Biomonitoring Equivalents for triclosan

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ABSTRACT

Recent efforts worldwide have resulted in a growing database of measured concentrations of chemicals in blood and urine samples taken from the general population. However, few tools exist to assist in the interpretation of the measured values in a health risk context. Biomonitoring Equivalents (BEs) are defined as the concentration or range of concentrations of a chemical or its metabolite(s) in a biological medium (blood, urine, or other medium) consistent with an existing health-based exposure guideline, and are derived by integrating available data on pharmacokinetics with existing chemical risk assessments. This study reviews available health-based exposure guidance values for triclosan based on recent evaluations from the United States Environmental Protection Agency (US EPA), the European Commission’s Scientific Committee on Consumer Products (EC SCCP) and the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS). BE values corresponding to the reference dose (RfD) or margin of safety (MOS) targets from these agencies were derived based on kinetic data (urinary excretion and plasma clearance) from human studies and measured blood concentration data in animal studies. Estimated BE values for urinary total triclosan (free plus conjugates) corresponding to the US EPA RfD and the EC-identified margin of safety target from the NOAEL are 6.4 and 2.6 mg/L, respectively (corresponding to 8.3 and 3.3 mg/g creatinine, respectively). Plasma BE values corresponding to the US EPA, EC, and Australian NICNAS values are 0.3, 0.9, and 0.4 mg/L, respectively. These values may be used as screening tools for evaluation of population biomonitoring data for triclosan in a risk assessment context.

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1. Introduction

Interpretation of measurements of concentrations of chemicals in samples of urine or blood from individuals in the general population is hampered by the general lack of screening criteria for evaluation of such biomonitoring data in a health risk context. Without such screening criteria, biomonitoring data can only be interpreted in terms of exposure trends, but cannot be used to evaluate which chemicals may be of concern in the context of current risk assessments. Such screening criteria would ideally be based on robust datasets relating potential adverse effects to biomarker concentrations in human populations (see, for example, the U.S. Centers for Disease Control and Prevention (CDC) blood lead level of concern; see http://www.cdc.gov/nceh/lead/). However, development of such epidemiologically-based screening criteria is a resource and time-intensive effort. As an interim approach, the development of Biomonitoring Equivalents (BEs)1 has been proposed, and guidelines for the derivation and communication of these values have been developed (Hays et al., 2007, 2008; LaKind et al., 2008).

A Biomonitoring Equivalent (BE) is defined as the concentration or range of concentrations of a chemical in a biological medium (blood, urine, or other medium) that is consistent with an existing health-based exposure guidance value such as a reference dose (RfD) or tolerable daily intake (TDI). BEs are estimated on the basis of existing chemical-specific pharmacokinetic data (animal or human) and the point of departure (e.g., NOAEL, LOAEL, BMD) used in the derivation of exposure guidance values (Hays et al., 2008).

1 Abbreviations used: BE, biomonitoring equivalent; BEPOD, biomonitoring equivalent point of departure; BMD, benchmark dose; BW, body weight; CAS, chemical abstracts services; EC, European Commission, LOAEL, lowest observed adverse effect level; MOE, margin of exposure; MOS, margin of safety; NHANES, National Health and Nutrition Examination Survey; NICNAS, National Industrial Chemicals Notification and Assessment Scheme; NOAEL, no observed adverse effect level; POD, point of departure; PK, pharmacokinetic; RED, re-registration eligibility decision; RfD, reference dose; SCCP, scientific committee on consumer products; TDI, tolerable daily intake; USEPA, United States Environmental Protection Agency.
BEs are intended for use as screening tools to allow an assessment of biomonitoring data to evaluate which chemicals have large, small, or no margins of safety compared to existing risk assessments and exposure guidance values. This document presents derivation of BEs for triclosan (Chemical Abstracts Services [CAS] Registry number 3380-34-5).

