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Screening-level Biomonitoring Equivalents for tiered interpretation of urinary 3-phenoxybenzoic acid (3-PBA) in a risk assessment context

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ABSTRACT

3-Phenoxybenzoic acid (3-PBA) is a common metabolite of several pyrethroid pesticides of differing potency and also occurs as a residue in foods resulting from environmental degradation of parent pyrethroid compounds. Thus, 3-PBA in urine is not a specific biomarker of exposure to a particular pyrethroid. However, an approach derived from the use of Biomonitoring Equivalents (BEs) can be used to estimate a conservative initial screening value for a tiered assessment of population data on 3-PBA in urine. A conservative generic urinary excretion fraction for 3-PBA was estimated from data for five pyrethroid compounds with human data. Estimated steady-state urinary 3-PBA concentrations associated with reference doses and acceptable daily intakes for each of the nine compounds ranged from 1.7 μg/L for cyhalothrin and deltamethrin to 520 μg/L for permethrin. The lower value can be used as a highly conservative Tier 1 screening value for assessment of population urinary 3-PBA data. A second tier screening value of 87 μg/L was derived based on weighting by relative exposure estimates for the different pyrethroid compounds, to be applied as part of the data evaluation process if biomonitoring data exceed the Tier 1 value. These BE values are most appropriately used to evaluate the central tendency of population biomarker concentration data in a risk assessment context. The provisional BEs were compared to available national biomonitoring data from the US and Canada.

1. Introduction

3-Phenoxybenzoic acid (3-PBA) has been included as a urinary analyte in the U.S. National Health and Nutrition Examination Survey (NHANES; CDC, 2009) and Canadian Health Measures Survey (CHMS; CHMS, 2010) biomonitoring programs, as well as other biomonitoring studies. 3-PBA is a shared metabolite of a number of commonly-used pyrethroid pesticides of differing structures and relative potency (Sudakin, 2006). In addition, it is possible that people may be exposed directly to 3-PBA (which is expected to be relatively non-toxic compared to the parent pyrethroid compounds) as a residue in foods resulting from environmental degradation of parent pyrethroid compounds (Erstfeld, 1999; George, 1985; Holmstead et al., 1978; Kaufman et al., 1977). Because of the non-specificity of urinary 3-PBA, no direct inference of exposure to a particular pyrethroid compound, much less estimation of the amount of exposure or comparison to risk assessment-based guidance values such as BEs, can be drawn based on measurement of urinary 3-PBA.

This analysis presents a tiered screening approach to the interpretation and assessment of urinary biomonitoring data for 3-phenoxybenzoic acid (3-PBA). This assessment is conducted using the basic concept of the Biomonitoring Equivalent (BE). BE values are estimates of the concentration of a chemical or its metabolite in blood or urine that corresponds to risk assessment-derived exposure guidance values such as reference doses or concentrations (RfDs or RfCs) or tolerable daily intakes (TDIs) (Hays et al., 2007, 2008; Angerer et al., 2011). BE values can be used as screening values for the assessment of biomonitoring data in order to provide an initial evaluation of whether the detected concentrations are well below, near, or above the concentrations corresponding to current exposure guidance values.

The conventional derivation and uses of BE values are not applicable to 3-PBA because it is a non-specific biomarker. However, available information can be used to construct a tiered approach to interpretation of urinary 3-PBA. The purpose of this report is to calculate and present estimates of Provisional BE values for 3-PBA for application in a tiered screening evaluation of urinary 3-PBA concentrations.

This report presents a description of the parent compounds metabolized to 3-PBA; an overview of information on the urinary excretion of 3-PBA; and a summary of current toxicity assessments for the parent pyrethroid compounds. These data are then used to estimate

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Provisional BE values for each parent pyrethroid compound under the assumption of constant steady-state exposure at the available exposure guidance values and similar initial metabolic behavior (hydrolysis of the main ester linkage) for all included compounds. The Tier 1 approach invokes the most conservative assumption by selection of the most stringent BE value from the set of estimates of pyrethroid-specific BE values as the Tier 1 Provisional BE. Estimated dietary exposure levels based on USDA pesticides residues and USEPA food commodity intake values are then used to estimate relative exposure weights for the individual pyrethroid compounds. These weights are then applied to the pyrethroid-specific BE values in order to estimate a Tier 2 Provisional BE value. The screening values presented here are not valid for interpretation of measurements of 3-PBA in individuals, but rather are appropriate for examination of population data in a screening context.

2. Methods

2.1. Chemical identification

Numerous pyrethroid compounds share 3-PBA as a common metabolite, resulting from cleaving of the compound molecules via hydrolysis at the ester linkage. We reviewed lists of currently registered pyrethroids in the U.S. to identify those that are known or likely to have 3-PBA as a metabolite (based on structure) (CDC, 2016; USEPA, 2011a). Chemical identification information for the identified parent pyrethroids and for 3-PBA are presented in Table 1. These molecules each have a two-part structure. Roughly one-half of the molecule contains the benzyl alcohol structural element leading to metabolic production of 3-PBA, while the other half of the molecule is a compound-specific molecular fragment joined to the 3-PBA unit by an ester linkage.

