United States Environmental Protection Agency

Office of Water
EPA 822 R 17 001
January 2017

Human Health Benchmarks for Pesticides: Updated 2017 Technical Document

Introduction

On March 22, 2010, former EPA Administrator Lisa P. Jackson announced a drinking water strategy[1] that outlined four principles to expand public health protection. One of these principles proposed using the authority of multiple statutes to help protect drinking water. In 2012, EPA's Office of Pesticide Program (OPP) and Office of Water (OW) first published Human Health Benchmarks for Pesticides (HHBPs) for non-carcinogenic effects of 352 pesticides registered for use on food crops, and in 2013, benchmarks for 11 new pesticides were added and benchmarks for 40 pesticides were revised with added cancer information. EPA continues to strive to update the HHBPs on a regular basis to reflect the latest scientific information. This current effort includes update of toxicity values for 41 pesticides. In addition, 38 new pesticides were added to the HHBP table. Additionally, all benchmarks were calculated with updated exposure (body weight and drinking water intake) assumptions. Three pesticides previously listed in the table were removed due to updated exposure pattern information demonstrating that these pesticides are no longer used on food nor do they have the potential for reaching drinking water sources (d-Allethrin, S-Bioallethrin, and Bioallethrin).

The HHBPs are not legally enforceable federal standards. EPA is providing the HHBPs for informational purposes for use by states, water systems and the public to help understand monitoring data for pesticides that have no drinking water standards or health advisories.

Derivation of HHBPs for Noncancer

EPA derived the HHBPs by applying the health effects data from pesticide registrations 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)[2] are not included in the HHBP table.

HHBPs have been developed based on EPA's HA methodology[2] combined with RfDs and/or cancer slope factors (CSFs) developed from health effects data during the pesticide registration process. 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

[1] EPA's drinking water strategy can be viewed online at http://water.epa.gov/lawsregs/rulesregs/sdwa/dwstrategy/index.cfm
[2] These HAs (one-day, ten-day, lifetime) and regulatory standards for drinking water contaminants, including some pesticides, can be obtained online at: http://water.epa.gov/drink/standards/hascience.cfm.

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, 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 from 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 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 is similar to that used to derive RfDs used to develop HAs for drinking water (i.e., the same EPA guidance[3] is used for reference dose determination).

EPA updated adult body weight (BW) used to calculate the benchmarks to 80 kilograms based on National Health and Nutrition Examination Survey (NHANES) data from 1999 to 2006 (USEPA 2011). This represents the mean body weight for adults ages 21 and older. Previously, 70 kilograms was used. EPA also updated the drinking water intake (DWI) for adults. A DWI of 2.5 L/d, rounded from 2.546 L/d, based on NHANES data from 2003 to 2006 as reported in EPA's Exposure Factors Handbook (U.S. EPA 2011a, Table 3-33) was used in the benchmark calculations. This rate represents the consumer's only estimate of combined direct and indirect community water ingestion at the 90th percentile for adults ages 21 and older. For children and females of reproductive age, the following exposure assumptions were used:

- For females of reproductive age (13-49 years), body weight was updated from 66 kg to 69 kg based on NHANES data from 1999 to 2006.
- 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 consumers only estimate of direct and indirect water ingestion based on

[3] USEPA. 2002. A Review of Reference Dose and Reference Concentration Processes. EPA/630/P-02/002F. This document can be accessed online at http://www.epa.gov/raf/publications/pdfs/RfD-final.pdf.

1994-1998 Continuing Survey of Food Intakes by Individuals (CSFII)[4] as reported in EPA's Exposure Factors Handbook (Table 3-19). 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 under FIFRA, EPA derives acute or chronic population adjusted doses (PADs) using an FQPA Safety Factor mandated by the FQPA taking into consideration potential pre and/or post natal toxicity and completeness of the data with respect to exposure and toxicity to infants and children. In the majority of instances, the PAD and the RfD are the same. It is only in those few instances when the FQPA Safety Factor is attributed to residual uncertainty with regard to exposure or pre/post natal toxicity that the RfD and PAD differ. More recently, FQPA Safety Factors can account for uncertainties in the overall completeness of the toxicity database, extrapolation from subchronic to a chronic study duration, and LOAEL to NOAEL extrapolation. 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:

Acute or one-day HHBP (for children) (ppb) =

$$\frac{\text{aRfD (mg/kg/day) x 1000 (µg/mg)}}{\text{0.15 (L/kg-day) DWI-BW ratio}}$$

Acute or one-day HHBP (females 13-49 years) (ppb) =

$$\frac{\text{aRfD (mg/kg/day) x 69 (kg) BW x 1000 (µg/mg)}}{\text{2.5 (L/day) DWI}}$$

Chronic non-cancer HHBP (general population) (ppb) =

$$\frac{\text{cRfD (mg/kg/day) x 80 (kg) BW x 1000 (µg/mg) x 0.2 RSC}}{\text{2.5 (L/day) DWI}}$$

Chronic non-cancer HHBP (females 13-49 years) (ppb) =

$$\frac{\text{cRfD (mg/kg/day) x 69 (kg) BW x 1000 (µg/mg) x 0.2 RSC}}{\text{2.5 (L/day) DWI}}$$

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.

[4] USEPA. Exposure Factors Handbook 2011 Edition (Final). U.S. Environmental Protection Agency, Washington, DC, EPA/600/R-09/052F, 2011. This document can be obtained online at: https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252.

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.

$$\text{Drinking Water Unit Risk } (\mu g/L^{-1} \text{ or ppb}) = \frac{\text{CSF (mg/kg/day) x 2.5 (L/day) (adult DWI)}}{\text{80 (kg) (Adult BW) x 1000 } (\mu g/mg)}$$

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

$$10^{-6} \text{ or } 10^{-4} \text{ Risk Level in Drinking Water (ppb)} = \frac{10^{-4} \text{ or } 10^{-6}}{\text{Drinking Water Unit Risk (ppb)}^{-1}}$$

EPA guidance describes application of age-dependent adjustment factors (ADAFs) to chemicals that mediate cancer through a mutagenic mode of action.[5] 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 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/f?p=HHBP:home

For More Information

For more information regarding the derivation of HHBPs, contact Jamie Strong in EPA's Office of Water at strong.jamie@epa.gov.

For information regarding the documentation for deriving the reference doses or cancer risk estimation, contact Brenda May in EPA's Office of Pesticide Programs at may.brenda@epa.gov.

[5] USEPA. Guidelines for Carcinogen Risk Assessment. U.S. Environmental Protection Agency, Washington, DC, EPA/630/P-03/001F, 2005. This document can be obtained online at: https://www.epa.gov/sites/production/files/2013-09/documents/cancer_guidelines_final_3-25-05.pdf.

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