Triclosan (5-chloro-2-(2,4-dichlorophenoxy)phenol) is a lipophilic (measured log n-octanol:water partition coefficient = 4.8 (Ciba-Geigy (1990) cited by NICNAS (2009))), broad-spectrum anti-microbial agent that has found widespread use in a variety of personal care products including toothpaste, mouthwash, bar soap, deodorant, shower gel as well as skin-care and make-up products (Engelhaupt, 2007; McGinnis, 2008; EC, 2009). It is also used in consumer products such as textiles, toys and plastic kitchenware (e.g., Adolfsson-Erici et al., 2002; Bhargava and Leonard, 1996; Perencevich et al., 2001; Yazdankhah et al., 2006). There has been increased focus on the occurrence of triclosan in biological matrices of individuals without occupational exposures as well as on the evaluation of the potential for endocrine-disrupting effects (Crofton et al., 2007; Zorrilla et al., 2009). A number of human biomonitoring studies have reported the occurrence of triclosan in breast milk, urine and plasma (Calafat et al., 2008; Hovander et al., 2002; Dayan, 2007; Allmyr et al., 2008; Wolff et al., 2007; Sandborgh-Englund et al., 2006). The analyses of 2517 single spot urine samples as part of the National Health and Nutrition Examination Survey (NHANES: 2003-04) indicated that three-quarters of the samples contained triclosan (Calafat et al., 2008).

The present study focused on establishing BEs for triclosan based on the available data on point of departure (POD) and guideline values, as well as the pharmacokinetic information.

2. Available data and approach

2.1. Exposure guidance values, critical effects, and mode of action

Based on our review of information from US, Canadian, Australian and European sources, three recent risk assessments and evaluations for triclosans were found to be available. Of these assessments, that of the Australian government (NICNAS, 2009) identified a NOAEL of 41 µg/mL (corresponding to the steady-state plasma level of triclosan in rats administered 40 mg/kg/d) as a basis for estimating MOE based on measured plasma values in humans. In essence, a BE value based on a target minimal margin of exposure of 100 was derived in the NICNAS (2009) risk assessment. However, we have included this derivation in this article for completeness. The US EPA Office of Pesticide Programs completed a recent re-registration eligibility decision (RED) document for triclosan. In that review, they based the derivation of a chronic reference dose (RDI) on a chronic dietary study conducted in baboons with a no-observed-adverse-effect-level of 30 mg/kg/d and a composite uncertainty factor of 100 comprised of interspecies and intraspecies uncertainty factors of 10 each (USEPA, 2008a) (Table 1).

The European Commission (2009) also recently evaluated triclosan. In that review, the European Commission’s Scientific Committee on Consumer Products (SCCP) identified a point of departure (POD) (NOAEL of 12 mg/kg-d) from a well-conducted rodent chronic bioassay and recommended a target margin of safety (MOS) of 100. Based on this assessment, a target daily dose level analogous to a reference dose or tolerable daily intake can also be derived (Table 1).

The information on mode of action in mammals and associated relevant dose metrics is limited for triclosan. The mechanism of antibacterial action of triclosan has been reported to involve the inhibition of lipid synthesis by blocking the enoyl-acyl reductase enzyme (McMurty et al., 1998; Heath et al., 1999). Inhibition of fatty acid synthesis in parasites has also been documented (Surolia et al., 2001; Samuel et al., 2003). Further, it has been demonstrated that this chemical prevents bacterial cell growth and proliferation by interfering with the formation of new cell membranes (Levy et al., 1999). However, the relevance or ability of these mechanisms leading to adverse health effects in humans has not been demonstrated (Sullivan et al., 2003; Sandborgh-Englund et al., 2006).

In mammals, triclosan is reported to alter serum concentration of thyroxine (Crofton et al., 2007) and to interact with P450-dependent enzymes, UDP-glucuronosyltransferases and the human pregnane X receptor (Hanioka et al., 1996; Jacobs et al., 2005; Wang et al., 2004). The relevance for humans of these interactions and toxicological endpoints identified in animal studies is not known (Calafat et al., 2008; USEPA, 2008a; Allmyr et al., 2009; EC, 2009).

