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The contribution of dermal exposure to the internal exposure of bisphenol A in man

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ABSTRACT

New findings on Bisphenol A (BPA) contents in thermal printing papers, and receipts, in g/kg concentrations and on its dermal uptake (up to 60%) prompted us to assess the risk arising from dermal exposure. Using physiologically based toxicokinetic modelling, we simulated concentrations in blood, in liver and kidney, the target organs exhibiting the lowest no observed adverse effect levels (NOAEL). By comparing organ concentrations at the dose level of the NOAEL divided by a safety factor of 100 (liver: 50 μg/kg/day; kidney: 500 μg/kg/day), with concentrations arising from the dermal dose of 0.97 μg/kg/day (worst case assumption by Biedermann et al., 2010) this dermal exposure can be assumed safe.

Additionally, based on the model simulations the high blood concentrations, reported earlier in the literature, are highly improbable because the related exposure levels are orders of magnitude higher than the currently estimated aggregate exposure levels.

1. Introduction

Bisphenol A (BPA) is an industrial chemical which in its monomeric form is widely used in the production of epoxy resins and polycarbonate plastics (EU, 2008; EFSA, 2006). Human exposure is via food and beverages which have been in contact with polycarbonate plastic materials, via polycarbonate tableware and by indirect exposure via the environment from emissions of BPA production plants. The extent of oral exposure resulting from food intake has been estimated by EFSA (2006) and EU (2008) for the European situation and by FAO/WHO at the international level (FAO/WHO, 2010) (see Table 1). As an additional source of exposure, in the EU risk assessment report (EU, 2003) the BPA content in kitchen rolls was explored. It ranged from 0.55 to 24.1 mg/kg (0.000055–0.00241%) in recycled papers whereas extracts from the majority of virgin papers contained negligible or no BPA with one sample having levels of 0.12 mg/kg (0.000012%) (EU, 2003). Because of the low extent of external exposure the results were not taken into consideration for the EU risk assessment. Recently, data have been published showing high concentrations of BPA in thermal printing papers (Mendum et al., 2010) and products made from thermal printing paper such as receipts, car park tickets, queue tickets, ATM receipts, lottery slips, and plane, train and bus tickets (Biedermann et al., 2010; Östberg and Noaksson, 2010). For example, 11 of 13 samples analyzed by Biedermann et al. (2010) contained 8–17 g/kg (0.8–1.7%) BPA. In the Swedish investigation, the average level of receipt and receipt-like papers amounted to 1.4% and 1.6%. Of these thermal papers, car park tickets and bus tickets were notable for levels as high as 3.2% and 2.3%, respectively.

The data of Biedermann et al. (2010) show that BPA is not only present in thermal printing papers but that BPA is taken up on the surface of the fingers when receipts are handled by the cashier and the customer. BPA is absorbed through skin. The published data vary between 10% (EU, 2003; Kaddar et al., 2008; Mørck et al., 2010) and 46% (Zalko et al., 2011). The data of Biedermann et al. (2010) might indicate an even higher extent of absorption of 60%. BPA is metabolised in human skin (Zalko et al., 2011). However, the extent of this "first pass" metabolism is lower than after oral absorption (Mielke and Gundert-Remy, 2009).

In humans, BPA is eliminated as phase II metabolites which are excreted in the urine (overview, see Hengstler et al., 2011). Hence, urinary biomonitoring data of BPA plus its metabolites provide an estimate of the cumulative exposure via all routes of exposure. In several studies, human exposure has been estimated using spot urine data from various populations (Völkel et al., 2008). Given the short half life of BPA (overview, see Hengstler et al., 2011) spot urine data have some disadvantages and 24 h urinary sampling data would provide more reliable estimates for a single individual. However, assuming that the urinary samples were taken randomly over the day, the results from nearly 4000 individuals worldwide can be seen as the urinary excretion at different sampling time points

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Table 1
BPA exposure by food. Dietary exposure estimates (μg/kg bw per day) by different agencies and regions.

