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Provisional Peer-Reviewed Toxicity Values for

4,4'-Dichlorobenzophenone
(CASRN 90-98-2)

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

COMMONLY USED ABBREVIATIONS

BMD	Benchmark Dose
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
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
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
RfC	inhalation reference concentration
RfD	oral reference dose
UF	uncertainty factor
UF_A	animal to human uncertainty factor
UF_C	composite uncertainty factor
UF_D	incomplete to complete database uncertainty factor
UF_H	interhuman uncertainty factor
UF_L	LOAEL to NOAEL uncertainty factor
UF_S	subchronic to chronic uncertainty factor

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR 4,4'-DICHLOROBENZOPHENONE (CASRN 90-98-2)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (U.S. EPA) 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. U.S. EPA's Integrated Risk Information System (IRIS).
2. Provisional Peer-Reviewed Toxicity Values (PPRTVs) used in U.S. 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 U.S. EPA's 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 U.S. EPA IRIS Program. All provisional toxicity values receive internal review by two U.S. EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multiprogram consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all U.S. EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a 5-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV documents 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 Resource Conservation and Recovery Act (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 document and understand the strengths

and limitations of the derived provisional values. PPRTVs are developed by the U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other U.S. 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 U.S. EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

No RfD, RfC, or cancer assessment for 4,4'-dichlorobenzophenone (chemical structure shown in Figure 1) is available on IRIS (U.S. EPA, 2009), the Drinking Water Standards and Health Advisories list (U.S. EPA, 2006), or in the HEAST (U.S. EPA, 1997). The Chemical Assessments and Related Activities (CARA) list (U.S. EPA, 1994, 1991) does not include any documents pertaining to 4,4'-dichlorobenzophenone. ATSDR (2009) has not published a toxicological profile for 4,4'-dichlorobenzophenone, and neither the World Health Organization (WHO, 2009) nor CalEPA (2009a, b) has assessed the toxicity of 4,4'-dichlorobenzophenone. Occupational exposure limits have not been established by the American Conference of Governmental Industrial Hygienists (ACGIH, 2008), the National Institute for Occupational Safety and Health (NIOSH, 2009), or the Occupational Safety and Health Administration (OSHA, 2009). The carcinogenicity of 4,4'-dichlorobenzophenone has not been assessed by the International Agency for Research on Cancer (IARC, 2009) or the National Toxicology Program (NTP, 2009, 2005).

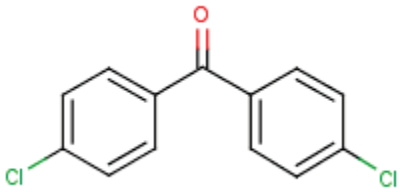

Figure 1. Chemical Structure of 4,4'-Dichlorobenzophenone

Literature searches were conducted from the 1960s through September 2009 for studies relevant to provisional toxicity values for 4,4'-dichlorobenzophenone. The databases searched include RTECS, HSDB, TSCATS, MEDLINE, TOXLINE, DART, CCRIS, GENETOX, CHEMABS, BIOSIS, and Current Contents (last 6 months).

REVIEW OF PERTINENT DATA

Human Studies

No studies were located regarding oral or inhalation exposure of humans to 4,4'-dichlorobenzophenone.

Animal Studies

Oral Exposure

In an unpublished subchronic toxicity study, Wistar rats (15/sex/dose) were administered 4,4'-dichlorobenzophenone (purity not reported) at 0, 100, or 1,250 ppm in the diet for 13 weeks and then sacrificed (Ambrose and Borzelleca, 1965). Doses of 0, 7, or 86 mg/kg-day for males and 0, 7, or 90 mg/kg-day for females were estimated for this assessment[1]. Body weights were recorded weekly. Average daily food consumption was measured based on 3-day observations during the fourth and thirteenth weeks. Hematological analyses, including hematocrit, hemoglobin concentration, and total and differential white blood cell counts were performed using blood samples collected from five rats/sex/dose in the fourth and thirteenth weeks. Urine samples collected from five rats of each sex at each dose were pooled at Weeks 4 and 13 to determine pH and the concentrations of protein and reducing substances. Average organ weights and organ-to-body weight ratios of the heart, liver, spleen, kidney, adrenal glands, and testes were recorded at 90-day sacrifice. Histopathological evaluations of the heart, lung, liver, spleen, kidney, urinary bladder, gastroenteric system, skeletal muscle, bone marrow, skin, brain, pituitary gland, thyroid, pancreas, adrenal glands, and gonad were performed.