The effects identified at levels exceeding the NOAEL levels in the baboon study were relatively non-specific. At doses above the NOAEL in the baboon study, clinical signs of vomiting, failure to eat and diarrhea (Ciba-Geigy, 1977; USEPA, 2008a). The rat NOAEL was based on hematotoxicity as well as decreases in absolute and relative spleen weights; at higher doses, mild clinical chemistry and/or hematology changes, together with histopathological changes in the liver were reported (EC, 2009; Ciba-Geigy, 1986; NICNAS, 2009).

Even though there is no definitive information on the mode of action or relevant dose metrics for the triclosan-induced effects in rats and baboons, it would appear that the parent chemical is likely to be the toxic form, given that triclosan does not undergo oxidative metabolism or bioactivation reaction and has been documented to conjugate with UDP-glucuronic acid and sulfate (DeSalva et al., 1989). Thus, plasma concentrations of triclosan would appear to be relevant to potential toxicity.

2.2. Available pharmacokinetic data

The available data on the pharmacokinetics of triclosan in animals and humans exposed by various routes and vehicles have
been summarized by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) of Australia (2009) and EC (2009). Triclosan is extensively conjugated with UDP-glucuronic acid and sulfate, and excreted via urine or feces. In humans, urinary excretion is the principal route of elimination; however, in the rat, triclosan is preferentially eliminated via the fecal route. The following discussion focuses on data relevant to the derivation of BE values for triclosan.

DeSalva et al. (1989) summarized the pharmacokinetic data associated with the 2-year chronic dietary bioassay in the rat. Specifically, the concentrations of triclosan in blood, liver and kidney of treated animals were determined at 3, 6, 12, 18 and 24 months of treatment. The data indicate: (i) the attainment of steady-state during chronic exposure to triclosan, (ii) the predominance of conjugates rather than free form in the various matrices, and (iii) the proportionality of triclosan with exposure dose in humans. In humans, urinary excretion is the principal route of elimination; however, in the rat, triclosan is preferentially eliminated via the fecal route. The following discussion focuses on data relevant to the derivation of BE values for triclosan.

\[ C_V = \frac{D \times BW \times F_{UE}}{V} \] (1)

2.3. Potential biomarkers

Triclosan glucuronide is the major metabolite and urinary excretion is the principal route of elimination in humans. As such, the total triclosan in urine (conjugates + free form) has been used as biomarker of exposure (e.g., Calafat et al., 2008; NICNAS, 2009). The plasma (or blood) level of total triclosan is also a relevant marker, as determined in a 2-year toxicological bioassay (DeSalva et al., 1989). As with other biomonitoring efforts, collection of urinary samples is less invasive and more straightforward than collection of blood samples, but sampling of blood or plasma may provide a more toxicologically relevant measure of exposure.

3. BE derivation

The BE for triclosan should ideally correspond to a dose measure in a biological matrix that relates most closely to the mode of action, is reflective of the available pharmacokinetic (PK) data, and is based on the relationship between the biomarker and the relevant internal dose metrics. Triclosan in plasma is likely to be a relevant dose metric for prediction of toxicity, but is only found in very low levels. Urinary triclosan (conjugates + free form), on the other hand, exhibits greater uncertainty compared to plasma concentrations in its relation to tissue concentrations but it is still useful as a biomarker of exposure. Figs. 1, 2a and b, illustrate the approaches used for computing the BE for urinary and plasma triclosan, for the two PODs and associated guideline values identified for triclosan (Table 1).