2.2. Identification of toxicity data and risk assessments

The pyrethroids have been the subject of extensive research with respect to the mechanisms of action for human and insect toxicity. In the U.S., the USEPA Office of Pesticide Programs requires toxicity testing and conducts periodic registration reviews which include review of toxicity data, selection of points of departure (PODs) and assignment of uncertainty factors in order to derive RfDs for a variety of populations and exposure routes/pathways. Internationally, the Joint Food and Agriculture Organization/World Health Organization Meeting on Pesticide Residues (JMPR) evaluates toxicity data and establishes Acceptable Daily Intakes (ADIs) for pesticides. The USEPA RfD and the JMPR ADI values for the pyrethroid compounds of interest were identified and tabulated.

Table 1
Chemical identification information for 3-PBA and for parent pyrethroid pesticides with 3-PBA as a common metabolite.

Biomarker or Parent Pyrethroid	CAS No.	MW
3-phenoxybenzoic acid	3739-38-6	214.22
Cyhalothrin (racemic)	68085-85-8	499.85
Lambda-cyhalothrin	91465-08-6	499.85
Gamma-cyhalothrin	76703-62-3	499.85
Permethrin	52645-53-1	391.28
Cypermethrin	52315-07-8	416.30
Deltamethrin	52918-63-5	505.21
Fenpropathrin	39515-41-8	349.42
Cyphenothrin	39515-40-7	375.46
Esfenvalerate	66230-04-4	419.90
Fluvalinate (racemic)	69409-94-5	502.91
Tau-fluvalinate	102851-06-9	502.91
d-Phenothrin	26002-80-2	350.45

2.3. Available pharmacokinetic data to support calculations

The BE approach as applied to urinary biomarkers relies upon estimates of urinary excretion fractions for the analyte of interest – in this case, 3-PBA. Urinary excretion fractions are defined here as estimates on a molar or mass basis of the fraction of administered dose that is recovered in urine. We conducted searches in PubMed, reviewed regulatory assessments, and conduced secondary retrieval from review of literature reference lists to identify studies that provide estimates of urinary excretion fractions for pyrethroid metabolites and evaluated the information for applicability across the pyrethroid class.

2.4. Derivation of urinary screening values

The biomarker of interest, urinary 3-PBA, dictates the general approach to the derivation of a screening value, which is the urinary mass balance approach, similar to that employed in previous chemical-specific assessments for compound-specific urinary biomarkers for the pyrethroids cyfluthrin and deltamethrin (Hays et al. 2009; Aylward et al., 2012). The parameters required for the approach are:

1. Target exposure guidance values such as TDIs or RfDs for each parent pyrethroid (reviewed above);
2. An estimate of the mass urinary excretion fraction in grams of 3-PBA excreted per day per gram of parent compound ingested. This fraction can be calculated from the molar excretion fraction and the relative molecular weight of 3-PBA compared to parent compound.
3. An estimate of average daily urinary volume per kg of body weight.

The metabolic reaction relevant to the production of 3-PBA-derived metabolites from all of the included parent compounds is the initial, rapid hydrolysis of the ester linkage between the two portions of the pyrethroid molecules (Fig. 1; ATSDR, 2003). Available human data confirms that this metabolic reaction occurs across the range of compounds examined (Table 4), and extrapolation of this reaction, at least qualitatively, across the full set of compounds would appear to be appropriate. This reaction can also occur in the course of environmental degradation, producing 3-PBA as a residue of multiple pyrethroids (Erstfeld, 1999; George, 1985; Holmstead et al., 1978; Kaufman et al., 1977).

The estimated molar urinary excretion fraction of 9% can be converted to a mass urinary excretion fraction for each pyrethroid based on the relative molecular weight of 3-PBA compared to each parent compound:

$$F_{UE,mass} = F_{UE,molar} * \frac{MW_{3PBA}}{MW_{parent}} \quad (1)$$

2.5. Estimation of compound-specific BE values

Average steady-state urinary concentrations of 3-PBA consistent with chronic exposure at a given exposure guidance value (RfD or ADI) can be calculated based on the mass-based urinary excretion fractions calculated with equation (1). On the basis of urinary concentration, the calculated BE value (C_i) for a given parent pyrethroid, i, is as follows:

$$C_i = \frac{(ADI_i \text{ or } RfD_i) \times F_{UE,\,mass,\,i}}{V_{24}} \quad (2)$$

where the ADI or RfD is entered in mg/kg-d and V_{24} is the average 24-h urinary volume rationalized to body weight (mL/kg-d). Parallel calculations normalized to daily creatinine excretion, or adjustment based on specific gravity or osmolality, are also possible, but the evaluation presented here is limited to concentrations on a urinary volume basis for the sake of simplicity. Issues associated with methods for hydration status adjustment are outside the scope of this evaluation but have been reviewed elsewhere (Barr et al., 2005; Yeh et al., 2015; Hays et al.,