-1}$ | $BMDL_{10}$ | 18.9 | 100 | Lieder et al. (2009a) |
| Chronic p-RfD (mg/kg-day) for $K^+$PFBS (salt) | Rat/F | Increased incidence of kidney hyperplasia. | $2 \times 10^{-2}$ | $BMDL_{10}$ | 18.9 | 1,000 | Lieder et al. (2009a) |
| Chronic p-RfD (mg/kg-day) for PFBS (free acid) | Rat/F | Increased incidence of kidney hyperplasia. | $2 \times 10^{-2}$ | $BMDL_{10}$ | 18.9 | 1,000 | Lieder et al. (2009a) |
| Subchronic p-RfC ($mg/m^3$) for $K^+$PFBS | NDr | | | | | | |
| Subchronic p-RfC ($mg/m^3$) for PFBS | NDr | | | | | | |
| Chronic p-RfC ($mg/m^3$) for $K^+$PFBS | NDr | | | | | | |
| Chronic p-RfC ($mg/m^3$) for PFBS | NDr | | | | | | |

[a]HED expressed in mg/kg-day.

NDr = not determined.

**Table 6. Summary of Provisional Cancer Values for PFBS (CASRN 375-73-5) and Related Compound $K^+$PFBS (CASRN 29420-49-3)**

| Toxicity Type | Species/Sex | Tumor Type | Cancer Value | Principal Study |
|---|---|---|---|---|
| p-OSF | NDr | | | |
| p-IUR | NDr | | | |

NDr = not determined.

**DERIVATION OF ORAL REFERENCE DOSES**

The database of oral toxicity studies for PFBS and the related compound $K^+$PFBS includes one subchronic-duration study and one reproductive toxicity study, both of which were conducted in rats using the potassium salt ($K^+$PFBS). From the subchronic-duration rat study by Lieder et al. (2009a), a NOAEL of 200 mg/kg-day and a LOAEL of 600 mg/kg-day were identified for both males and females based on histopathological findings in the kidneys (mild to moderate hyperplasia). No treatment-related effects were reported in the liver. Although a statistically significant decrease in hematocrit and hemoglobin levels was observed at 200 mg/kg-day in male rats, these effects were considered mild, were not accompanied by bone marrow abnormalities or any other hematological changes, and were only observed in males. Thus, the biological relevance of these hematological findings is uncertain. The Lieder et al. (2009a) study was peer-reviewed, used GLP guidelines, and met the standards of study design and performance with regards to the number of animals used, examination of potential toxicity endpoints, and presentation of information.

The reproductive toxicity study in rats by Lieder et al. (2009b) identified a NOAEL of 100 mg/kg-day and a LOAEL of 300 mg/kg-day in F0- and F1-generation animals based on increased incidences and severity of kidney histopathology observed in both sexes. Although increased liver weights and hepatocellular hypertrophy were noted in males, these hepatic effects were not observed in females and no increased response was seen in F1-generation males when compared to F0-generation males. Furthermore, no liver changes in either sex were observed in the subchronic-duration study by Lieder et al. (2009a); thus, the biological relevance of liver effects in males of the reproductive toxicity study is not clear. Hematological parameters were not assessed in this study. There were no abnormal clinical or necropsy observations in the F2 generation. This report was peer-reviewed, employed an adequate number of animals, and was performed according to U.S. EPA guidelines.

Both the subchronic-duration study by Lieder et al. (2009a) and the reproductive toxicity study by Lieder et al. (2009b) in rats suggest the kidney as a major target organ of $K^+$PFBS toxicity, with kidney effects (hyperplasia) observed both in males and females. Thus, increased incidence of kidney hyperplasia is selected as the critical effect. Benchmark dose (BMD) analyses were conducted on the kidney hyperplasia data from males and females for both studies using the U.S. EPA's Benchmark Dose Software (BMDS version 2.3). Results of BMD modeling are summarized in Appendix C. BMD modeling of the kidney hyperplasia data was performed using a benchmark response (BMR) of 10%. For kidney hyperplasia data from the subchronic-duration study by Lieder et al. (2009a), the Exponential model provided the best fit with a $BMDL_{10}$ of 96.7 mg/kg-day for males and a $BMDL_{10}$ of 78.7 mg/kg-day for females (see Tables C-1 and C-2). Kidney hyperplasia data from the reproductive study by Lieder et al. (2009b) provided a $BMDL_{10}$ of 73.2 mg/kg-day and a $BMDL_{10}$ of 126 mg/kg-day for F0-generation and F1-generation males, respectively (see Tables C-3 and C-4). The reproductive toxicity study also provided a $BMDL_{10}$ of 26.6 mg/kg-day for F0-generation females and a $BMDL_{10}$ of 52.4 mg/kg-day for F1-generation females (see Tables C-5 and C-6) for kidney hyperplasia, which are lower than the BMDLs obtained with data from the subchronic-duration study. However, the analyses from the reproductive toxicity study provide less reliable BMD estimates because they do not contain a data point near the BMR (unlike the subchronic-duration study), which is recommended for adequate BMD modeling (U.S. EPA, 2012b). Therefore, the $BMDL_{10}$ of 78.7 mg/kg-day based on increased incidence of kidney hyperplasia in females from

the subchronic-duration study is selected as the point of departure (POD) for derivation of the subchronic p-RfD.

**Derivation of Subchronic p-RfD**

The U.S. EPA endorses a hierarchy of approaches to derive human equivalent oral exposures from data from laboratory animal species, with the preferred approach being physiologically based toxicokinetic modeling. Another approach may include using chemical-specific information, including what is known about the toxicokinetics and toxicodynamics of the chemical, to derive chemical-specific adjustments. In lieu of chemical-specific information to derive human equivalent oral exposures, U.S. EPA endorses body-weight scaling to the 3/4 power (i.e., $BW^{3/4}$) as a default to extrapolate toxicologically equivalent doses of orally administered agents from all laboratory animals to humans for the purpose of deriving an RfD under certain exposure conditions (U.S. EPA, 2011b). More specifically, the use of $BW^{3/4}$ scaling for deriving an RfD is recommended when the observed effects are associated with the parent compound or a stable metabolite but not for portal-of-entry effects or developmental endpoints. Although the pharmacokinetic study by Olsen et al. (2009) suggests a longer half-life for $K^+$PFBS in humans than in rats, these results were obtained by single-dose administration and it is uncertain whether this reflects the compound's half-life after repeated dosing. Furthemore, clearance is a more relevant parameter than serum half-life to determine chemical elimination, but no information on the clearance rate in humans is provided by Olsen et al. (2009). Thus, due to a lack of definitive information regarding potential pharmacokinetic differences between species, the use of $BW^{3/4}$ scaling to obtain a human equivalent dose (HED) is considered appropriate in this case.

Following U.S. EPA guidance, the POD for the rat subchronic-duration study is converted to an HED through an application of a dosimetric adjustment factor (DAF) derived as follows:

$$DAF = (BW_a^{1/4} \div BW_h^{1/4})$$

Where:

DAF = dosimetric adjustment factor
$BW_a$ = animal body weight
$BW_h$ = human body weight

Using a $BW_a$ of 0.25 kg for rats and a standard $BW_h$ of 70 kg for humans the resulting DAF is 0.24. Applying this DAF to the $BMDL_{10}$ obtained from modeling the kidney hyperplasia data from the $K^+$PFBS rat subchronic-duration study yields a $BMDL_{10HED}$ as follows:

$BMDL_{10HED}$ for $K^+$PFBS = $BMDL_{10}$ (mg/kg-day) × DAF
= 78.7 (mg/kg-day) × 0.24
= 18.9 mg/kg-day

The subchronic p-RfD for $K^+$PFBS, based on the $BMDL_{10HED}$ of 18.9 mg/kg-day for kidney hyperplasia in female rats, is derived as follows:

**Subchronic p-RfD for $K^+$PFBS** = $BMDL_{10HED} \div UF_C$
= 18.9 mg/kg-day ÷ 100
= **$2 \times 10^{-1}$ mg/kg-day**

The data for $K^+$PFBS can be used to derive a subchronic p-RfD for the free acid (PFBS), as $K^+$PFBS is fully dissociated in water at the environmental pH range of 4−9 (NICNAS, 2005a). In order to calculate the subchronic p-RfD for the free acid, the subchronic p-RfD for the potassium salt is adjusted to compensate for differences in molecular weight between $K^+$PFBS (338.19) and PFBS (300.10). The subchronic p-RfD for PFBS (free acid) is calculated as follows:

**Subchronic p-RfD for PFBS (free acid)** = p-RfD for $K^+$PFBS salt × (MW free acid ÷ MW salt)
= $2 \times 10^{-1}$ mg/kg-day × (300.10 ÷ 338.19)
= $2 \times 10^{-1}$ mg/kg-day × (0.89)
= **$2 \times 10^{-1}$ mg/kg-day**

Table 7 summarizes the uncertainty factors for the subchronic p-RfDs for PFBS and $K^+$PFBS.

**Table 7. Uncertainty Factors for the Subchronic p-RfD for PFBS (CASRN 375-73-5) and the Related Compound $K^+$PFBS (CASRN 29420-49-3)**

| UF | Value | Justification |
|---|---|---|
| $UF_A$ | 3 | A $UF_A$ of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicodynamic differences between mice and humans following oral $K^+$PFBS/PFBS exposure. The toxicokinetic uncertainty has been accounted for by calculation of a human equivalent dose (HED) through application of a dosimetric adjustment factor (DAF) as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b). |
| $UF_D$ | 3 | A $UF_D$ of 3 is applied because the database includes one acceptable two-generation reproductive toxicity study in rats (Lieder et al., 2009b), but there is no acceptable developmental toxicity study via the oral route. |
| $UF_H$ | 10 | A $UF_H$ of 10 is applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of $K^+$PFBS/PFBS in humans. |
| $UF_L$ | 1 | A $UF_L$ of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a BMDL. |
| $UF_S$ | 1 | A $UF_S$ of 1 is applied because a subchronic-duration study was selected as the principal study. |
| $UF_C$ | 100 | Composite Uncertainty Factor = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$ |

The confidence in the subchronic p-RfD for PFBS and $K^+$PFBS is medium as explained in Table 8 below.