	Mean exposure (μg/kg/day)	High estimate (μg/kg/day)
EFSA (2006)		1.45[a]
EU (2008)		1.5[b]
FAO/WHO (2010)	0.4–1.4[c]	1.0–4.2 (95th percentile)

[a] 1 kg of canned foods and 2 l of canned beverages, 60 kg body weight plus 0.25 μg/kg/day from polycarbonate plastic tableware.
[b] 0.8 μg/kg/day from canned food, 0.3 μg/kg/day from beverages. 0.17 μg/kg/day from wine plus 0.25 μg/kg/day from polycarbonate plastic tableware.
[c] Worst case is assuming the daily consumption of 100% packaged food, and the best case is assuming the daily consumption of 25% packaged food. Because of the use of the budget method model, maximum consumption is reported in these upper range of exposure estimates.

in the population and thus giving some estimates of the exposure in the population (overview, see Hengstler et al., 2011). Braun et al. (2011) reported that in the subgroup of cashiers, subjects with high skin contact with BPA containing material, higher urinary excretion of BPA was measured as compared to the other participants of the study. This is an indication that BPA can be absorbed through the skin and after entering the body be excreted in the urine.

Recently, we simulated the blood concentration of the parent compound BPA after oral exposure at levels estimated by EFSA (2006) and EU (2008) as well as at levels taken from urinary biomonitoring data (Mielke and Gundert-Remy, 2009). In this paper, we use newly available information on dermal exposure and dermal absorption. We simulate the concentration of the parent compound BPA in blood and liver, the organ with the lowest no-observed adverse effect level (NOAEL) and in the kidney with the next lowest NOAEL from oral studies (Tyl et al., 2002, 2008). We also calculate external doses which would lead to blood/plasma/serum BPA concentrations measured by various authors. The results enable discussion of possible health effects related to the simulated concentrations taking into account the dermal exposure route and liver as the target organ for the derivation of TDI. They also allow conclusions on the safety of dermal exposure considering effects on organs other than liver. The plausibility of BPA plasma concentrations reported in the literature is re-evaluated in the light of dermal exposure.

2. Methods

2.1. PBPK model

The physiologically based human model previously published and validated using human experimental data was used to simulate the plasma concentration of unchanged BPA (parent compound) (Mielke and Gundert-Remy, 2009). The model was modified to include absorption through skin.

2.2. Parameters

Excretion was modelled by metabolism in the liver to glucuronides and sulphate conjugated metabolites (Fig. 1). The relevant metabolic parameters for the glucuronidation pathway, K_m and V_{max}, were taken from Kuester and Sipes (2007) who specifically investigated the parameters in human liver cells. In the original model the sulfation pathway was modelled such that its capacity in the adult is 15% of the glucuronidation pathway based on urinary excretion data. This model assumption was refined in the model used here by newly available experimental data on in vitro BPA metabolism in human liver cell indicating that the contribution of the sulphate pathway is 7.4% of the total intrinsic hepatic clearance (Kurebayashi et al., 2010). Oral absorption was assumed to be 90% estimated from the data of Völkel et al. (2002, 2005) who reported urinary recovery of 97% in males and 84% in females, after oral intake in human volunteers. Newly available data showed that the extent of first pass by the intestine is 1.2% of that of the liver as measured by unbound internal clearance (Mazur et al., 2010). This information is in line with the general information that activities in the gastrointestinal tract are typically less than

