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# Human Health Benchmarks for Pesticides: Updated 2013 Technical Document

## Introduction

On March 22, 2010, former EPA Administrator Lisa P. Jackson announced a drinking water strategy<sup>1</sup> 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. Working together, in 2012, EPA's pesticide registration and drinking water programs first published Human Health Benchmarks for Pesticides (HHBPs) for non-carcinogenic effects of 352 pesticides registered for use on food crops. At that time, EPA committed to updating the HHBPs on a regular basis to reflect the latest scientific information. This technical document has been developed to support the first such HHBP update. In this update, EPA is adding 11 new benchmarks for a total of 363 HHBPs, and revising 10 of the HHBPs published in 2012 to reflect new scientific information. This update also includes benchmarks for 40 pesticides that require quantification of carcinogenic risk using a linear approach [i.e., cancer slope factor (CSF)].

The HHBPs are advisory values only, and are not legally enforceable federal standards. They are intended to provide states, tribes, the public and other stakeholders with information to support their internal decision-making processes (e.g., assist in the interpretation of the drinking water monitoring data).

## Derivation of HHBPs

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)<sup>2</sup> are not included in the HHBP table.

HHBPs have been developed based on EPA's HA methodology<sup>2</sup> combined with RfDs and/or 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 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 children, general population or females of reproductive age. The chronic reference dose (cRfD) are usually derived for general population or

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<sup>1</sup> EPA's drinking water strategy can be viewed online at <http://water.epa.gov/lawsregs/rulesregs/sdwa/dwstrategy/index.cfm>.

<sup>2</sup> 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>.

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.

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. With regard to the cRfD, in most cases it is determined for the general population although in rare situations, EPA derives specific cRfD for females of reproductive age. The same sensitive population is then used for the chronic HHBP. In general, the methodology to derive the RfDs for pesticide registration is similar to that used to derive HAs for drinking water (i.e., the same EPA guidance<sup>3</sup> is used for reference dose determination).

The HHBPs are derived based on the same default exposure assumptions<sup>2</sup> which are used to derive the HAs for drinking water. When more than one RfD is available for target populations (e.g., 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 bodyweight basis 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.

To derive the acute (one-day) HHBP for children, EPA assumes that the exposed child has a body weight of 10 kg and consumes 1L of water daily. For deriving the one-day HHBP for females of reproductive age, a default body weight of 66 kg and daily water consumption of 2L are used. The exposure assumptions for females represent that for the non pregnant women of reproductive age. For deriving the lifetime (chronic) HHBP, a body weight of 70 kg (general population) or 66 kg (females 13-49 years), and a daily water consumption of 2L (for both general population and females 13-49 years) are used. In deriving the benchmarks, alternate bodyweights and drinking water intake may be considered for certain specific life stages (e.g., infants, children, pregnant mothers) and these could be found in the 'Exposure factors handbook 2011 Edition'<sup>4</sup>. When there is a cancer concern for a pesticide that requires quantification and the linear approach is deemed appropriate, a CSF is assigned. Most pesticides do not have a CSF (e.g., non-carcinogens or threshold type carcinogens). In the case of threshold type carcinogens, the chronic RfDs (and calculated HHBPs) are considered protective of cancer effects because there is sufficient data for the chemical to show that carcinogenic effects are not likely to occur below this defined dose (i.e., RfD or HHBP). For complete details for each chemical, consult the supporting documentation link in the HHBP table.

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<sup>3</sup>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>.

<sup>4</sup>In deriving the benchmarks, alternate bodyweights and drinking water intake may be considered for certain specific life stages (e.g., infants, children, pregnant mothers) and these could be found in the 'Exposure Factors Handbook 2011 Edition' at <http://www.epa.gov/ncea/efh/pdfs/efh-complete.pdf>.

For pesticide registrations under FIFRA, if there are concerns identified for exposure and/or residual uncertainties for pre and/or post natal toxicity in the toxicity database, EPA derives acute or chronic population adjusted doses (PADs) using a FQPA Safety Factor mandated by the FQPA. 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. The HA methodology under SDWA does not include this factor. Therefore, HHBP values were calculated using RfDs, as they are for HAs. Pesticides for which an FQPA Safety Factor was applied to account for residual uncertainty during the pesticide registration process are identified in the HHBP table and footnotes are provided to indicate the magnitude of the factor applied (e.g., 3 or 10).

The 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 RfD 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 carcinogenic HHBPs.

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

$$\text{Acute or one-day HHBP (for children) (ppb)} = \frac{\text{aRfD mg/kg BW /day} \times 10 \text{ kg BW} \times 1000 \text{ (}\mu\text{g/mg)}}{1 \text{ L}}$$

$$\text{Acute or one-day HHBP (females 13-49 years) (ppb)} = \frac{\text{aRfD mg/kg BW /day} \times 66 \text{ kg BW} \times 1000 \text{ (}\mu\text{g/mg)}}{2 \text{ L}}$$

$$\text{Chronic non-cancer HHBP (general population) (ppb)} = \frac{\text{cRfD mg/kg BW /day} \times 70 \text{ kg BW} \times 1000 \text{ (}\mu\text{g/mg)} \times 0.2 \text{ (RSC)}}{2 \text{ L}}$$

$$\text{Chronic non-cancer HHBP (females 13-49 years) (ppb)} = \frac{\text{cRfD mg/kg BW /day} \times 66 \text{ kg BW} \times 1000 \text{ (}\mu\text{g/mg)} \times 0.2 \text{ (RSC)}}{2 \text{ L}}$$

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. EPA generally uses the linearized multistage model for its quantitative cancer risk assessment. 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<sup>2</sup>. 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<sup>-6</sup> to 10<sup>-4</sup> (1 in 1,000,000 to 1 in 10,000) cancer risk levels in water. The following formulae are applied to estimate the drinking water unit risk and subsequently, to derive the 10<sup>-6</sup> to 10<sup>-4</sup> cancer risk levels.

$$\text{Drinking Water Unit Risk } (\mu\text{g/L}^{-1} \text{ or ppb}) = \frac{\text{CSF (mg/kg-day)}^{-1} \times 2 \text{ (L/day) (Adult DW Intake)}}{70 \text{ (kg) (Adult BW)} \times 1000 \text{ } (\mu\text{g/mg)}}$$

From the drinking water unit risk, the following 10<sup>-6</sup> to 10<sup>-4</sup> cancer risk specific levels in water are determined.

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

For some carcinogens (e.g., threshold type carcinogens), an 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 <http://www.epa.gov/pesticides/hhbp>.

## For More Information

For more information regarding the derivation of HHBPs, contact Santhini Ramasamy in EPA's Office of Water at [ramasamy.santhini@epa.gov](mailto:ramasamy.santhini@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](mailto:may.brenda@epa.gov).

## Abbreviations

aRfD - Acute Reference Dose  
 BW – Body Weight  
 cRfD - chronic Reference Dose  
 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