**Table 8. Confidence Descriptors for Subchronic p-RfD for PFBS (CASRN 375-73-5) and the Related Compound $K^+$PFBS (CASRN 29420-49-3)**

| Confidence Categories | Designation[a] | Discussion |
|---|---|---|
| Confidence in study | H | Confidence in the key study is high. Lieder et al. (2009a) utilized an adequate subchronic-duration study design in rats. This study is also peer-reviewed, and experiments were performed according to GLP guidelines. |
| Confidence in database | M | The database includes one subchronic-duration study in rats Lieder et al. (2009a) and one reproductive toxicity study in rats (Lieder et al., 2009b). However, no developmental toxicity studies have been identified. |
| Confidence in subchronic p-RfD[b] | M | The overall confidence in the subchronic p-RfD is medium. |

[a]L = low, M = medium, H = high.
[b]The overall confidence cannot be greater than lowest entry in table.

**Derivation of Chronic Provisional RfD (Chronic p-RfD)**

There are no chronic-duration studies available for PFBS and $K^+$PFBS. Therefore, based on the same database and similar considerations, the chronic p-RfD for $K^+$PFBS is derived as follows using the $BMDL_{10HED}$ of 18.9 mg/kg-day for increased incidence of kidney hyperplasia in female rats from the subchronic-duration study by Lieder et al. (2009a) as the POD:

$$\textbf{Chronic p-RfD for } \mathbf{K^+PFBS} = BMDL_{10HED} \div UF_C$$
$$= 18.9 \text{ mg/kg-day} \div 1{,}000$$
$$= \mathbf{2 \times 10^{-2} \text{ mg/kg-day}}$$

The chronic p-RfD for PFBS (free acid) is calculated using the ratio of molecular weights, as follows:

$$\textbf{Chronic p-RfD} = \text{p-RfD for salt} \times (\text{MW free acid} \div \text{MW salt})$$
$$\textbf{for PFBS (free acid)} = 2 \times 10^{-2} \text{ mg/kg-day} \times (300.10 \div 338.19)$$
$$= 2 \times 10^{-2} \text{ mg/kg-day} \times (0.89)$$
$$= \mathbf{2 \times 10^{-2} \text{ mg/kg-day}}$$

Table 9 summarizes the uncertainty factors for the chronic p-RfD for PFBS and $K^+$PFBS.

**Table 9. Uncertainty Factors for the Chronic p-RfD for PFBS (CASRN 375-73-5) and the Related Compound $K^+$PFBS (CASRN 29420-49-3)**

| UF | Value | Justification |
|---|---|---|
| $UF_A$ | 3 | A $UF_A$ of 3 ($10^{0.5}$) is applied to account for uncertainty in characterizing the toxicodynamic differences between mice and humans following oral $K^+$PFBS/PFBS exposure. The toxicokinetic uncertainty has been accounted for by calculation of a human equivalent dose (HED) through application of a dosimetric adjustment factor (DAF) as outlined in the EPA's *Recommended Use of Body Weight$^{3/4}$ as the Default Method in Derivation of the Oral Reference Dose* (U.S. EPA, 2011b). |
| $UF_D$ | 3 | A $UF_D$ of 3 is applied because the database includes one acceptable two-generation reproductive toxicity study in rats (Lieder et al., 2009b), but there is no acceptable developmental toxicity study via the oral route. |
| $UF_H$ | 10 | A $UF_H$ of 10 is applied for inter-individual variability to account for human-to-human variability in susceptibility in the absence of quantitative information to assess the toxicokinetics and toxicodynamics of $K^+$PFBS/PFBS in humans. |
| $UF_L$ | 1 | A $UF_L$ of 1 is applied for LOAEL-to-NOAEL extrapolation because the POD is a BMDL. |
| $UF_S$ | 10 | A $UF_S$ of 10 is applied to extrapolate from less than chronic-duration exposure. |
| $UF_C$ | 1,000 | Composite Uncertainty Factor = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$ |

The confidence in the chronic p-RfD for PFBS and $K^+$PFBS is medium as explained in Table 10 below.

**Table 10. Confidence Descriptors for Chronic p-RfD for PFBS (CASRN 375-73-5) and the Related Compound $K^+$PFBS (CASRN 29420-49-3)**

| Confidence Categories | Designation[a] | Discussion |
|---|---|---|
| Confidence in study | H | Confidence in the key study is high. Lieder et al. (2009a) utilized an adequate subchronic-duration study design in rats. This study is also peer-reviewed, and experiments were performed according to GLP guidelines. |
| Confidence in database | M | The database includes one subchronic-duration study in rats Lieder et al. (2009a) and one reproductive toxicity study in rats Lieder et al. (2009b). However, no developmental toxicity or chronic-duration studies have been identified. |
| Confidence in chronic p-RfD[b] | M | The overall confidence in the subchronic p-RfD is medium. |

[a]L = low, M = medium, H = high.
[b]The overall confidence cannot be greater than lowest entry in table.

## DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No suitable published studies investigating the effects of subchronic- or chronic-duration inhalation toxicity of PFBS and the related compound $K^+$PFBS in humans or animals have been identified.

## CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 11 identifies the cancer weight-of-evidence (WOE) descriptor for PFBS and the related compound $K^+$PFBS.

**Table 11. Cancer WOE Descriptor for PFBS (CASRN 375-73-5) and the Related Compound $K^+$PFBS (CASRN 29420-49-3)**

| Possible WOE Descriptor | Designation | Route of Entry (oral, inhalation, or both) | Comments |
|---|---|---|---|
| *"Carcinogenic to Humans"* | NS | NA | There are no human carcinogenicity data identified to support this descriptor. |
| *"Likely to Be Carcinogenic to Humans"* | NS | NA | There are no animal carcinogenicity studies identified to support this descriptor. |
| *"Suggestive Evidence of Carcinogenic Potential"* | NS | NA | There are no animal carcinogenicity studies identified to support this descriptor. |
| ***"Inadequate Information to Assess Carcinogenic Potential"*** | **Selected** | **Both** | **This descriptor is selected due to the lack of any information on carcinogenicity of PFBS and the related compound $K^+$PFBS.** |
| *"Not Likely to Be Carcinogenic to Humans"* | NS | NA | Although the genotoxicity studies were negative or equivocal, there are no data to indicate that PFBS or $K^+$PFBS is not carcinogenic. |

NA = not applicable; NS = not selected.

## DERIVATION OF PROVISIONAL CANCER RISK VALUES

The lack of data on the carcinogenicity of PFBS and the related compound $K^+$PFBS precludes the derivation of quantitative estimates for either oral (p-OSF) or inhalation (p-IUR) exposure.

## APPENDIX A. SCREENING PROVISIONAL VALUES

No screening values for PFBS or the related compound $K^+$PFBS are identified.

## APPENDIX B. DATA TABLES

**Table B-1. Body Weight Data on Sprague-Dawley Rats Exposed to $K^+$PFBS via Gavage for 90 Days[a,b]**

| Dose (mg/kg-day) | Number of animals (M/F) | Body weight at Day 1(g) | | Terminal body weight (g) | |
|---|---|---|---|---|---|
| | | Males | Females | Males | Females |
| 0 | 10/10 | 192.1 ± 7.3 | 161.5 ± 9.6 | 510.9 ± 47.0 | 276.5 ± 24.0 |
| 60 | 10/10 | 192.9 ± 6.8 (100) | 161.0 ± 7.7 (100) | 482.6 ± 60.4 (94.5) | 286.0 ± 21.5 (103) |
| 200 | 10/10 | 190.0 ± 7.2 (98.9) | 157.9 ± 11.2 (97.8) | 479.6 ± 30.3 (93.9) | 284.8 ± 30.1 (103) |
| 600[c] | 10/10 | 193.1 ± 7.2 (101) | 158.1 ± 10.9 (97.9) | 485.3 ± 49.4(95.0)[c] | 264.6 ± 19.5 (95.7) |

[a]Values obtained from Lieder et al. (2009a), Table 1, page 47.
[b]Data are presented as mean values ± SD (% of control); % of control calculated by U.S. EPA.
[c]Terminal body weights for this dose in males exclude the value for one rat found dead on Day 85 of study.

**Table B-2. Selected Organ Weight Data on Male Sprague-Dawley Rats Exposed to $K^+$PFBS via Gavage for 90 Days[a,b,c]**

| | Dose in mg/kg-day (Number of animals) | | | |
|---|---|---|---|---|
| **Organ measurement** | **0 (*N* = 10)** | **60 (*N* = 10)** | **200 (*N* = 10)** | **600 (*N* = 9[d])** |
| Absolute liver weight (g) | 14.48 ± 1.76 | 13.83 ± 2.67 (95.5) | 13.50 ± 1.28 (93.2) | 14.78 ± 1.78 (102) |
| Relative liver weight (%) | 2.832 ± 0.198 | 2.846 ± 0.273 (100) | 2.814 ± 0.175 (99.4) | 3.049 ± 0.220 (108) |
| Absolute kidney weight (g) | 4.18 ± 0.48 | 4.15 ± 0.55 (99.3) | 3.93 ± 0.30 (94.0) | 4.18 ± 0.33 (100) |
| Relative kidney weight (%) | 0.818 ± 0.058 | 0.859 ± 0.053 (105) | 0.818 ± 0.053 (100) | 0.864 ± 0.049 (106) |
| Absolute spleen weight (g) | 0.93 ± 0.13 | 0.77 ± 0.10** (82.8) | 0.83 ± 0.06* (89.2) | 0.80 ± 0.11** (86.0) |
| Relative spleen weight (%) | 0.181 ± 0.018 | 0.158 ± 0.015** (87.3) | 0.172 ± 0.017 (95.0) | 0.163 ± 0.020* (90.1) |

[a]Values obtained from Lieder et al. (2009a), Table 2, page 48.
[b]Values expressed as mean ± SD (% of control); % of control calculated by U.S. EPA. Relative weights denote organ weight to terminal body weight ratios.
[c]Dosage occurred on Days 1 through 90, 91, 92, or 93 of study.
[d]Excludes values for one rat found dead on Day 85 of study.

