Human Health Benchmarks for Pesticides: Updated 2021 Technical Document

Introduction

The 2021, HHBPs were derived for 430 pesticides that currently have no federal drinking water standards or HAs. 406 of the pesticides included in the 2021 HHBP table are currently registered for food use. We are now able to include values for 24 pesticides that are only registered for non-food uses for which data are available. The HHBPs in the table were updated for all pesticides included in the 2017 table based on revised exposure factors. For 104 pesticides listed in the 2017 table, HHBPs were updated with new toxicity values. HHBPs for 43 pesticides that now have toxicity values were added and HHBPs for 3 pesticides, removed in 2017 based on a lack of food use, were added back to the 2021 table. EPA continues to strive to update the HHBPs on a regular basis in order to reflect the latest toxicity information available through the pesticide registration and registration review processes and the latest exposure factor information. Among the pesticides included in the 2021 table, the pesticides with the most frequent USGS detections in U.S. streams are imidacloprid, azoxystrobin, propiconazole, and carbendazim.¹

The HHBPs are not legally enforceable federal standards. EPA is providing the HHBPs for pesticides that have no drinking water standards or health advisories. EPA’s HHBPs provide information about adverse health effects from drinking water exposure to pesticides that have no drinking water standards or health advisories. HHBPs can be used by states, tribes, drinking water systems, and the public when pesticides are detected through monitoring.

History of development of HHBPs

EPA first developed the human health benchmarks for pesticides (HHBP) in 2012 to enable states, tribes, water systems, public and other stakeholders to better determine whether the detection of a pesticide in drinking water or source waters for drinking water may indicate a potential health risk. HHBPs were developed with the same methods used by the Agency to calculate health advisories for drinking water and are based on toxicity data that were peer-reviewed as part of EPA’s pesticide registration and registration review processes. Since 2012, benchmarks have been updated based on updated toxicity values in 2013, 2017, and now in 2021. In 2021, EPA has now included a subset of pesticides registered for non-food uses for which data are available.

Derivation of HHBPs for Noncancer

EPA derived the HHBPs by applying the health effects data from pesticide registration and registration review processes under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and tolerances under the Federal Food, Drug, and Cosmetic Act (FFDCA) as amended by the Food Quality Protection Act (FQPA) to the typical methods used for developing drinking water health advisories (HAs) under the Safe Drinking Water Act (SDWA). Pesticides that have existing HAs or National Primary Drinking Water Regulations (Maximum Contaminant Levels (MCLs) and Maximum Contaminant Level Goals (MCLGs)) are not included in the HHBP table.

HHBPs have been developed based on EPA’s HA methodology combined with RfDs and/or cancer slope factors (CSFs) developed from health effects data during the pesticide registration and registration review processes. The HHBPs include only active ingredients unless metabolites were assessed with the parent compound. Inert compounds used in pesticide formulations were not included in this update. HHBPs have been developed for acute (one-day), chronic (non-cancer), and carcinogenic effects (10^{-6} - 10^{-4} risk level) to protect against adverse health effects from exposure to pesticides that may be found in surface or ground water used for drinking. The HHBP table lists the acute as well as chronic RfD and PAD, the noncancer benchmarks for the sensitive population/lifestage and, when appropriate, the CSF and the corresponding carcinogenic benchmarks. The acute reference doses (aRfD) are usually determined for the general population and sensitive populations, including children and females of reproductive age. The chronic reference doses (cRfD) are usually derived for general population or females of reproductive age. The documentation supporting the RfD and/or CSF derivation for the specific pesticide is provided by clicking the name of the pesticide in the benchmarks’ website. The number of significant figures for each benchmark corresponds to the number of significant figures in the toxicity value used to derive the benchmark.