Four rats died during the course of the experiment; two were control females, and two were low-dose males (Ambrose and Borzelleca, 1965). The data showed no dose-related effects on average body weights, food consumption, or hematological or urinalysis values after treatment with 4,4'-dichlorobenzophenone (only mean values were shown; no statistical analyses were reported). The only statistically significant finding reported was a reduction (≈18% decrease) in the heart-to-body weight ratio in males administered the high dose of 4,4'-dichlorobenzophenone. Neither a *p*-value nor the statistical test used to establish significance was provided by the authors; a t-test specifically performed for this document showed $p < 0.02$. Absolute heart weight did not differ considerably from controls in this group. There was no effect of treatment on absolute or relative heart weight in females at any dose. Because no treatment-related histopathological changes were detected in the heart or any other tissue in either sex, this response for the decreased heart-to-body weight ratio is not considered biologically significant, and therefore, a LOAEL is not identified. For the purpose of this review, the highest dose tested of 86 mg/kg-day is identified as a NOAEL for subchronic toxicity in rats; however, confidence in this value is low due to incomplete reporting of methods and results.

[1]Calculated by multiplying the dietary concentration (in ppm [mg chemical/kg food]) by the time weighted average (TWA) daily food consumption rate (normalized for body weight) for each dose. TWA daily food intake was calculated as the sum for all samples taken during an interval and divided by the total sampling time of values reported for the fourth and thirteenth weeks. For example, in low-dose females, the dose was calculated to be 0.073 kg food/kg-bw ([0.097 × 4 + 0.063 × 9] ÷ 13) × 100 mg chemical/kg food = 7 mg/kg-day.

Inhalation Exposure

No studies were located regarding inhalation exposure of animals to 4,4'-dichlorobenzophenone.

Other Studies

Genotoxicity

Limited genotoxicity testing of 4,4'-dichlorobenzophenone in vitro has produced negative results. 4,4'-Dichlorobenzophenone did not significantly increase the number of His^+ revertants in several strains of *Salmonella typhimurium* with or without metabolic activation (DeFlora et al., 1984; Bartsch et al., 1980; Planche et al., 1979) or significantly impair DNA repair in *Escherichia coli* (DeFlora et al., 1990).

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR 4,4'-DICHLOROBENZOPHENONE

Because the toxicity data based on the unpublished study (Ambrose and Borzelleca, 1965) are not peer reviewed, no provisional chronic or subchronic RfDs are developed. However, the Appendix of this document contains screening chronic and subchronic p-RfD values that may be useful in certain instances. Please see the attached Appendix for details.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR 4,4'-DICHLOROBENZOPHENONE

Provisional RfC values for 4,4'-dichlorobenzophenone cannot be derived because of the lack of human or animal inhalation data.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR 4,4'-DICHLOROBENZOPHENONE

Weight-of-Evidence Descriptor

Under the 2005 *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is "*Inadequate Information to Assess the Carcinogenic Potential*" of 4,4'-dichlorobenzophenone. No human or animal carcinogenicity data are available. A limited data set based on in vitro studies in *S. typhimurium* and *E. coli* suggests that 4,4'-dichlorobenzophenone is not likely to be genotoxic.

Quantitative Estimates of Carcinogenic Risk

Derivation of quantitative estimates of cancer risk for 4,4'-dichlorobenzophenone is precluded by the lack of data.

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APPENDIX A. DERIVATION OF A SCREENING VALUE FOR 4,4'-DICHLOROBENZOPHENONE (CASRN 90-98-2)

For reasons noted in the main PPRTV document, it is inappropriate to derive provisional toxicity values for 4,4'-dichlorobenzophenone. However, information is available for this chemical which, although insufficient to support derivation of a provisional toxicity value, under current guidelines, may be of limited use to risk assessors. In such cases, the Superfund Health Risk Technical Support Center summarizes available information in an Appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the PPRTV documents to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there is considerably more uncertainty associated with the derivation of an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the Superfund Health Risk Technical Support Center.