*Significantly different from controls, $p < 0.05$.
**Significantly different from controls, $p < 0.01$.

**Table B-3. Selected Organ Weight Data on Female Sprague-Dawley Rats Exposed to $K^+$PFBS via Gavage for 90 Days[a,b,c]**

| | Dose in mg/kg-day (Number of animals) | | | |
|---|---|---|---|---|
| **Organ measurement** | **0 (*N* = 10)** | **60 (*N* = 10)** | **200 (*N* = 10)** | **600 (*N* = 10)** |
| Absolute liver weight (g) | 7.71 ± 0.78 | 8.30 ± 0.72 (108) | 8.23 ± 0.91 (107) | 7.79 ± 0.36 (101) |
| Relative liver weight (%) | 2.788 ± 0.152 | 2.902 ± 0.154 (104) | 2.890 ± 0.100 (104) | 2.951 ± 0.204 (106) |
| Absolute kidney weight (g) | 2.34 ± 0.22 | 2.40 ± 0.30 (103) | 2.40 ± 0.18 (103) | 2.39 ± 0.41 (102) |
| Relative kidney weight (%) | 0.847 ± 0.069 | 0.838 ± 0.071 (98.9) | 0.846 ± 0.059 (99.9) | 0.906 ± 0.150 (107) |
| Absolute spleen weight (g) | 0.58 ± 0.09 | 0.59 ± 0.11 (102) | 0.57 ± 0.07 (98.3) | 0.65 ± 0.11 (112) |
| Relative spleen weight (%) | 0.209 ± 0.033 | 0.208 ± 0.037 (99.5) | 0.202 ± 0.030 (96.7) | 0.248 ± 0.046 (119) |

[a]Values obtained from Lieder et al. (2009a), Table 3, page 48.
[b]Values expressed as mean ± SD (% of control); % of control calculated by U.S. EPA. Relative weights denote organ weight to terminal body weight ratios.
[c]Dosage occurred on Days 1 through 90, 91, 92, or 93 of study.

*Significantly different from controls, $p < 0.05$.
**Significantly different from controls, $p < 0.01$.

**Table B-4. Selected Clinical Chemistry Data on Male and Female Sprague-Dawley Rats Exposed to $K^+$PFBS via Gavage for 90 Days[a,b,c]**

| | Dose in mg/kg-day (Number of animals) | | | |
|---|---|---|---|---|
| **Measurement** | **0 (*N* = 10)** | **60 (*N* = 10)** | **200 (*N* = 10)** | **600 (*N* = 9[d,e])** |
| **Males** | | | | |
| Total protein (g/dL) | 6.6 ± 0.33 | 6.5 ± 0.15 (98.5) | 6.4 ± 0.19 (97.0) | 6.5 ± 0.50 (98.5) |
| Albumin (g/dL) | 4.1 ± 0.17 | 4.1 ± 0.19 (100) | 4.0 ± 0.11 (97.6) | 4.0 ± 0.26 (97.6) |
| Blood urea nitrogen (mg/dL) | 15 ± 1.4 | 14 ± 1.5 (93.0) | 14 ± 2.2 (93.0) | 15 ± 1.4 (100) |
| Creatinine (mg/dL) | 0.3 ± 0.05 | 0.2 ± 0.05 (66.7) | 0.3 ± 0.06 (100) | 0.3 ± 0.05 (100) |
| ALT (U/L) | 42 ± 5.8 | 45 ± 7.1 (107) | 41 ± 4.6 (97.6) | 43 ± 7.8 (102) |
| AST (U/L) | 84 ± 11.2 | 90 ± 10.9 (107) | 88 ± 7.5 (105) | 91 ± 12.7 (112) |
| ALK (U/L) | 94 ± 15.0 | 90 ± 12.0 (95.7) | 96 ± 12.1 (102) | 107 ± 12.7 (114) |
| Chloride (mmol/L) | 98 ± 2.0 | 100 ± 1.2 (102) | 100 ± 1.4 (102) | 101 ± 1.7** (103) |
| **Females** | | | | |
| Total protein (g/dL) | 7.2 ± 0.40 | 7.2 ± 0.34 (100) | 7.1 ± 0.40 (98.6) | 6.7 ± 0.23* (93.1) |
| Albumin (g/dL) | 4.9 ± 0.38 | 4.8 ± 0.29 (98.0) | 4.7 ± 0.31 (95.9) | 4.4 ± 0.23* (89.8) |
| Blood urea nitrogen (mg/dL) | 16 ± 1.9 | 16 ± 1.6 (100) | 15 ± 1.8 (93.8) | 16 ± 2.9 (100) |
| Creatinine (mg/dL) | 0.4 ± 0.05 | 0.4 ± 0.04 (100) | 0.3 ± 0.05 (75.0) | 0.4 ± 0.05 (100) |
| ALT (U/L) | 44 ± 11.6 | 55 ± 23.6 (125) | 49 ± 30.7 (111) | 44 ± 13.3 (100) |
| AST (U/L) | 85 ± 15.8 | 95 ± 25.8 (112) | 94 ± 51.0 (111) | 96 ± 19.6 (113) |
| ALK (U/L) | 44 ± 8.0 | 46 ± 13.3 (105) | 45 ± 12.1 (102) | 59 ± 18.2 (134) |
| Chloride (mmol/L) | 101 ± 2.5 | 101 ± 2.3 (101) | 102 ± 2.2 (101) | 102 ± 1.1 (101) |

[a]Values obtained from Lieder et al. (2009a), Table 4, page 49.
[b]Values expressed as mean ± SD (% of control); % of control calculated by U.S. EPA.
[c]Dosage occurred on Days 1 through 90, 91, 92, or 93 of study.
[d]Excludes values for one male rat found dead on Day 85 of study.
[e]Excludes one female rat that did not have sufficient sample volume.

*Significantly different from controls, $p < 0.05$.
**Significantly different from controls, $p < 0.01$.

**Table B-5. Selected Hematology Data on Male and Female Sprague-Dawley Rats Exposed to $K^+$PFBS via Gavage for 90 Days[a,b,c]**

| Dose in mg/kg-day (Number of animals) | | | | |
|---|---|---|---|---|
| **Measurement** | **0 (*N* = 10)** | **60 (*N* = 10)** | **200 (*N* = 10)** | **600 (*N* = 9[d])** |
| **Males** | | | | |
| WBC ($10^3$/mm$^3$) | 17.0 ± 3.66 | 15.4 ± 3.50 (90.6) | 14.7 ± 2.31 (86.5) | 15.2 ± 2.80 (89.4) |
| RBC ($10^6$/mm$^3$) | 7.76 ± 0.469 | 7.62 ± 0.443 (98.2) | 7.55 ± 0.282 (97.3) | 7.19 ± 0.481* (92.7) |
| HGB (g/dL) | 16.4 ± 0.96 | 16.0 ± 0.41 (97.6) | 15.6 ± 0.48* (95.1) | 15.5 ± 0.78* (94.5) |
| HCT (%) | 44.2 ± 2.32 | 42.7 ± 1.44 (96.6) | 41.9 ± 1.50* (94.8) | 40.9 ± 2.24** (92.5) |
| MCV (µm$^3$) | 57.0 ± 1.25 | 56.2 ± 2.12 (98.6) | 55.6 ± 1.38 (97.5) | 57.0 ± 2.08 (100) |
| MCH (pg) | 21.2 ± 0.53 | 21.1 ± 1.18 (99.5) | 20.7 ± 0.51 (97.6) | 21.6 ± 1.01 (102) |
| MCHC (%) | 37.2 ± 0.50 | 37.5 ± 1.11 (101) | 37.2 ± 0.69 (100) | 37.8 ± 0.96 (102) |
| **Females** | | | | |
| WBC ($10^3$/mm$^3$) | 12.2 ± 3.95 | 11.5 ± 3.10 (94.3) | 12.1 ± 3.77 (99.2) | 13.5 ± 3.94 (111) |
| RBC ($10^6$/mm$^3$) | 7.17 ± 0.315 | 6.95 ± 0.226 (96.9) | 7.16 ± 0.309 (99.9) | 6.95 ± 0.297 (96.9) |
| HGB (g/dL) | 15.9 ± 0.61 | 15.8 ± 0.57 (99.4) | 15.6 ± 0.69 (98.1) | 15.3 ± 0.82 (96.2) |
| HCT (%) | 43.3 ± 1.85 | 42.1 ± 1.56 (97.2) | 42.7 ± 2.14 (98.6) | 41.2 ± 1.71 (95.1) |
| MCV (µm$^3$) | 60.5 ± 1.08 | 60.6 ± 1.47 (100) | 59.5 ± 1.50 (98.3) | 59.2 ± 1.21 (97.9) |
| MCH (pg) | 22.2 ± 0.64 | 22.7 ± 0.65 (102) | 21.8 ± 0.61 (98.2) | 22.0 ± 0.75 (99.1) |
| MCHC (%) | 36.7 ± 0.69 | 37.4 ± 0.54* (102) | 36.7 ± 0.51 (100) | 37.1 ± 0.70 (101) |

[a]Values obtained from Lieder et al. (2009a), Table 5, page 49.
[b]Values expressed as mean ± SD (% of control); % of control calculated by U.S. EPA.
[c]Dosage occurred on Days 1 through 90, 91, 92, or 93 of study.
[d]Excludes values for one rat found dead on Day 85 of study.

