Toxicological Summary for: Bisphenol A

CAS: 80-05-7

Synonyms: BPA; 4’-(1-Methylethylidene)bisphenol 4,4’-Bisphenol A; 4,4’-Isopropylidenediphenol; Phenol, 4,4’-(1-methylethylidene)bis- p,p’-isopropylidenebisphenol; 2,2-bis(4-hydroxyphenyl)propane

Acute Non-Cancer Health Risk Limit ($nHRL_{Acute}$) = Not Derived (Insufficient Data)

Short-term Non-Cancer Health Risk Limit ($nHRL_{Short-term}$) = 100 µg/L

$\dfrac{\text{(Reference Dose, mg/kg/d)} \times \text{(Relative Source Contribution)} \times \text{(Conversion Factor)}}{\text{(Short-term intake rate, L/kg-d)}}$

$= \dfrac{(0.16 \text{ mg/kg/d}) \times (0.2^*) \times (1000 \text{ µg/mg})}{0.289 \text{ L/kg-d}}$

$= 111$ rounded to 100 µg/L

*MDH utilizes the EPA Exposure Decision Tree (EPA 2000) to select appropriate RSCs. Given the significant potential non-drinking water sources of exposure from multiple sources available for infants, an RSC of 0.2 is selected rather than the default value of 0.5 used for nonvolatile chemicals.

Reference Dose/Concentration: 0.16 mg/kg-d (rat)

Source of toxicity value: MDH, 2014

Point of Departure (POD): 2.7 mg/kg-d (NOAEL, Delclos et al. 2014)

Human Equivalent Dose (MDH, 2011): 2.7 x 5.8 = 16 mg/kg-d [chemical-specific DAF for neonatal rats]

Total uncertainty factor: 100

Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty (additional studies to evaluate latent effects of early life exposure, neurobehavioral, immune system, and metabolic disease are warranted)

Critical effect(s): Developmental (decreased pup body weight), increased total T3 in male pups

Co-critical effect(s): Developmental (decreased number and viability of offspring, pup and fetal body weight effects, delayed puberty in male and females; decreased weanling spleen and testes weights, undescended testes, seminiferous tubule hypoplasia), Female reproductive (decreased number and viability of offspring; changes in hormone ratios), Liver (changes serum liver parameters, organ weight, morphology and histology), Male reproductive effects (changes in hormone ratios, reduced...
Additivity endpoint(s): Developmental, Female reproductive system (E), Hepatic (liver) system, Male reproductive system (E), Renal (kidney) system, Thyroid (E)

**Subchronic Non-Cancer Health Risk Limit (nHRL\textsubscript{Subchronic}) = 20 \mu g/L**

\[
\text{(Reference Dose, mg/kg/d)} \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor}) \\
(\text{Subchronic intake rate, L/kg-d})
\]

\[
= \left(0.0065 \text{ mg/kg/d} \right) \times (0.2) \times (1000 \mu g/mg) \\
\left(0.077 \text{ L/kg-d}\right)
\]

\[
= 16.9 \text{ rounded to } 20 \mu g/L
\]

Reference Dose/Concentration: 0.0065 mg/kg-d (mouse)
Source of toxicity value: MDH, 2014
Point of Departure (POD): 5.0 mg/kg-d (NOAEL, Tyl et al. 2008)
Human Equivalent Dose (MDH, 2011): 5 x 0.13 = 0.65 mg/kg-d
Total uncertainty factor: 100
Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty (additional studies to evaluate latent effects of early life exposure, neurobehavioral, immune system, and metabolic disease are warranted)

Critical effect(s): Centrilobular hepatocyte hypertrophy; increased kidney weight
Co-critical effect(s): Increased centrilobular hepatocyte hypertrophy, liver weight effects
Additivity endpoint(s): Hepatic (liver) system, Renal (kidney) system

**Chronic Non-Cancer Health Risk Limit (nHRL\textsubscript{Chronic}) = nHRL\textsubscript{Subchronic} = 20 \mu g/L**

\[
\text{(Reference Dose, mg/kg/d)} \times (\text{Relative Source Contribution}) \times (\text{Conversion Factor}) \\
(\text{Chronic intake rate, L/kg-d})
\]

\[
= \left(0.0065 \text{ mg/kg/d} \right) \times (0.2) \times (1000 \mu g/mg) \\
\left(0.043 \text{ L/kg-d}\right)
\]

\[
= 30.2 \text{ rounded to 30 \mu g/L}
\]

Reference Dose/Concentration: 0.0065 mg/kg-d (mouse)
Source of toxicity value: MDH, 2014
Point of Departure (POD): 5.0 mg/kg-d (NOAEL, Tyl et al. 2008)
Human Equivalent Dose (MDH, 2011): 5 x 0.13 = 0.65
Total uncertainty factor: 100
Uncertainty factor allocation: 3 for interspecies differences (for toxicodynamics), 10 for intraspecies variability, and 3 for database uncertainty (additional studies to evaluate latent effects of early life exposure, neurobehavioral, immune system, and metabolic disease are warranted)