### Table 2
Summary of urinary excretion data for triclosan in baboons and humans.

<table>
<thead>
<tr>
<th>Species</th>
<th>Study description</th>
<th>Excretion rate</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>–</td>
<td>44–57% of the oral dose was excreted within 48 h</td>
<td>Ciba-Geigy Limited (1976) from NICNAS (2009)</td>
</tr>
<tr>
<td>Human</td>
<td>Ten volunteers were orally exposed to a single dose (4 mg)</td>
<td>54% of the oral dose was excreted by 96 h</td>
<td>Sandborgh-Englund et al. (2006)</td>
</tr>
<tr>
<td>Baboons</td>
<td>Oral administration of approximately 5 mg/kg bw</td>
<td>53–60% was excreted in urine 20–30% was excreted in the feces after 144 h</td>
<td>Ciba-Geigy Limited (1977) from NICNAS (2009)</td>
</tr>
</tbody>
</table>

### 3.1. Urinary BE values

The existing data on elimination kinetics of triclosan (as parent compound or conjugated) suggest a simple mass-balance approach, with an assumption of steady-state intake and excretion, for derivation of BE values for urinary triclosan (Fig. 1). In this regard, the amount of triclosan excreted in urine every day will be approximately equal to the human-equivalent amount ingested times the urinary excretion fraction. The median of the estimated fraction of oral triclosan dose excreted via urine from ten individuals (54% at 48 h) obtained from Sandborgh-Englund et al. (2006) was combined with age-specific estimates of bodyweight and average 24-h urinary volumes (or average 24-h creatinine excretion) to provide an estimate of the 24-h average urinary concentration associated with a unit dose of triclosan per day (Table 3) for different age groups. No assessment values for children under age 6 were presented due to the lack of reliable data on urinary volume and creatinine excretion rates. Specifically, the estimated triclosan urinary concentration on a volume associated with a unit dose of triclosan for a specific population sub-group was calculated using the following formula:

\[ C_V = \frac{D \times BW \times F_{UE}}{V} \] (1)
where $C_V$ is the average urinary concentration on a volume basis of triclosan, $D$ is a unit dose of triclosan (1 μg/kg-d) as shown in Table 3, BW is the bodyweight for the group, $F_{UE}$ is the urinary excretion fraction, i.e., fraction of the applied dose excreted in the urine (0.54), and $V$ is the 24-h average urinary volume. Similarly, the creatinine-adjusted concentration associated with a unit dose of triclosan was calculated as follows:

$$C_C = \frac{D \times BW \times F_{UE}}{CE}$$  

(2)

where $C_C$ is the creatinine-adjusted 24-h urinary concentration of triclosan, and CE is the 24-h creatinine excretion rate. Data on urinary volume and creatinine excretion rates were drawn from a variety of studies (see footnotes to Table 3). It is relevant to note that $F_{UE}$ in Eqs. (1) and (2) above refers to the fraction of the dose appearing in the urine. It does not make any particular assumptions regarding bioavailability or absorbed fraction; rather it represents the ratio of the amount appearing in the urine in relation to the administered dose, based on actual data. The urinary concentrations of triclosan associated with a unit dose of triclosan ($D$) for the different age groups are presented in Table 3. Because the average concentrations associated with a unit dose of triclosan varied little across age and gender groups, the average across all age groups was estimated and carried forward in calculations. Using the estimates of the 24-h average urinary concentration associated with a unit dose of triclosan, the urinary concentrations (on both a volume and creatinine-adjusted basis) for the human-equivalent POD (original POD divided by the interspecies uncertainty factor) and guidance values listed in Table 1 were estimated and reported in Table 4.

3.2. Plasma BE values

For the guidance values described in Table 1, different approaches were used in the derivation of BE values for plasma concentrations based on the available datasets (see Figs. 2a and b). Because measured blood concentrations and estimates of corresponding plasma concentrations were available from the chronic rat bioassay used as the basis of the EC, 2009 risk assessment, we derived a BE starting directly from those measured data using the following approach (Fig. 2a):

(1) Estimate the steady-state plasma concentration in the experimental animals dosed at the POD based on data from the underlying study (DeSalva et al., 1989). Based on the values of blood concentration reported in Ciba-Geigy’s 2-year study in Sprague–Dawley rats (see DeSalva et al. 1989), the EC, 2009 converted the measured blood concentrations to an estimated average steady-state plasma concentration of 28.16 mg/L at the POD (Table 27 in EC, 2009). However, this value corresponds to the interim measured value for female rats (exposed at approximately 17 mg/kg-d), while the EC-identified NOAEL was set at the dose level for male rats (12 mg/kg-d). The corresponding interim estimated plasma concentration in male rats is 21.8 mg/L (Table 27, EC, 2009), and this value is used here for the BE derivation.