*Significantly different from controls, $p < 0.05$.
**Significantly different from controls, $p < 0.01$.

**Table B-6. Incidences of Selected Histopathological Findings in Male and Female Sprague-Dawley Rats Exposed to $K^+$PFBS via Gavage for 90 Days[a,b]**

| Observation | | Dose in mg/kg-day (Number of animals) | | | |
|---|---|---|---|---|---|
| | | 0 (*N* = 10) | 60 (*N* = 10) | 200 (*N* = 10) | 600 (*N* = 10) |
| **Males** | | | | | |
| Kidney | Hyperplasia, tubular/ductal epithelium papilla | 1 | 0 | 0 | 8** |
| | Edema, focal papillary | 0 | 0 | 0 | 3 |
| | Necrosis, papillary | 0 | 0 | 0 | 1 |
| | Basophilia, tubular, multifocal | 1 | 0 | 0 | 3 |
| | Hyaline droplets, cortical tubules | 2 | 0 | 0 | 1 |
| | Mineralization, multifocal | 0 | 0 | 0 | 0 |
| | Mononuclear cell infiltration | 1 | 2 | 4 | 0 |
| Stomach | Dilation, mucosal glands | 2 | 1 | 2 | 1 |
| | Necrosis, limiting ridge | 0 | 2 | 2 | 8** |
| | Hyperplasia/hyperkeratosis, limiting ridge | 0 | 0 | 0 | 5* |
| **Females** | | | | | |
| Kidney | Hyperplasia, tubular/ductal epithelium papilla | 0 | 0 | 1 | 6* |
| | Edema, focal papillary | 0 | 0 | 0 | 3 |
| | Necrosis, papillary | 0 | 0 | 0 | 0 |
| | Basophilia, tubular, multifocal | 0 | 0 | 0 | 1 |
| | Hyaline droplets, cortical tubules | 0 | 0 | 0 | 1 |
| | Mineralization, multifocal | 5 | 5 | 2 | 2 |
| | Mononuclear cell infiltration | 0 | 3 | 0 | 2 |
| Stomach | Dilation, mucosal glands | 0 | 3 | 0 | 0 |
| | Necrosis, limiting ridge | 1 | 0 | 1 | 9** |
| | Hyperplasia/hyperkeratosis, limiting ridge | 0 | 0 | 0 | 7** |

[a]Values obtained from Lieder et al. (2009a), Table 6, page 50.
[b]Values expressed as number of animals with lesions.

*Significantly different from controls ($p < 0.05$, Fisher's Exact test), independently calculated by U.S. EPA.
**Significantly different from controls ($p < 0.01$, Fisher's Exact test), independently calculated by U.S. EPA.

**Table B-7. Sperm Analysis of F0- and F1-Generation Male Sprague-Dawley Rats Exposed to $K^+$PFBS via Gavage[a,b]**

| | | Dose in mg/kg-day | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Generation** | **0** | **30** | **100** | **300** | **1,000** |
| Motility | F0 | 96 ± 4 [*N* = 30] | 95 ± 5 (99.0) [*N* = 30] | 94 ± 12 (97.9) [*N* = 30] | 95 ± 4 (99.0) [*N* = 30] | 95 ± 5 (99.0) [*N* = 28] |
| | F1 | 92 ± 10 [*N* = 28] | 92 ± 10 (100) [*N* = 26] | 94 ± 6 (102) [*N* = 29] | 95 ± 3 (103) [*N* = 27] | 92 ± 10 (100) [*N* = 27] |
| Morphology (% abnormal) | F0 | 1.7 ± 1.5 [*N* = 30] | 2.0 ± 1.3 (118) [*N* = 30] | 1.6 ± 1.0 (94.1) [*N* = 30] | 1.5 ± 0.6 (88.2) [*N* = 30] | 2.0 ± 0.6 (118) [*N* = 29] |
| | F1 | 1.5 ± 0.7 [*N* = 29] | 1.3 ± 0.6 (86.7) [*N* = 27] | 1.4 ± 0.5 (93.3) [*N* = 29] | 1.5 ± 0.6 (100) [*N* = 27] | 1.9 ± 0.5* (127) [*N* = 29] |
| Testicular sperm count ($10^6$/g) | F0 | 148 ± 39 [*N* = 30] | 136 ± 34 (91.9) [*N* = 30] | 146 ± 36 (98.6) [*N* = 30] | 132 ± 21(89.2) [*N* = 30] | 122 ± 36* (82.4) [*N* = 29] |
| | F1 | 124 ± 33 [*N* = 29] | 109 ± 34 (87.9) [*N* = 27] | 107 ± 29 (86.3) [*N* = 29] | 110 ± 24 (88.7) [*N* = 27] | 107 ± 32 (86.3) [*N* = 27] |
| Epididymal sperm count ($10^6$/g) | F0 | 1,030 ± 209 [*N* = 30] | 1,033 ± 226 (100) [*N* = 30] | 957 ± 217 (92.9) [*N* = 30] | 1,019 ± 181 (98.9) [*N* = 30] | 969 ± 275 (94.1) [*N* = 29] |
| | F1 | 837 ± 237 [*N* = 29] | 770 ± 282 (92.0) [*N* = 27] | 840 ± 262 (100) [*N* = 29] | 857 ± 222 (102) [*N* = 27] | 928 ± 273 (111) [*N* = 27] |

[a]Values obtained from Lieder et al. (2009b), Table 1, page 35.
[b]Values expressed as mean ± SD (% of control); % of control calculated by U.S. EPA.

*Significantly different from controls, $p < 0.05$.

*N* = number of animals examined.

**Table B-8. Delivery Outcomes of F0- and F1-Generation Sprague-Dawley Dams Exposed to $K^+$PFBS via Gavage[a]**

| | | Dose in mg/kg-day | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Generation** | **0** | **30** | **100** | **300** | **1,000** |
| Number of dams delivering | F0 | 26 | 29 | 29 | 29 | 25 |
| | F1 | 24 | 26 | 28 | 25 | 27 |
| Length of gestation, days (mean ± SD) | F0 | 22.7 ± 0.5 | 22.8 ± 0.4 | 22.8 ± 0.5 | 22.8 ± 0.4 | 22.7 ± 0.4 |
| | F1 | 22.7 ± 0.5 | 22.8 ± 0.5 | 22.6 ± 0.5 | 22.6 ± 0.5 | 22.8 ± 0.4 |
| Deliveries (%) | F0 | 100 | 100 | 100 | 100 | 100 |
| | F1 | 100 | 100 | 100 | 100 | 100 |
| Percentage with live-born pups[b] | F0 | 100 | 100 | 100 | 100 | 100 |
| | F1 | 100 | 100 | 100 | 100 | 100 |
| Number with stillborn pups[c] | F0 | 2 | 5 | 1 | 4 | 2 |
| | F1 | 5 | 1 | 5 | 5 | 1 |
| Mean implantation sites (mean ± SD) | F0 | 15.2 ± 1.8 | 14.6 ± 3.0 | 14.3 ± 2.3 | 14.7 ± 1.7 | 14.0 ± 2.3 |
| | F1 | 14.3 ± 2.3 | 14.6 ± 2.3 | 15.2 ± 2.0 | 15.2 ± 2.8 | 15.3 ± 2.0 |
| Mean pups delivered (mean ± SD) | F0 | 14.2 ± 2.2 | 13.9 ± 3.0 | 13.8 ± 3.0 | 14.0 ± 2.0 | 13.6 ± 2.3 |
| | F1 | 13.2 ± 2.3 | 13.8 ± 2.2 | 14.1 ± 2.3 | 14.0 ± 2.1 | 14.0 ± 2.1 |

[a]Values obtained from Lieder et al. (2009b), Table 6, page 37.
[b]Indicates the number of dams producing a litter containing at least one live-born pup.
[c]Indicates the number of dams with at least one stillborn pup.

*Significantly different from controls, $p < 0.05$.
**Significantly different from controls, $p < 0.01$.

**Table B-9. Litter Outcomes for F1- and F2-Generation Pups Exposed to $K^+$PFBS via Gavage[a]**

| | | Dose in mg/kg-day | | | | |
|---|---|---|---|---|---|---|
| **Parameter** | **Generation** | **0** | **30** | **100** | **300** | **1,000** |
| Number of litters delivered | F1 | 26 | 29 | 29 | 29 | 25 |
| | F2 | 24 | 26 | 28 | 25 | 27 |
| Mean (± SD) live-born (*N*) | F1 | 14.2 ± 2.2 | 13.5 ± 2.8** | 13.7 ± 3.0 | 13.8 ± 2.0 | 13.5 ± 2.3 |
| | F2 | 13.0 ± 2.3 | 13.6 ± 2.3 | 13.9 ± 2.4 | 13.6 ± 2.6 | 14.0 ± 2.0 |
| Mean (± SD) stillborn (*N*) | F1 | 0.1 ± 0.3 | 0.2 ± 06 | 0.1 ± 0.4 | 0.1 ± 04 | 0.1 ± 0.3 |
| | F2 | 0.2 ± 0.4 | 0.1 ± 0.6 | 0.2 ± 0.5 | 0.4 ± 1.0 | 0.0 ± 0.2 |
| Mean (± SD) pup weight at birth | F1 | 6.4 ± 0.4 | 6.5 ± 0.5 | 6.6 ± 0.5 | 6.4 ± 0.4 | 6.3 ± 0.5 |
| | F2 | 6.3 ± 0.6 | 6.4 ± 0.5 | 6.4 ± 0.4 | 6.2 ± 0.5 | 6.2 ± 0.8 |
| Mean (± SD) pup weight at weaning (g) | F1 | 40.2 ± 5.6 | 40.2 ± 6.8 | 40.8 ± 7.8 | 39.2 ± 5.9[b] | 39.3 ± 4.4 |
| | F2 | 36.4 ± 7.7[c] | 39.4 ± 7.3 | 37.1 ± 5.1 | 36.3 ± 6.6 | 35.0 ± 5.6[d] |
| Viability index (%)[e] | F1 | 98.1 | 96.7* | 98.2 | 99.2 | 99.4* |
| | F2 | 95.5 | 96.9 | 97.2 | 96.8 | 95.8 |
| Lactation index (%)[f] | F1 | 99.4 | 98.7 | 97.4** | 97.7** | 99.7 |
| | F2 | 97.0 | 96.5 | 98.2 | 97.3 | 93.1* |

[a]Values obtained from Lieder et al. (2009b), Table 7, page 38.
[b]*N* = 28. Excludes values for litters with no surviving pups.
[c]*N* = 23. Excludes values for litters with no surviving pups.
[d]*N* = 25. Excludes values for litters with no surviving pups.
[e](Number of pups alive on Day 4/number of pups alive on Day 1) × 100
[f](Number of pups alive on Day 21/number of pups alive on Day 4) × 100

*Significantly different from controls, $p < 0.05$.
**Significantly different from controls, $p < 0.01$.