Critical effect(s): Centrilobular hepatocyte hypertrophy, increased kidney weight

Co-critical effect(s): Increased centrilobular hepatocyte hypertrophy, liver weight effects

Additivity endpoint(s): Hepatic (liver) system, Renal (kidney) system

The Chronic nHRL must be protective of the acute, short-term, and subchronic exposures that occur within the chronic period and therefore, the Chronic nHRL is set equal to the Subchronic nHRL of 20 µg/L. Additivity endpoints: Hepatic (liver) system, Renal (kidney) system

Cancer Health Risk Limit (cHRL) = Not Applicable

Cancer classification: No cancer classification is available for bisphenol A
Slope factor: Not applicable
Source of slope factor: Not applicable
Tumor site(s): Not applicable

Volatile: No

Summary of Guidance Value History:
No previous 1993/1994 HRLs exist for Bisphenol A. In 1998, a chronic noncancer Health-Based Value (nHBV) of 300 µg/L was derived. In 2012, new nHBVs were developed for acute (300 µg/L), short-term (300 µg/L) and subchronic (100 µg/L) durations and the chronic nHBV was lowered to (100 µg/L). In 2014, BPA was re-evaluated. The acute HBV was removed, the short-term value decreased to 100 µg/L and the subchronic/chronic nHBVs decreased to 20 µg/L based upon 1) a re-evaluation of the toxicity data with inclusion of more recent information, and (2) new life-stage toxicokinetic information that resulted in revised dose-adjustment factors (DAFs). In 2015, the 2014 HBVs were adopted into rule as HRLs.

Summary of toxicity testing for health effects identified in the Health Standards Statute:

<table>
<thead>
<tr>
<th>Tested?</th>
<th>Endocrine</th>
<th>Immunotoxicity</th>
<th>Development</th>
<th>Reproductive</th>
<th>Neurotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effects?</td>
<td>Yes¹</td>
<td>Yes²</td>
<td>Yes³</td>
<td>Yes⁴</td>
<td>Yes⁵</td>
</tr>
</tbody>
</table>

Note: Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. Most chemicals have been subject to multiple studies in which researchers identify a dose where no effects were observed, and the lowest dose that caused one or more effects. A toxicity value based on the effect observed at the lowest dose across all available studies is considered protective of all other effects that occur at higher doses.
Comments on extent of testing or effects:

1. Unconjugated (free) BPA is a well-known endocrine-active substance and has been extensively studied. BPA is metabolized quickly in the liver to an endocrine-inactive form (i.e., glucuronide conjugate) that is rapidly excreted in human urine. The estrogenic potency of free BPA is more than 1,000-fold lower than estrogens and BPA has a weaker binding affinity to classical hormone receptors than endogenous hormones. Estrogen, testosterone and thyroid hormone levels and hormone receptor results from laboratory animal studies at doses below 5 mg/kg-d have been inconsistent and contradictory. However, study design limitations, dose-response interpretation issues, inconsistencies in results and conflicting data in the low dose region exists. The RfDs are considered protective for endocrine effects in humans, in part, because humans and non-human primates efficiently metabolize BPA to its endocrine-inactive conjugate which is rapidly excreted in the urine. In a rodent study assessing effects resulting from early life (in utero and direct dosing for 3 months after birth) changes in estradiol, thyroid hormone, progesterone and prolactin levels were reported only at doses more than 3,000-fold higher than the RfDs presented above. No effects were reported on FSH or LH at doses 30,000 times higher than the subchronic RfD. Effects on serum levels of sex hormone ratios are considered as co-critical effects for the short-term duration.

2. Immunotoxicity of BPA has not been thoroughly evaluated, but a limited number of studies evaluating either direct or in utero exposure to BPA using non-standard test methods suggest that BPA may interfere with immune homeostasis (cytokine activity, macrophage activity, tumor necrosis factor secretion, and T-cell activity). Several studies found no effect on adult spleen or thymus weights or histopathology of adult immune organs but one study reported spleen and thymus atrophy at a dose 4,500 times higher than the short-term RfD. BPA is a skin sensitizer in humans exposed dermally but there is no clear evidence that BPA interferes with overall immune system function. In general, doses more than 90 times higher than the short-term RfD and more than 2,000 times higher than the subchronic/chronic RfDs are required to elicit a significant immune response. A few studies reported immune-related cellular effects at lower doses, including increased IgG1, IL-4, and various splenocyte T-cell populations at doses more than 6 times higher than the subchronic RfD. Inconsistent results have been reported for IgG2a, interferon-γ, and splenic cell numbers. These low dose cellular-level effects have not been associated with adverse functional immune outcomes related to enhancement or suppression of response to pathogens and the biological significance is uncertain. Database limitations and uncertainties regarding available immune system data were considered in the derivation of the RfDs. The spleen, an immune system organ, was identified as a co-critical developmental additivity endpoint based on transient organ weight effects in weanling animals.