(2) Apply the pharmacodynamic component of the interspecies uncertainty factor (10^0.5) to derive estimated plasma concentrations for the human-equivalent BEPOD; and

(3) Apply the intraspecies uncertainty factor to the BEPOD to derive the BE.

A similar approach was used for the NICNAS (2009) risk assessment, except that risk assessment was based entirely on the measured plasma concentrations in rats in DeSalva et al. (1989), and explicitly specified a minimal margin of exposure 100 on a plasma concentration basis to identify a target plasma concentration. For the NOAEL of 30 mg/kg-d in the baboons identified by USEPA (2008a) as the POD, the plasma values associated with the BEPOD and BE were derived as follows (Fig. 2b):

(1) Apply the interspecies uncertainty factor to identify the human-equivalent POD on an external dose basis.

(2) Estimate the steady-state plasma concentration, $C_P$, in mg/L in humans associated with the human-equivalent POD (i.e., BEPOD) by dividing the daily dose, $D$, in mg/kg-d by the clearance, CL (plasma clearance normalized to the fraction of dose absorbed; 0.041 L/(h kg)), estimated by Sandborgh-Englund et al. (2006) according to this formula:

$$C_P = \frac{D}{CL \times 24}$$  

(3)

(3) Apply the intraspecies uncertainty factor to the BEPOD to derive the BE.
The derivation and the resulting values for both guidance values are summarized in Table 5.

4. Discussion

4.1. Sources of variability and uncertainty

The urinary and plasma BE values for triclosan derived in this evaluation were based on the average values of input parameters; however, the resulting values accounted for inter-individual variability by way of the use of uncertainty factors.

For the derivation of urinary BE values, the median urinary excretion fraction of 54% of an oral dose of triclosan reported by Sandborgh-Englund et al. (2006) was used. This value was obtained with 10 study subjects aged between 26 and 42 years (5 females and 5 males). The authors reported that the major fraction of triclosan was excreted within the first 24 h. The lower and upper quartile values of fraction excreted were 47% and 61% at 48 h; the individual values of the fraction excreted, however, varied from 24% to 83% after 4 days of exposure (median value = 54%) (Sandborgh-Englund et al., 2006). In other words, the ratio of the maximal to the median value of excretion fraction for triclosan was less than a factor of 2, or well within the inter-individual variability of

$$10^{0.5}$$ used in risk assessments (to represent PK variability), and this uncertainty factor component was retained in the derivation of the urinary BE values presented here. The intersubject variability in the excretion fraction might result from variation of bioavailability, distribution kinetics, metabolic clearance and/or fraction eliminated via renal clearance (Sandborgh-Englund et al., 2006). Additional sources of potential variation in measured urinary concentrations, even under conditions of exposure consistent with the RfD, include variations in hydration status and creatinine excretion rates, which could impact measured concentrations in spot urine sample. The appropriateness of adjustment for hydration status using creatinine excretion has been debated (Garde et al., 2004; Barr et al., 2005) because creatinine excretion also can vary substantially due to variations in dietary pattern as well as other individual factors (gender, age, muscle mass, seasonal and daily variation, diet) (Garde et al., 2004; Barr et al., 2005).