**Table B-10. Selected Organ Weight Data on F0- and F1-Generation Male Sprague-Dawley Rats Exposed to $K^+$PFBS via Gavage[a,b]**

| | | Dose in mg/kg-day | | | | |
|---|---|---|---|---|---|---|
| **Measurement** | **Generation** | **0** | **30** | **100** | **300** | **1,000** |
| Terminal body weight (g) | F0 | 552 ± 56 [*N* = 30] | 569 ± 53 (103) [*N* = 30] | 570 ± 45 (103) [*N* = 30] | 572 ± 69 (104) [*N* = 30] | 551 ± 46 (99.8) [*N* = 29] |
| | F1 | 594 ± 45 [*N* = 29] | 583 ± 61 (98.1) [*N* = 27] | 593 ± 73 (99.8) [*N* = 29] | 598 ± 65 (101) [*N* = 27] | 549 ± 38**(92.4) [*N* = 27] |
| Absolute liver weight (g) | F0 | 19.2 ± 2.4 [*N* = 30] | 20.0 ± 2.9 (104) [*N* = 30] | 20.5 ± 2.4 (107) [*N* = 30] | 21.5 ± 2.9**(112) [*N* = 30] | 2.7 ± 2.8[c] [*N* = 29] |
| | F1 | 20.6 ± 2.5 [*N* = 29] | 20.1 ± 2.7 (97.6) [*N* = 27] | 21.2 ± 4.4 (98.1) [*N* = 29] | 21.7 ± 3.2 (105) [*N* = 27] | 21.1 ± 2.2 (102) [*N* = 27] |
| Relative liver weight (%) | F0 | 3.4 ± 0.3 [*N* = 30] | 3.5 ± 0.4 (103) [*N* = 30] | 3.6 ± 0.3 (106) [*N* = 30] | 3.8 ± 0.3**(112) [*N* = 30] | 4.1 ± 0.4**(121) [*N* = 29] |
| | F1 | 3.5 ± 0.4 [*N* = 29] | 3.4 ± 0.3 (97.1) [*N* = 27] | 3.5 ± 0.4 (100) [*N* = 29] | 3.6 ± 0.3 (103) [*N* = 27] | 3.8 ± 0.3**(109) [*N* = 27] |
| Absolute left kidney weight (g) | F0 | 2.10 ± 0.21 [*N* = 30] | 2.17 ± 0.20 (103) [*N* = 30] | 2.18 ± 0.20 (104) [*N* = 30] | 2.20 ± 0.28 (105) [*N* = 30] | 2.20 ± 0.26 (105) [*N* = 29] |
| | F1 | 2.04 ± 0.21 [*N* = 29] | 2.06 ± 0.23 (101) [*N* = 27] | 2.08 ± 0.20 (102) [*N* = 29] | 2.14 ± 0.24 (105) [*N* = 27] | 1.97 ± 0.16 (96.6) [*N* = 27] |
| Relative left kidney weight (%) | F0 | 0.375 ± 0.034 [*N* = 30] | 0.382 ± 0.035 (102) [*N* = 30] | 0.383 ± 0.032 (102) [*N* = 30] | 0.385 ± 0.042 (103) [*N* = 30] | 0.400 ± 0.047 (107) [*N* = 29] |
| | F1 | 0.344 ± 0.030 [*N* = 29] | 0.352 ± 0.021 (102) [*N* = 27] | 0.353 ± 0.033 (103) [*N* = 29] | 0.358 ± 0.038 (104) [*N* = 27] | 0.357 ± 0.029 (104) [*N* = 29] |
| Absolute right kidney weight (g) | F0 | 2.15 ± 0.22 [*N* = 30] | 2.18 ± 0.21 (101) [*N* = 30] | 2.20 ± 0.21 (102) [*N* = 30] | 2.21 ± 0.28 (103) [*N* = 30] | 2.22 ± 0.25 (103) [*N* = 29] |
| | F1 | 2.05 ± 0.20 [*N* = 29] | 2.08 ± 0.22 (101) [*N* = 27] | 2.09 ± 0.20 (102) [*N* = 28] | 2.14 ± 0.25 (104) [*N* = 27] | 2.00 ± 0.18 (97.6) [*N* = 27] |
| Relative right kidney weight (%) | F0 | 0.383 ± 0.041 [*N* = 30] | 0.384 ± 0.034 (100) [*N* = 30] | 0.385 ± 0.033 101) [*N* = 30] | 0.387 ± 0.042 (101) [*N* = 30] | 0.403 ± 0.040 (105) [*N* = 29] |
| | F1 | 0.346 ± 0.030 [*N* = 29] | 0.356 ± 0.020 (103) [*N* = 27] | 0.356 ± 0.029 (103) [*N* = 28] | 0.359 ± 0.040 (104) [*N* = 27] | 0.364 ± 0.032 (105) [*N* = 27] |

**Table B-10. Selected Organ Weight Data on F0- and F1-Generation Male Sprague-Dawley Rats Exposed to $K^+$PFBS via Gavage[a,b]**

| | | Dose in mg/kg-day | | | | |
|---|---|---|---|---|---|---|
| **Measurement** | **Generation** | **0** | **30** | **100** | **300** | **1,000** |
| Absolute spleen weight (g) | F0 | 0.86 ± 0.13 [*N* = 30] | 0.92 ± 0.18 (107) [*N* = 30] | 0.89 ± 0.11 (103) [*N* = 30] | 0.88 ± 0.19 (102) [*N* = 30] | 0.86 ± 0.09 (100) [*N* = 29] |
| | F1 | 0.90 ± 0.19 [*N* = 29] | 0.88 ± 0.08 (97.8) [*N* = 27] | 0.87 ± 0.17 (96.7) [*N* = 29] | 0.84 ± 0.14 (93.3) [*N* = 27] | 0.79 ± 0.12 (87.8) [*N* = 27] |
| Relative spleen weight (%) | F0 | 0.153 ± 0.023 [*N* = 30] | 0.161 ± 0.030 (105) [*N* = 30] | 0.156 ± 0.017 (102) [*N* = 30] | 0.153 ± 0.025 (100) [*N* = 30] | 0.157 ± 0.019 (103) [*N* = 29] |
| | F1 | 0.151 ± 0.033 [*N* = 29] | 0.151 ± 0.018 (100) [*N* = 27] | 0.147 ± 0.025 (97.4) [*N* = 29] | 0.141 ± 0.024 (93.4) [*N* = 27] | 0.144 ± 0.023 (95.4) [*N* = 27] |

[a]Values obtained from Lieder et al. (2009b), Table 11, page 40.
[b]Values expressed as mean ± SD (% of control); % of control calculated by U.S. EPA. Relative weights denote organ weight to terminal body weight ratios. *N* = number of animals measured.
[c]This appears to be a typographical error in the original publication.

*Significantly different from controls, $p < 0.05$.
**Significantly different from controls, $p < 0.01$.

**Table B-11. Selected Organ Weight Data on F0- and F1-Generation Female Sprague-Dawley Rats Exposed to $K^+$PFBS via Gavage[a,b,c]**