The NOAEL of 86 mg/kg-day (highest dose tested) in an unpublished 90-day study (Ambrose and Borzelleca, 1965) could serve as a basis for development of screening subchronic and chronic p-RfDs.

Oral Toxicity Values

Screening Subchronic p-RfD

Oral data for 4,4'-dichlorobenzophenone are limited to a single subchronic study in rats (Ambrose and Borzelleca, 1965) in which no biologically significant effects were found after treatment with 4,4'-dichlorobenzophenone at the highest dose tested. The highest dose tested and identified from this study (i.e., 86 mg/kg-day) serves as a NOAEL for the derivation of the screening subchronic p-RfD.

Using the NOAEL of 86 mg/kg-day from the subchronic study in rats (Ambrose and Borzelleca, 1965) as the point of departure (POD), **a screening subchronic p-RfD** is derived for 4,4'-dichlorobenzophenone as follows:

Screening Subchronic p-RfD = NOAEL ÷ UF
= 86 mg/kg-day ÷ 1,000
= **0.09 or 9×10^{-2} mg/kg-day**

The composite uncertainty factor (UF) of 1,000 is composed of the following UFs:

- UF_H: A factor of 10 is applied to account for intraspecies variability, including variability in susceptibility in human populations and life-stages.
- UF_A: A factor of 10 is applied for animal-to-human extrapolation, as data for evaluating toxicokinetic or toxicodynamic differences are insufficient.
- UF_D: A factor of 10 is applied for database inadequacies, as data for evaluating developmental and reproductive toxicity are not available.

Confidence in the principal study (Ambrose and Borzelleca, 1965) is low because reporting of methods and results was incomplete, particularly with regard to standard deviations and statistical tests for body weight, food intake, and hematology values. Confidence in the

database is low because supporting subchronic data were unavailable and developmental and reproductive effects were not evaluated. Confidence in the subchronic p-RfD is accordingly low.

Screening Chronic p-RfD

Oral data for 4,4'-dichlorobenzophenone are limited to a single subchronic study in rats (Ambrose and Borzelleca, 1965); no chronic studies are available. In the absence of adequate chronic data, the POD used to derive the subchronic p-RfD was also used to derive a screening chronic p-RfD. A **screening chronic p-RfD** for 4,4'-dichlorobenzophenone is derived as follows:

$$\begin{aligned} \textbf{Screening Chronic p-RfD} &= \text{NOAEL} \div \text{UF} \\ &= 86 \text{ mg/kg-day} \div 10{,}000 \\ &= \textbf{0.009 or } \mathbf{9 \times 10^{-3}} \textbf{ mg/kg-day} \end{aligned}$$

The composite UF of 10,000 is composed of the following UFs:

- UF_H: A factor of 10 is applied to account for intraspecies variability, including variability in susceptibility in human populations and life-stages.
- UF_A: A factor of 10 is applied for animal-to-human extrapolation, as data for evaluating toxicokinetic or toxicodynamic differences are insufficient.
- UF_D: A factor of 10 is applied for database inadequacies, as data for evaluating developmental and reproductive toxicity are not available.
- UF_S: A factor of 10 is applied for using data from a subchronic study to assess potential effects from chronic exposure, as data for evaluating response after chronic exposure are not available.

As discussed for the subchronic p-RfD, confidence is low in the principal study (Ambrose and Borzelleca, 1965), the database, and the overall assessment. Additionally, a surrogate study for 4,4'-dichlorobenzophenone (Moudgal et al., 2003) based on structural similarity (structural surrogates) and toxicokinetics (metabolic surrogates) has suggested the use of the IRIS chronic RfD for chlorobenzilate, of 2×10^{-2} mg/kg-day (U.S. EPA, 1989), as an alternate RfD for 4,4'-dichlorobenzophenone. This alternate RfD, which differs by approximately a factor of 2, is in support of the **screening chronic p-RfD**.