3. The National Toxicology Program (NTP) has identified the brain, behavior, and prostate as developmental endpoints of “some concern” for fetuses, infants, and children. In other words, NTP considers there are insufficient data from human studies to support possible effects on the brain, behavior and the prostate; however, limited evidence in some animal studies cannot be dismissed. NTP concluded that the significance of the limited data from animal studies to humans is unknown at this time. See footnote #5 below for information about neurodevelopmental effects for brain and behavior. A few reports suggest that BPA exposure during gestation and infancy may increase susceptibility to prostate cancer, mammary cancer, impact mammary gland development, or contribute to metabolic diseases (e.g., obesity, diabetes) later in life; however, current data are inadequate to determine whether BPA exposure in early life leads to cancer or metabolic disease in adulthood. A statistically significant increase in mammary gland ductal hyperplasia, a potential indicator of mammary gland development, was reported in rats at a dose over 30,000 times higher than the chronic RfD. The biological significance of this finding will not be known until results from an ongoing chronic study become available. Delayed puberty in male and female animals has been reported, although a recent large-scale study in rats found no effects on pubertal onset, except for delayed testes descent reported.
at a dose over 1,000 times higher than the short-term RfD. Developmental effects are considered as critical and co-critical effects for the short-term duration RfD and uncertainties related to neurobehavioral effects and metabolic disease are addressed in the derivation of the RfDs using a database uncertainty factor.

Female reproductive effects, including decreased numbers of litters per breeding pair and changes in hormone ratios, are considered co-critical effects in the derivation of the short-term RfD. Estrous cycle effects were reported at doses 450 times higher than the short-term RfD and over 11,000 times higher than the subchronic/chronic RfDs. Male reproductive effects were reported in adult animals and included multinucleated giant cells in seminiferous tubules, reduced spermatogenesis in pubertal animals and various reproductive organ weight effects (testes, prostate, seminal vesicles, and epididymis). Reports of BPA effects on sperm parameters and testosterone are inconsistent. Male and female reproductive effects are considered as co-critical effects for the derivation of the short-term RfD.

NTP has identified the brain and behavior as endpoints of “some concern” for fetuses, infants and children. This means that there are insufficient data from human studies, but limited evidence of potential neurotoxicity in some animal studies cannot be dismissed, although significance to humans is unknown. Experimental evidence in a well-conducted developmental neurotoxicity study in rats does not support brain developmental neuropathological changes in offspring exposed via maternal dietary doses up to 700 times higher than the short-term RfD. Low dose (defined as doses < 5 mg/kg-d) gestational and/or neonatal exposures have been reported to cause various neurodevelopmental effects in offspring in a variety of studies. Some studies suggest possible effects of early life exposure on various sexually dimorphic behaviors, changes in maternal behaviors nursing and nesting behaviors, anxiety, aggression and learning performance resulting from doses below the short-term RfD; however, there has been a lack of consistency, reproducibility and a variety of study design or reporting limitations in existing data. Several brain morphology studies with various methodological flaws and/or using routes of exposure that are not relevant for evaluating the oral route (e.g., injection studies) have reported effects on various biochemical and neurotransmitter gene expression changes in brain tissues. Developmental neurobehavioral endpoints were identified as areas of data uncertainty in the derivation of acute and short-term RfDs/HRLs.

Acute or short-term exposure to adult animals has resulted in nervous system effects in some studies including piloerection, decreased locomotor activity, sedation, lethargy, arched back, and vocalization. These effects occurred at high gavage doses that were over 700 times higher than the short-term RfD. One study reported decreased serum cholinesterase in female rats exposed to a dose that was about 900 times higher than the short-term RfD, but this effect has not been evaluated in other studies and the biological significance is unknown.

References:


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Camacho, L., C. Chang, M. Basavarajappa, T. Han, J. C. Fuscoe, S. Lewis, et al. (2014). Effect of oral bisphenol a (BPA) and ethinyl estradiol (EE2) on genome-wide gene expression in prostates from 4-day old rats (meeting abstract). *The Toxicologist: Supplement to Toxicological Sciences* 138(1): 447.


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Ryan, B. C., A. K. Hotchkiss, K. M. Crofton and L. E. Gray, Jr. (2010a). In utero and lactational exposure to bisphenol A, in contrast to ethinyl estradiol, does not alter sexually dimorphic