| | | Dose in mg/kg-day | | | | |
|---|---|---|---|---|---|---|
| **Measurement** | **Generation** | **0** | **30** | **100** | **300** | **1,000** |
| Terminal body weight (g) | F0 | 346 ± 23 [*N* = 26] | 343 ± 26 (99.1) [*N* = 29] | 351 ± 23 (101) [*N* = 29] | 344 ± 30 (99.4) [*N* = 28] | 336 ± 22 (97.1) [*N* = 25] |
| | F1 | 331 ± 29 [*N* = 23] | 350 ± 33* (106) [*N* = 26] | 353 ± 26** (107) [*N* = 28] | 347 ± 16* (105) [*N* = 25] | 348 ± 23* (105) [*N* = 25] |
| Absolute left kidney weight (g) | F0 | 1.41 ± 0.12 [*N* = 26] | 1.42 ± 0.15 (101) [*N* = 29] | 1.41 ± 0.15 (100) [*N* = 29] | 1.48 ± 0.18 (105) [*N* = 28] | 1.42 ± 0.17 (101) [*N* = 25] |
| | F1 | 1.51 ± 0.16 [*N* = 23] | 1.51 ± 0.13 (100) [*N* = 26] | 1.52 ± 0.14 (101) [*N* = 28] | 1.52 ± 0.18 (101) [*N* = 25] | 1.48 ± 0.16 (98.0) [*N* = 25] |
| Relative left kidney weight (%) | F0 | 0.407 ± 0.032 [*N* = 26] | 0.416 ± 0.035 (102) [*N* = 29] | 0.402 ± 0.034 (98.8) [*N* = 29] | 0.430 ± 0.055 (106) [*N* = 28] | 0.422 ± 0.051 (104) [*N* = 25] |
| | F1 | 0.462 ± 0.092 [*N* = 23] | 0.434 ± 0.039 (93.9) [*N* = 26] | 0.433 ± 0.032 (93.7) [*N* = 28] | 0.438 ± 0.046 (94.8) [*N* = 25] | 0.428 ± 0.047 (92.6) [*N* = 25] |
| Absolute right kidney weight (g) | F0 | 1.41 ± 0.13 [*N* = 26] | 1.39 ± 0.14 (98.6) [*N* = 29] | 1.42 ± 0.16 (101) [*N* = 29] | 1.44 ± 0.19 (102) [*N* = 28] | 1.40 ± 0.15 (99.3) [*N* = 25] |
| | F1 | 1.55 ± 0.18 [*N* = 23] | 1.58 ± 0.13 (102) [*N* = 26] | 1.57 ± 0.14 (101) [*N* = 28] | 1.57 ± 0.18 (101) [*N* = 25] | 1.56 ± 0.18 (101) [*N* = 25] |
| Relative right kidney weight (%) | F0 | 0.406 ± 0.035 [*N* = 26] | 0.407 ± 0.036 (100) [*N* = 29] | 0.406 ± 0.036 (100) [*N* = 29] | 0.420 ± 0.053 (103) [*N* = 28] | 0.418 ± 0.044 (103) [*N* = 25] |
| | F1 | 0.474 ± 0.101 [*N* = 23] | 0.454 ± 0.042 (95.8) [*N* = 26] | 0.446 ± 0.024 (94.0) [*N* = 28] | 0.454 ± 0.046 (95.8) [*N* = 25] | 0.450 ± 0.048 (94.9) [*N* = 25] |
| Absolute spleen weight (g) | F0 | 0.74 ± 0.15 [*N* = 26] | 0.70 ± 0.12 (94.6) [*N* = 29] | 0.71 ± 0.16 (95.9) [*N* = 29] | 0.74 ± 0.23 (100) [*N* = 28] | 0.67 ± 0.12 (90.5) [*N* = 25] |
| | F1 | 0.62 ± 0.12 [*N* = 23] | 0.70 ± 0.11*(113) [*N* = 26] | 0.70 ± 0.13*(113) [*N* = 28] | 0.71 ± 0.11* (115) [*N* = 25] | 0.67 ± 0.09 (108) [*N* = 25] |

**Table B-11. Selected Organ Weight Data on F0- and F1-Generation Female Sprague-Dawley Rats Exposed to $K^+$PFBS via Gavage[a,b,c]**

| | | Dose in mg/kg-day | | | | |
|---|---|---|---|---|---|---|
| **Measurement** | **Generation** | **0** | **30** | **100** | **300** | **1,000** |
| Relative spleen weight (%) | F0 | 0.213 ± 0.045 [*N* = 26] | 0.206 ± 0.033 (96.7) [*N* = 29] | 0.202 ± 0.043 (94.8) [*N* = 29] | 0.215 ± 0.061 (101) [*N* = 28] | 0.198 ± 0.036 (93.0) [*N* = 25] |
| | F1 | 0.186 ± 0.034 [*N* = 23] | 0.201 ± 0.030 (108) [*N* = 26] | 0.198 ± 0.035 (106) [*N* = 28] | 0.204 ± 0.035 (110) [*N* = 25] | 0.193 ± 0.027 (104) [*N* = 25] |

[a]Values obtained from Lieder et al. (2009b), Table 12, page 41.
[b]Values expressed as mean ± SD (% of control); % of control calculated by U.S. EPA. Relative weights denote organ weight to terminal body weight ratios. *N* = number of animals measured.
[c]Study authors did not provide liver weight measurements for females but stated that "with the exception of splenic weights, all organ weights were similar to control values" in female rats.

*Significantly different from controls, $p < 0.05$.
**Significantly different from controls, $p < 0.01$.

**Table B-12. Incidences of Selected Histopathological Findings on F0- and F1-Generation Male and Female Sprague-Dawley Rats Exposed to $K^+$PFBS via Gavage[a,b]**

| | | | Dose in mg/kg-day (Number of animals) | | |
|---|---|---|---|---|---|
| **Organ** | **Observation** | **Generation** | **0 (*N* =30)** | **300 (*N* = 30)** | **1,000 (*N* = 30)** |
| **Males** | | | | | |
| Kidney | Papillary epithelial tubular/ductal hyperplasia | F0 | 0 | 9** (7+; 2++) | 19** (9+; 9++; 1+++) |
| | | F1 | 3 (3+) | 5 (4+; 1++) | 21** (8+; 13++) |
| | Focal papillary edema | F0 | 1 (1+) | 2 (2+) | 6 (5+; 1++) |
| | | F1 | 1 (1+) | 0 | 9* (9+) |
| | Focal necrosis of the papilla | F0 | 0 | 0 | 1 (1++) |
| | | F1 | 0 | 2 (2+) | 0 |
| | Focal cortical tubular dilation | F0 | 0 | 0 | 1 (1+) |
| | | F1 | 0 | 0 | 1 (1+) |
| Liver | Hepatocellular hypertrophy | F0 | 0 | 3 (3+) | 26** (25+; 1++) |
| | | F1 | 0 | 3 (3+) | 14** (13+; 1++) |
| **Females** | | | | | |
| Kidney | Papillary epithelial tubular/ductal hyperplasia | F0 | 3 (1+; 2++) | 16** (7+; 8++; 1+++) | 21** (9+; 12++) |
| | | F1 | 2 (2+) | 13** (7+; 5++; 1+++) | 15** (7+; 7++; 1+++) |
| | Focal papillary edema | F0 | 1 (1+) | 8* (7+; 1++) | 7* (7+) |
| | | F1 | 0 | 7* (6+; 1++) | 4 (3+; 1++) |
| | Focal necrosis of the papilla | F0 | 0 | 3 (1+; 2++) | 0 |
| | | F1 | 0 | 1 (1++) | 1 (1++) |
| | Focal cortical tubular dilation | F0 | 0 | 1 (+++) | 1 (1++) |
| | | F1 | 1 (1++) | 1 (1+) | 0 |
| Liver | Hepatocellular hypertrophy | F0 | 0 | 0 | 0 |
| | | F1 | 0 | 0 | 0 |

[a]Values obtained from Lieder et al. (2009b), Table 10, page 40.
[b]Values expressed as number of animals with lesions (degree of severity: + = minimal severity, ++ = mild severity, +++ = moderate severity).

*Significantly different from controls ($p < 0.05$, Fisher's Exact test), independently calculated by U.S. EPA.
**Significantly different from controls ($p < 0.01$, Fisher's Exact test), independently calculated by U.S. EPA.

# APPENDIX C. BENCHMARK DOSE MODELING RESULTS

## MODELING PROCEDURE FOR DICHOTOMOUS DATA

The benchmark dose (BMD) modeling of dichotomous data was conducted with EPA's BMD Software (version 2.3). For these data, all of the dichotomous models (i.e., Gamma, Multistage, Logistic, Log-logistic, Probit, Log-probit, Weibull, and Quantal-linear models) available within the software were fit using a 10% benchmark response (BMR). An adequate fit was judged based on the $\chi^2$ goodness-of-fit *p*-value ($p > 0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. Among all models providing adequate fit, the benchmark dose lower confidence limit (BMDL) from the model with the lowest Akaike's Information Criteria (AIC) was selected as a potential point of departure (POD) from which to derive the reference dose (RfD).

## INCREASED INCIDENCE OF KIDNEY HYPERPLASIA IN MALE RATS TREATED WITH $K^+$PFBS FOR 90 DAYS VIA GAVAGE

**Table C-1. Model Predictions for Increased Incidence of Kidney Hyperplasia in Male Sprague-Dawley Rats Treated with $K^+$PFBS**

| Model | *p*-Value[a] | AIC for Fitted Model | $BMD_{10}$ (mg/kg-day) | $BMDL_{10}$ (mg/kg-day) | Conclusions |
|---|---|---|---|---|---|
| Gamma | 0.3057 | 30.45 | 240 | 110 | |
| Logistic | 0.3372 | 29.14 | 192 | 119 | |
| Log-logistic | 0.3059 | 30.46 | 242 | 115 | |
| Log-probit | 0.305 | 30.45 | 233 | 116 | |
| Multistage 2 | 0.3812 | 29.33 | 167 | 85.6 | |
| **Multistage 3** | **0.5824** | **28.48** | **245** | **96.7** | **Lowest AIC, best fitting** |
| Probit | 0.271 | 29.47 | 170 | 109 | |
| Weibull | 0.3069 | 30.47 | 256 | 107 | |
| Quantal-linear | 0.0636 | 34.08 | 71.0 | 40.9 | |

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose.