To develop RfDs, EPA examines the entire toxicity database for a pesticide available to the Agency through the registration process and from this determines the appropriate studies and endpoints for the acute and chronic dietary risk assessments. EPA’s pesticide risk assessment documents contain a detailed explanation of the basis for establishing the RfDs. If the toxicity database indicates that toxic effects can be observed following a single oral dose, an aRfD will be selected. Acute RfDs established for the general population based on systemic/target organ toxicity are typically also relevant for infants and children and so are also suitable for deriving the one-day HHBP. Acute RfDs established for females of reproductive age are often based on developmental and reproductive toxicity, which are not appropriate endpoints for deriving HHBPs for children because they do not represent an effect relevant to that life stage. When RfDs are available for multiple target populations (e.g., an aRfD for general population, females of reproductive age, or children), the aRfD that provides the most health protective drinking water benchmark will be selected while taking exposure assumptions into consideration. Since children consume more drinking water per body weight compared to adults, the aRfD derived specifically for children would be most appropriate for deriving the acute drinking water benchmarks. However, since this age-specific value is often not available, the aRfD for general population is used as a surrogate for children. In such situations, the application of children-specific exposure assumptions yields the health protective acute benchmarks. For chronic benchmarks, the cRfD derived for general population or females of reproductive age form the basis for deriving the chronic drinking water benchmarks. In general, the methodology to derive the RfDs for pesticide registration and registration review is similar to that used to derive RfDs used to develop HAs for drinking water (i.e., the same EPA guidance is used for reference dose determination).

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2These HAs (one-day, ten-day, lifetime) and regulatory standards for drinking water contaminants, including some pesticides; Available online at: [http://water.epa.gov/drink/standards/hascience.cfm](http://water.epa.gov/drink/standards/hascience.cfm).

A normalized ratio of drinking water intake to body weight (DWI/ BW) of 0.0338 L/kg/day was calculated using data for general population (all ages) and this represents the 90th percentile values of the two-day average, consumer-only estimate of combined direct and indirect community water ingestion based on the 2005-2010 National Health and Nutrition Examination Survey (NHANES) as reported in EPA’s update for Chapter 3 of the Exposure Factors Handbook4 (Table 3-21). For children and females of reproductive age, the following exposure assumptions were used:

- For females of reproductive age (13-49 years), a normalized ratio of drinking water intake to body weight (DWI/ BW) of 0.0354 L/kg/day was calculated using data for women of childbearing age and this represents the 90th percentile values of the two-day average, consumer-only estimate of direct and indirect community water ingestion based on U.S. EPA analysis of 2005–2010 NHANES as reported in EPA’s 2019 update of the Exposure Factors Handbook4 (Table 3-63).

- For children, a normalized ratio of drinking water intake to body weight (DWI/ BW) of 0.15 L/kg/day was calculated using data for infants (birth to <12 months) and this represents the 90th percentile values of the consumer-only estimate of direct and indirect water ingestion based on 1994-1998 Continuing Survey of Food Intakes by Individuals (CSFII) as reported in EPA’s 2019 update of the Exposure Factors Handbook4 (Table 3-58). The time weighted average of DWI/BW ratios values was derived from multiplication of age-specific DWI/BW ratios (birth to <1 month, 1 to <3 months, 3 to <6 months, and 6 to <12 months) by the age-specific fraction of infant exposures for these time periods (mL/kg/day).

For pesticide registrations and registration reviews conducted under FIFRA, EPA derives acute or chronic population adjusted doses (PADs) using an FQPA safety factor mandated by the FQPA that takes into consideration potential prenatal and/or postnatal toxicity and completeness of the data with respect to exposure and toxicity to women of child-bearing age, infants, and children. The FQPA safety factor can also account for uncertainties in the overall completeness of the toxicity database, extrapolation from subchronic to a chronic study duration, and lowest observed adverse effect level (LOAEL) to no observed adverse effect level (NOAEL)4. In most cases, the PAD and the RfD are the same. When the FQPA Safety Factor is attributed to residual uncertainty with regard to exposure or prenatal and/or postnatal toxicity, the RfD and PAD differ. For this reason, HHBP values were calculated using the PADs.

A Relative Source Contribution (RSC) of 20% is used for derivation of chronic non-cancer HHBPs and is a conservative assumption used in EPA’s drinking water HA methodology. The RSC refers to the percentage of the PAD remaining for drinking water after other sources of exposure to a contaminant are considered (e.g., diet). Consistent with EPA policies and procedures, the RSC is used only in deriving chronic HHBPs; it is not used in deriving acute or the carcinogenic HHBPs.