In the present work, BE values were estimated for triclosan on the basis of creatinine excretion as well as on the basis of urinary volume. Samples collected for a 24-h period would be expected to be influenced less than spot samples by both variations in hydration status and creatinine excretion. Even though the value of excretion fraction used in the calculations (54%) was based on a limited dataset from a human volunteer study (Sandborgh-Englund et al., 2006), this value is consistent with other available

| Table 3 |

Assumptions for average bodyweight, 24-h urinary volume, and 24-h creatinine excretion rate and estimates of creatinine-adjusted and volume-based urinary concentration per unit dose of triclosan (μg/kg-d) by age group (considering a urinary excretion fraction of 54%)².

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Bodyweight (kg)</th>
<th>Average 24 h urinary volume (L) (creatinine excretion, g)²</th>
<th>Triclosan urinary concentration per μg/kg-d steady-state dose (μg/L) (μg/g creatinine)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children, 6–11</td>
<td>32</td>
<td>0.66 (0.5)</td>
<td>26.2 (34.6)</td>
</tr>
<tr>
<td>Adolescents, 11–16</td>
<td>57</td>
<td>1.65 (1.2)</td>
<td>18.7 (25.7)</td>
</tr>
<tr>
<td>Men, &gt;16</td>
<td>70</td>
<td>1.7 (1.5)</td>
<td>22.2 (25.2)</td>
</tr>
<tr>
<td>Women, &gt;16</td>
<td>55</td>
<td>1.6 (1.2)</td>
<td>18.6 (24.8)</td>
</tr>
</tbody>
</table>

² Urinary excretion fraction of 54% from Sandborgh-Englund et al. (2006).

| Table 4 |

Derivation of BE values for triclosan urinary concentration (on a volume and creatinine-adjusted basis) consistent with the guideline values derived from USEPA (2008a) and EC (2009), according to the scheme presented in Fig. 1. Reported concentrations are the sum of both free and conjugated triclosan in urine.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Species, endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POD (NOAEL)² (mg/kg-d)</td>
<td>30</td>
<td>12</td>
</tr>
<tr>
<td>UF, interspecies</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Human-equivalent POD (mg/kg-d)</td>
<td>3</td>
<td>1.2</td>
</tr>
<tr>
<td>BCexp, mg/L in urine (mg/g creatinine)</td>
<td>64</td>
<td>26</td>
</tr>
<tr>
<td>UF, intraspecies</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>BE, mg/L in urine (mg/g creatinine)</td>
<td>6.4</td>
<td>2.6</td>
</tr>
</tbody>
</table>

² From Table 1.

b Estimated using the increments in urinary concentrations per unit of steady-state dose reported in Table 3.
information in the literature. In other human studies involving a single oral dose ranging from 5 to 200 mg, the average cumulative amount of triclosan excreted in 24-h urine corresponded to about 40%, with maximal percent approaching 60% in 4–6 days (DeSalva et al., 1989). The inter-individual coefficient of variation in urinary excretion fraction was on the order of 30% in dermal and oral exposure studies (Queckenberg et al., 2009), which is likely to be reflective of differences in rate and extent of absorption as well as metabolism and renal clearance.

The human plasma clearance data used in deriving the blood-based BE for triclosan (0.041 L/kg h, or 2.9 L/kg d) was also obtained from Sandborgh-Englund et al. (2006). In this study, the subject-specific values of clearance ranged from 0.032 to 0.049 L/h/kg, following a single oral dose of 4 mg/day (which was swallowed completely, contrary to 5–40% fraction swallowed under normal human usage of products containing triclosan – such as toothpaste) (reviewed in Sandborgh-Englund et al., 2006). The clearance values reported by Sandborgh-Englund et al. (2006) and used in the present study correspond to plasma clearance divided by the fraction of dose absorbed, and thus they incorporate variability in the extent of absorption in study subjects.

The available data do not support any age or gender related changes in the pharmacokinetics of triclosan. For example, the plasma half-lives in adults and children estimated in various studies using toothpaste, dental slurry capsules or aqueous solution were comparable, and ranged between 13.4 and 21 h (EC, 2009). The pharmacokinetic study of Sandborgh-Englund et al. (2006) did not find any consistent gender difference among adults, in either clearance or plasma half-life of triclosan.