## INCREASED INCIDENCE OF KIDNEY HYPERPLASIA IN FEMALE RATS TREATED WITH $K^+$PFBS FOR 90 DAYS VIA GAVAGE

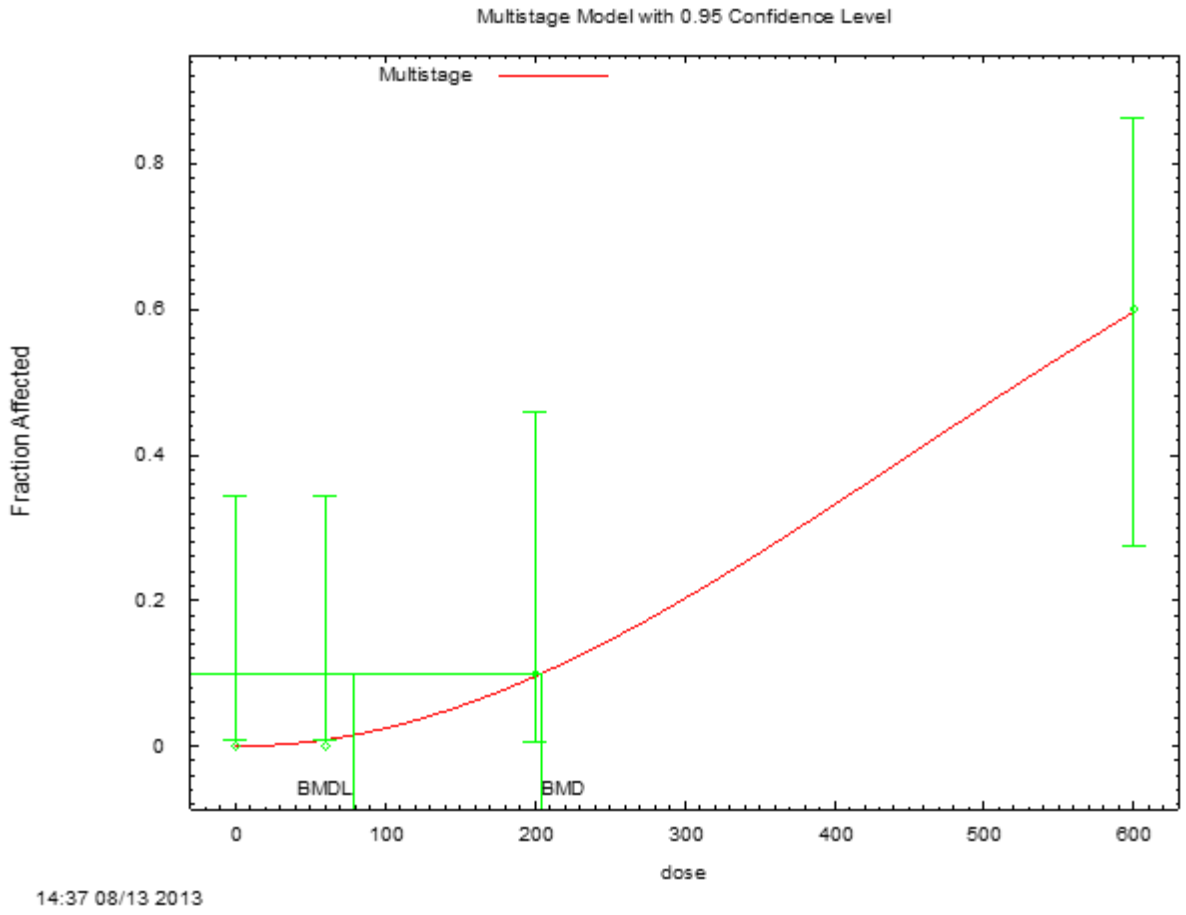
**Table C-2. Model Predictions for Increased Incidence of Kidney Hyperplasia in Female Sprague-Dawley Rats Treated with $K^+$PFBS**

| Model | *p*-Value[a] | AIC for Fitted Model | $BMD_{10}$ (mg/kg-day) | $BMDL_{10}$ (mg/kg-day) | Conclusions |
|---|---|---|---|---|---|
| Gamma | 0.9716 | 24.06 | 211 | 81.3 | |
| Logistic | 0.7182 | 24.86 | 288 | 179 | |
| Log-logistic | 0.9692 | 24.07 | 210 | 84.8 | |
| Log-probit | 0.9925 | 23.98 | 204 | 103 | |
| **Multistage 2** | **0.9926** | **22.15** | **204** | **78.7** | **Lowest AIC, best fitting** |
| Multistage 3 | 0.953 | 24.14 | 212 | 78.3 | |
| Probit | 0.7868 | 24.62 | 264 | 165 | |
| Weibull | 0.9533 | 24.13 | 215 | 79.7 | |
| Quantal-linear | 0.6045 | 24.53 | 97.9 | 55.1 | |

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose.

**BMD Output for Multistage 2 Model for Increased Incidence of Kidney Hyperplasia in Female Rats after Exposure to $K^+$PFBS via Gavage for 90 days**




```
==========================================================================
        Multistage Model
==========================================================================

BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = background + (1-background)*[1-EXP(
                 -beta1*dose^1-beta2*dose^2)]

   The parameter betas are restricted to be positive


   Dependent variable = Effect
   Independent variable = Dose

 Total number of observations = 4
 Total number of records with missing values = 0
 Total number of parameters in model = 3
 Total number of specified parameters = 0
```

Degree of polynomial = 2

Maximum number of iterations = 250
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values
Background = 0
Beta(1) = 3.43191e-005
Beta(2) = 2.50059e-006

Asymptotic Correlation Matrix of Parameter Estimates

( *** The model parameter(s) -Background -Beta(1)
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix )

| | Beta(2) |
|---|---|
| Beta(2) | 1 |

Parameter Estimates

| Variable | Estimate | Std. Err. | 95.0% Wald Confidence Interval Lower Conf. Limit | Upper Conf. Limit |
|---|---|---|---|---|
| Background | 0 | * | * | * |
| Beta(1) | 0 | * | * | * |
| Beta(2) | 2.52309e-006 | * | * | * |

* - Indicates that this value is not calculated.

Analysis of Deviance Table

| Model | Log(likelihood) | # Param's | Deviance | Test d.f. | P-value |
|---|---|---|---|---|---|
| Full model | -9.98095 | 4 | | | |
| Fitted model | -10.0729 | 1 | 0.183913 | 3 | 0.9801 |
| Reduced model | -18.5491 | 1 | 17.1362 | 3 | 0.0006626 |

AIC: 22.1458

Goodness of Fit

| Dose | Est._Prob. | Expected | Observed | Size | Scaled Residual |
|---|---|---|---|---|---|
| 0.0000 | 0.0000 | 0.000 | 0.000 | 10 | 0.000 |
| 60.0000 | 0.0090 | 0.090 | 0.000 | 10 | -0.302 |
| 200.0000 | 0.0960 | 0.960 | 1.000 | 10 | 0.043 |
| 600.0000 | 0.5968 | 5.968 | 6.000 | 10 | 0.021 |

Chi^2 = 0.09 d.f. = 3 P-value = 0.9926

```
   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        204.349

            BMDL =        78.7178

            BMDU =         291.15

Taken together, (78.7178, 291.15 ) is a 90     % two-sided confidence
interval for the BMD
```

## INCREASED INCIDENCE OF KIDNEY HYPERPLASIA IN F0-GENERATION MALE RATS TREATED WITH $K^+$PFBS VIA GAVAGE—REPRODUCTIVE STUDY

**Table C-3. Model Predictions for Increased Incidence of Kidney Hyperplasia in F0 Male Sprague-Dawley Rats Treated with $K^+$PFBS in Reproductive Study**

| Model | *p*-Value[a] | AIC for Fitted Model | $BMD_{10}$ (mg/kg-day) | $BMDL_{10}$ (mg/kg-day) | Conclusions |
|---|---|---|---|---|---|
| **Gamma** | **0.9188** | **78.2** | **99.5** | **73.2** | **Lowest AIC, best fitting** |
| Logistic | 0.0191 | 87.7 | 276 | 208 | |
| Log-logistic | 1 | 80.1 | 93.5 | 45.6 | |
| Log-probit | 0.5914 | 79.1 | 168 | 127 | |
| **Multistage 2** | **0.9188** | **78.2** | **99.5** | **73.2** | **Lowest AIC, best fitting** |
| **Multistage 3** | **0.9188** | **78.2** | **99.5** | **73.2** | **Lowest AIC, best fitting** |
| Probit | 0.0233 | 87.0 | 257 | 197 | |
| **Weibull** | **0.9188** | **78.2** | **99.5** | **73.2** | **Lowest AIC, best fitting** |
| **Quantal-linear** | **0.9188** | **78.2** | **99.5** | **73.2** | **Lowest AIC, best fitting** |

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose.

## INCREASED INCIDENCE OF KIDNEY HYPERPLASIA IN F1-GENERATION MALE RATS TREATED WITH $K^+$PFBS VIA GAVAGE—REPRODUCTIVE STUDY

**Table C-4. Model Predictions for Increased Incidence of Kidney Hyperplasia in F1 Male Sprague-Dawley Rats Treated with $K^+$PFBS in Reproductive Study**

| Model | *p*-Value[a] | AIC for Fitted Model | $BMD_{10}$ (mg/kg-day) | $BMDL_{10}$ (mg/kg-day) | Conclusions |
|---|---|---|---|---|---|
| Gamma | NA | 89.19 | 340 | 140 | Does not meet goodness-of-fit criteria |
| Logistic | 0.6206 | 87.43 | 265 | 199 | |
| Log-logistic | NA | 89.19 | 339 | 156 | Does not meet goodness-of-fit criteria |
| Log-probit | NA | 89.19 | 333 | 173 | Does not meet goodness-of-fit criteria |
| **Multistage 2** | **0.832** | **87.24** | **311** | **126** | **Lowest AIC, best fitting** |
| Multistage 3 | NA | 89.19 | 348 | 122 | Does not meet goodness-of-fit criteria |
| Probit | 0.5219 | 87.60 | 242 | 186 | |
| Weibull | NA | 89.19 | 346 | 137 | Does not meet goodness-of-fit criteria |
| Quantal-linear | 0.0675 | 90.81 | 119 | 82.8 | |

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.

NA = $\chi^2$-test for fit is not valid; AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose.