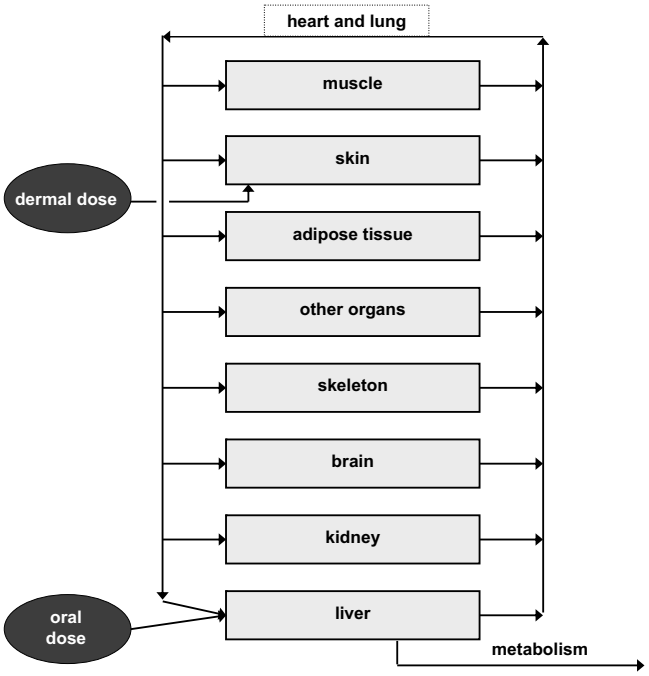

Fig. 1. Structural model.

10% of the hepatic activity (Fisher et al., 2001; Soars et al., 2002). Because of the low value of the first pass by the intestinal wall we decided not to change the previously used model which was modelled without implementing intestinal first pass.

2.3. Dermal exposure simulation

Newly available data on dermal absorption is reported by several authors and values of 10% (EU, 2003), 13% (Mørck et al., 2010), 46% (Zalko et al., 2011) and 60% (Biedermann et al., 2010) have been published. As the available information in the publications was not detailed we could not decide whether the high extent of absorption through skin (46% and 60%) is an artefact of impaired skin integrity in the in vitro model. However, there are data showing that absorption of substances through skin can be high. For example, dermal absorption of coumarin can vary between 60% (coumarin in 70% ethanolic solution in vivo), 64% (coumarin in 70% ethanolic solution in vitro) and 97% (oil/water emulsion of coumarin in vitro) depending on the vehicle and the experimental conditions applied (Beckley-Kartey et al., 1997; Yourick and Bronaugh, 1997; Ford et al., 2001). Hence we decided to use all reported values for simulation of internal concentrations of parent compound. Dermal BPA metabolism presented in the paper of Zalko et al. (2011) was not implemented in the model because the extent of metabolism to inactive BPA–glucuronide and –sulphate was only 2% within the first 24 h the time in which 90% of the dermal dose is absorbed.

Oral absorption half-life was assumed to be 15 min as maximum urinary concentrations of labelled BPA were observed at roughly 1 h (Tsukioka et al., 2004) and after oral administration of 5 mg d16-bisphenol A plasma concentrations of the metabolite, BPA–glucuronide, peaked at 80 min (Völkel et al., 2002). Dermal absorption half-life was estimated to be 8 h taken from the information in the paper of Biedermann et al. (2010) where a total external exposure of 71 μg is calculated from which 41 μg are absorbed within 12 h.

The values used to parameterise the model are given in Table 2.

2.4. Exposure scenarios

We simulated concentrations in blood, liver and kidney after dermal intake of a daily dose of 71 μg/day (0.97 μg/kg/day) as estimated by Biedermann et al. (2010) with varying extent of absorption (10%, EU, 2003; 13%, Mørck et al., 2010; 46% Zalko et al., 2011; and 60%; Biedermann et al., 2010) and derived the corresponding areas under the concentration time curve (AUCs) and peak concentrations (C_{max}).

For comparison we modelled the concentrations in blood, liver and kidney after oral intake of the dose of 71 μg/day (0.97 μg/kg/day) as three divided doses over 12 h which is the same as the dermal dose. We did the same with a daily oral dose of 0.05 mg/kg/day (50 μg/kg/day) which is the TDI, based on an oral NOAEL of 5 mg/kg/day with liver as the target organ (EFSA, 2006). We also simulated data after oral exposure by 500 μg/kg/day. This dose is derived from the next lowest NOAEL with the kidney as the target organ in which after doses higher than 50 mg/kg/day minimal to mild nephropathy was observed (Tyl et al., 2008).