Both the plasma- and urine-based BE values for triclosan were derived using clearance and excretion fraction data obtained in single oral dose studies of Sandborgh-Englund et al. (2006). Oral route is the route of exposure in the critical toxicity studies; furthermore, it is the most important route of human exposure to triclosan based on product use as well as the extent of absorption (Bagley and Lin, 2000; Moss et al., 2000; Allmyr et al., 2008; Queckenberg et al., 2009). The use of pharmacokinetic data from single dose studies would appear to be relevant since the dose-normalized AUC was similar for ingestion of triclosan following single or multiple exposures (EC, 2009). This is supported by the animal studies and repeated human exposure studies with toothpaste and soap use, which indicate that steady-state is reached after about 7–10 days (EC, 2009). Accordingly, the uncertainty associated with the use of the single oral dose human study of Sandborgh-Englund et al. (2006) for deriving BEs for triclosan would appear to be low.

For deriving BE associated with the EC (2009) assessment, in addition to the human clearance data from Sandborgh-Englund et al. (2006), an estimated steady-state plasma concentration of 21.8 mg/L in rats was used. This plasma concentration was obtained from EC (2009), based on the interim sacrifice data in male rats from the critical toxicological study. EC (2009) indicated that the plasma concentration at interim sacrifice was 21.8 (±9) and 28.1 (±12.9) mg/L in male and female rats respectively, whereas at terminal sacrifice it was 26.5 (±18) and 10.6 (±3.4) mg/L in female and male rats. These plasma concentrations were derived from the reported blood concentrations in the original study, based on volume adjustment (plasma = 40 ml/kg, blood = 64 ml/kg). Noting the loss of body weight towards the end of the 2-year rat study, EC (2009) used the estimated plasma values associated with the interim sacrifice. Given that the NOAEL in male rats of 12 mg/kg/d used in the EU assessment, we chose the corresponding plasma value of 21.8 mg/L (intram sacrifice value) as the basis for developing the BE, with its associated uncertainty as indicated above.

### 4.2. Confidence assessment

The guidelines for derivation of BE values (Hays et al., 2008) specify consideration of two main elements in the assessment of confidence in the derived BE values: robustness of the available pharmacokinetic data and models, and understanding of the relationship between the measured biomarker and the critical or relevant target tissue dose metric.

For urine-based BE, the cumulative fraction of 54% (at 96 h) used in the present study, based on data obtained in ten volunteers receiving a single oral dose of 4 mg (Sandborgh-Englund et al., 2006), is comparable to the observations (44–57% at 48 h) in a number of different clinical and preclinical studies summarized by DeSalva et al. (1989). However, the relevance of the total triclosan level in urine to the target tissue exposure to the toxic form of the chemical is not known. Thus, the assessment of the confidence level in the derived urinary BE values based on these two factors is as follows:

- **Robustness of pharmacokinetic data**: MEDIUM
- **Relevance of biomarker to relevant dose metrics**: LOW

The assessment of the confidence level associated with the plasma-based BE values is as follows:

- **Robustness of pharmacokinetic data**: MEDIUM
- **Relevance of biomarker to relevant dose metrics**: MEDIUM

This reflects the relevance of the blood or plasma level of triclosan to the toxic effects (reviewed in NICNAS, 2009); however it does not differentiate between the various forms of triclosan.

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### Table 5

Derivation of plasma BE values based on the USEPA (2008b) and EC (2009) risk assessments (Table 1) according to the schemes presented in Fig. 2a (for the EC and NICNAS risk assessments) and Fig. 2b (for the USEPA risk assessment).