## INCREASED INCIDENCE OF KIDNEY HYPERPLASIA IN F0-GENERATION FEMALE RATS TREATED WITH $K^+$PFBS VIA GAVAGE—REPRODUCTIVE STUDY

**Table C-5. Model Predictions for Increased Incidence of Kidney Hyperplasia in F0 Female Sprague-Dawley Rats Treated with $K^+$PFBS in Reproductive Study**

| Model | *p*-Value[a] | AIC for Fitted Model | $BMD_{10}$ (mg/kg-day) | $BMDL_{10}$ (mg/kg-day) | Conclusions |
|---|---|---|---|---|---|
| Gamma | 0.0968 | 104 | 79.6 | 56.4 | Does not meet goodness-of-fit criteria |
| Logistic | 0.01 | 109 | 173 | 131 | Does not meet goodness-of-fit criteria |
| **Log-logistic** | **0.4561** | **102** | **44.7** | **26.6** | **Lowest AIC, best fitting** |
| Log-probit | 0.0449 | 105 | 132 | 93.2 | Does not meet goodness-of-fit criteria |
| Multistage 2 | 0.0968 | 104 | 79.6 | 56.4 | Does not meet goodness-of-fit criteria |
| Multistage 3 | 0.0968 | 104 | 79.6 | 56.4 | Does not meet goodness-of-fit criteria |
| Probit | 0.0106 | 108 | 169 | 131 | Does not meet goodness-of-fit criteria |
| Weibull | 0.0968 | 104 | 79.6 | 56.4 | Does not meet goodness-of-fit criteria |
| Quantal-linear | 0.0968 | 104 | 79.6 | 56.4 | Does not meet goodness-of-fit criteria |

[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose.

## INCREASED INCIDENCE OF KIDNEY HYPERPLASIA IN F1-GENERATION FEMALE RATS TREATED WITH $K^+$PFBS VIA GAVAGE—REPRODUCTIVE STUDY

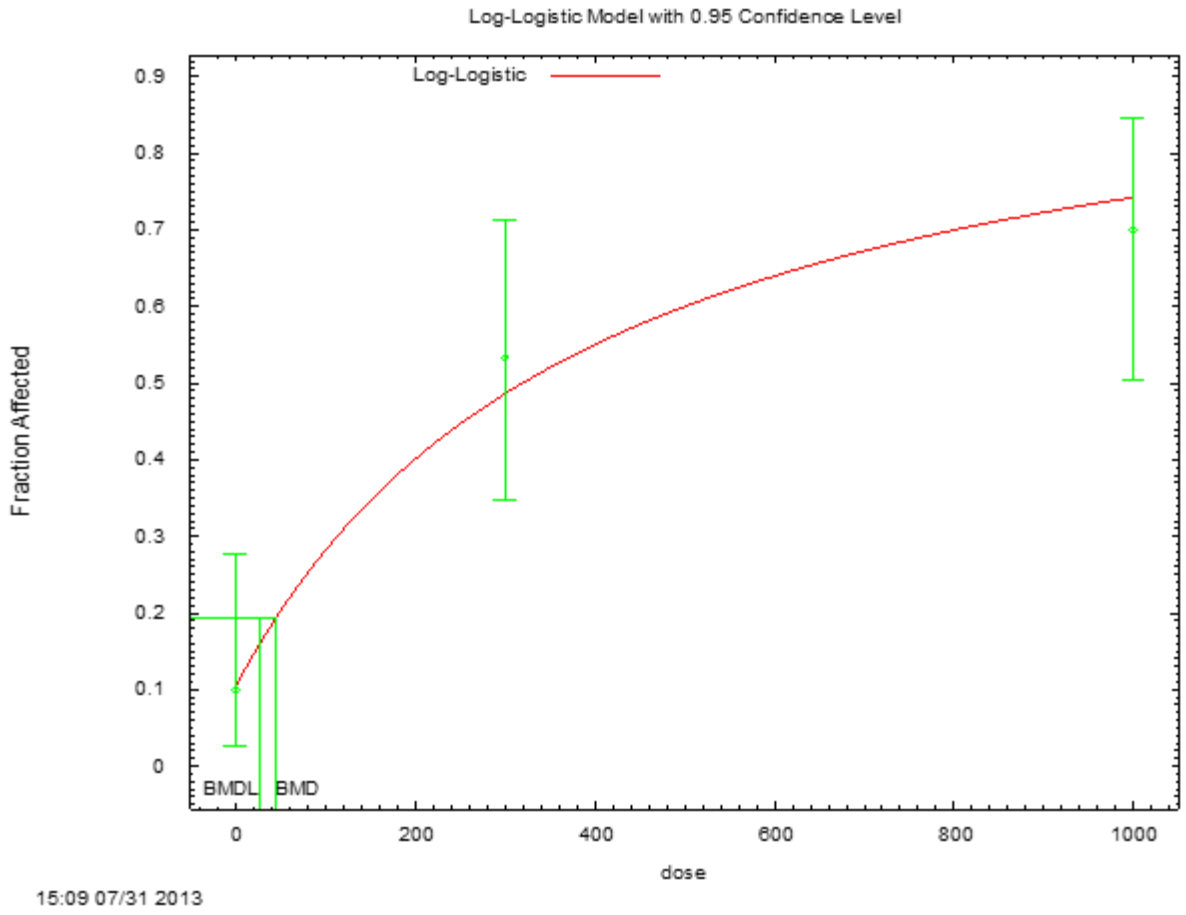
**Table C-6. Model Predictions for Increased Incidence of Kidney Hyperplasia in F1 Female Sprague-Dawley Rats Treated with $K^+$PFBS in Reproductive Study**

| Model | *p*-Value[a] | AIC for Fitted Model | $BMD_{10}$ (mg/kg-day) | $BMDL_{10}$ (mg/kg-day) | Conclusions |
|---|---|---|---|---|---|
| Gamma | 0.036 | 106 | 135 | 89.9 | Does not meet goodness-of-fit criteria |
| Logistic | 0.008 | 109 | 280 | 206 | Does not meet goodness-of-fit criteria |
| **Log-logistic** | **0.112** | **104** | **89.0** | **52.4** | **Lowest AIC, best fitting** |
| Log-probit | 0.0055 | 109 | 229 | 150 | Does not meet goodness-of-fit criteria |
| Multistage 2 | 0.036 | 106 | 135 | 89.9 | Does not meet goodness-of-fit criteria |
| Multistage 3 | 0.036 | 106 | 135 | 89.9 | Does not meet goodness-of-fit criteria |
| Probit | 0.0087 | 108 | 266 | 198 | Does not meet goodness-of-fit criteria |
| Weibull | 0.036 | 106 | 135 | 89.9 | Does not meet goodness-of-fit criteria |
| Quantal-linear | 0.036 | 106 | 135 | 89.9 | Does not meet goodness-of-fit criteria |

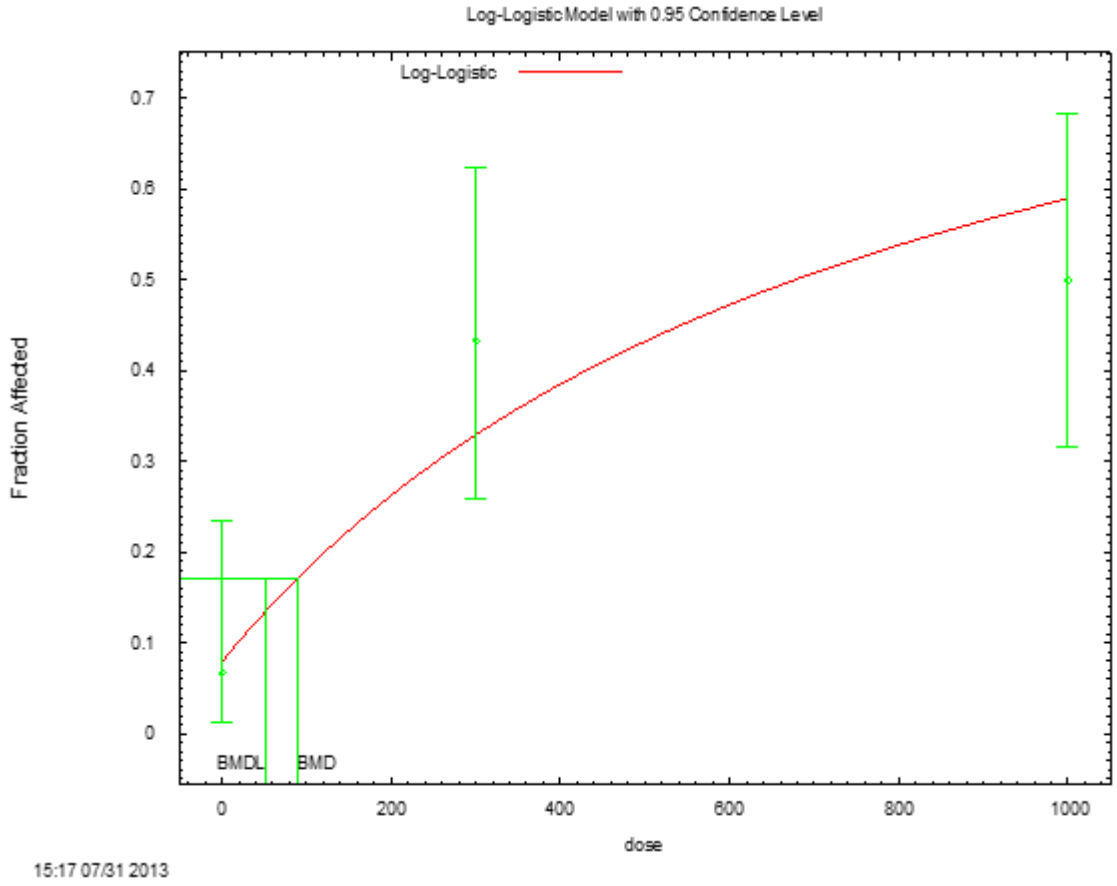
[a]Values <0.10 fail to meet conventional goodness-of-fit criteria.

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose.

**Log-Logistic Model for Increased Incidence of Kidney Hyperplasia in F0-Generation Female Rats after Oral Gavage Exposure to $K^+$PFBS in Reproductive Study**



**Log-Logistic Model for Increased Incidence of Kidney Hyperplasia in F1-Generation Female Rats after Oral Gavage Exposure to $K^+$PFBS in Reproductive Study**



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