The formulas for determining the acute and chronic HHBPs are presented below:

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\text{Acute or one-day HHBP (for children) (ppb) } = \frac{aPAD \text{ (mg/kg/day)} \times 1000 \text{ (µg/mg)}}{0.15 \text{ (L/kg-day) DWI-BW ratio}}
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Acute or one-day HHBP (females 13-49 years) (ppb) =
aPAD (mg/kg/day) x 1000 (µg/mg)  
0.0354 (L/kg/day) DWI-BW ratio

Chronic non-cancer HHBP (general population) (ppb) =
cPAD (mg/kg/day) x 1000 (µg/mg) x 0.2 RSC  
0.0338 (L/kg/day) DWI-BW ratio

Chronic non-cancer HHBP (females 13-49 years) (ppb) =
cPAD (mg/kg/day) x 1000 (µg/mg) x 0.2 RSC  
0.0354 (L/kg/day) DWI-BW ratio

Derivation of HHBPs for Cancer

For pesticides that mediate cancer effects via linear dose responses, mathematical models are used to estimate an upper-bound excess cancer risk associated with lifetime oral exposure. The data used in these estimates usually come from lifetime exposure studies in animals. This model fits linear dose-response curves to low doses and is consistent with a no-threshold model of carcinogenesis, i.e., exposure to even a very small amount of the substance produces a finite increased risk of cancer.

The linearized multistage model uses dose-response data from the most appropriate carcinogenic study to calculate a CSF for humans. The CSF is then used to determine the concentrations of the chemical in drinking water that are associated with theoretical upper-bound excess lifetime cancer risks (1 in 1,000,000 to 1 in 10,000) over a lifetime of exposure.

A two-step process is applied to determine the benchmarks specific for cancer effects as in HA methodology. In the first step, a drinking water unit risk is determined. In the second step, the drinking water unit risk is translated to the $10^{-6}$ to $10^{-4}$ (1 in 1,000,000 to 1 in 10,000) cancer risk levels in water. The following formulas are applied to estimate the drinking water unit risk and subsequently, to derive the $10^{-6}$ to $10^{-4}$ cancer risk levels.

**Drinking Water Unit Risk (µg/L⁻¹ or ppb)**  
\[ \text{Drinking Water Unit Risk (µg/L⁻¹ or ppb)} = \frac{\text{CSF (mg/kg/day)}}{1000 (µg/mg)} \times \frac{0.0338 (L/kg/day) (adult DWI-BW ratio)}{\text{(adult DWI-BW ratio)}} \]

From the drinking water unit risk, the following $10^{-6}$ to $10^{-4}$ cancer risk specific levels in water are determined.

\[ 10^{-6} \text{ or } 10^{-4} \text{ Risk Level in Drinking Water (ppb)} = \frac{10^{-6} \text{ or } 10^{-4}}{\text{Drinking Water Unit Risk (ppb)}} \]

EPA guidance describes application of age-dependent adjustment factors (ADAFs) to chemicals that mediate cancer through a mutagenic mode of action. No pesticides listed in the table have been identified as having a mutagenic mode of action and therefore ADAFs were not used to calculate HHBPs. For some carcinogens (e.g., threshold type carcinogens), a RfD or Margin of Exposure (MOE) approach

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may be considered protective of cancer risk and, therefore, no separate drinking water cancer risk levels are needed. If the pesticides are determined to not have carcinogenic potential to humans, or there is inadequate evidence to determine carcinogenic potential, no separate drinking water cancer risk levels were determined.

**How to View the HHBPs**
To view the table of HHBPs and supporting information online go to https://iaspub.epa.gov/apex/pesticides/?p=HHBP:home

**For More Information**
For more information regarding the derivation of HHBPs, contact Susan Euling in EPA’s Office of Water at euling.susan@epa.gov.

For information regarding the documentation for deriving the reference doses or cancer risk estimation, contact Gregory Akerman in EPA’s Office of Pesticide Programs at akerman.gregory@epa.gov.

**Abbreviations**

aPAD- Acute Population Adjusted Dose  
aRfD-Acute Reference Dose  
BW – Body Weight  
cPAD- Chronic Population Adjusted Dose  
cRfD-Chronic Reference Dose  
DW- Drinking Water  
DWI-Drinking Water Intake  
EPA – Environmental Protection Agency  
FIFRA - Federal Insecticide, Fungicide, and Rodenticide Act  
FFDCA - Federal Food, Drug, and Cosmetic Act  
FQPA - Food Quality Protection Act  
HA- Health Advisory  
HHBPs – Human Health Benchmarks for Pesticides  
MCL - Maximum Contaminant Level  
MCLG - Maximum Contaminant Level Goal  
MOE - Margin of Exposure  
PAD – Population Adjusted Dose  
ppb -parts per billion  
CSF- Cancer Slope Factor  
RfD - Reference Dose  
RSC - Relative Source Contribution  
SDWA - Safe Drinking Water Act