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Species, endpoint</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POD (NOAEL), external dosea (mg/kg-d)</td>
<td>30</td>
<td>12</td>
<td>41</td>
<td>NA</td>
</tr>
<tr>
<td>POD (NOAEL), plasma concentrationb (mg/L)</td>
<td>2.5</td>
<td>10*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UF, interspecies</td>
<td>10</td>
<td>2.5*</td>
<td>10*</td>
<td></td>
</tr>
<tr>
<td>Human-equivalent POD, external dose (mg/kg-d)</td>
<td>3</td>
<td>8.7</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>BE_POD, plasma concentration (mg/L)</td>
<td>3.0</td>
<td>10</td>
<td>10*</td>
<td></td>
</tr>
<tr>
<td>UF, intraspecies</td>
<td>10</td>
<td>10</td>
<td>10*</td>
<td></td>
</tr>
<tr>
<td>BE, plasma concentration (mg/L)</td>
<td>0.3</td>
<td>0.9</td>
<td>0.4</td>
<td></td>
</tr>
</tbody>
</table>

a From Table 1.
b From DeSalva et al. (1989) as reported by EC (2009).
c Estimated using Eq. (3) and median clearance rate measured by Sandborgh-Englund et al. (2006).
d Because a relevant internal dose metric is used here, the pharmacokinetic component of the interspecies uncertainty factor is set to 1. We have retained the pharmacodynamic component of the interspecies uncertainty factor (2.5, according to WHO (1999); guidance used in EC risk assessments).
e Specified value on a plasma concentration basis in the NICNAS risk assessment.
The BE values presented here represent estimates of the 24-h average concentrations of triclosan in urine that are consistent with the existing exposure guidance values resulting from the risk assessments conducted by various governmental agencies as listed in Table 1. These BE values were derived based on current understanding of the pharmacokinetic properties of these compounds in humans. These BE values should be regarded as interim screening values that can be updated or replaced if the exposure guidance values are updated or if the scientific and regulatory communities develop additional data on acceptable or tolerable concentrations in human biological media.

The appropriate uses and limitations of BE values have been discussed previously (Aylward and Hays, 2008; Hays and Aylward, 2008; Hays et al., 2008). These BE values can be used as a screening tool to evaluation population- or cohort-based biomonitoring data in the context of existing risk assessments. Concentrations in excess of the BE values, but less than the BEPOD values represent medium priority for risk assessment follow-up, while those in excess of the BEPOD indicate high priority for risk assessment follow-up. Based on the results of such comparisons, an evaluation can be made of the need for additional studies on exposure pathways, potential health effects, other aspects affecting exposure or risk, or other risk management activities.

BE values do not represent diagnostic criteria and cannot be used to evaluate the likelihood of an adverse health effect in an individual or even among a population. Measured values in excess of the identified BE values may indicate exposures at or above the current exposure guidance values that are the basis of the BE derivations. However, as discussed above, measured concentrations above the BE values, which are based on 24-h average urinary concentrations, would be expected even if exposures do not exceed the exposure guidance values due to the transient concentration profiles in urine expected for these compounds, variations in hydration status, and other factors discussed further above. Thus, interpretation of data for individuals or of tails of the distribution in population-monitoring studies is not appropriate.

In addition, the exposure guidance values for triclosan were derived with a substantial margin from doses that resulted in no observed effect in the most sensitive animal toxicity studies. Thus, these values are not “bright lines” that distinguish safe from unsafe exposure levels. Chronic exposure guidance values are set at exposure levels that are expected to be protective over a lifetime of exposure. For short-lived compounds such as triclosan, an exceedance of the corresponding BE value in a single urine sample may or may not reflect continuing elevated exposure. As demonstrated in the limited available datasets and based on the kinetics of urinary elimination, spot urinary concentrations may vary substantially both within and across days in an individual. Thus, occasional exceedances of the BE value in individuals in cross-sectional studies do not imply that adverse health effects are likely to occur, but can serve as an indicator of relative priority for further risk assessment follow-up. Further discussion of interpretation and communication aspects of the BE values is presented in LaKind et al. (2008) and at www.biomonitoringequivalents.net.

### 5. Conflict of interest statement

The authors declare they have no conflicts of interest.

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