Physiological Modeling Prediction of Equivalent Skin Burdens from Oral and Transdermal Doses of TCDD

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Introduction

Computer models of absorption, distribution, and metabolic clearance have been successful in describing the disposition of TCDD in orally dosed rodents.[1, 2] Adding representations of the biochemical consequences of TCDD delivery to tissues permits replication of the observed responses and their extrapolation to other doses. The utility of such models for interpretation of experimental results and assessment of risks to health from chronic exposure is enhanced by increasing biological realism in the representations of the animal's physiology and biochemical responses to TCDD.[3]

Physiological modeling is also useful in the design of experiments. The Tg.AC transgenic mouse, which carries a v-Ha-*ras* construct, develops high incidences of skin papillomas and carcinomas after 26 weeks of dermal exposure to a number of mutagenic and nonmutagenic tumor promoters.[4] As mice develop tumors following oral[5] and dermal[6] doses of TCDD, a study comparing the induction of skin tumors in Tg.AC mice by oral and dermal administration could clarify whether systemic exposure entails a risk of skin cancer or if that end point is a local response at the site of dermal application.

Methods

A previously constructed model of TCDD disposition in the rat[2] was described in the SCoP simulation language.[7, 8] This model included first-order absorption from the gut (the rate constant was scaled by (body weight)$^{0.75}$), reversible binding of TCDD to serum proteins, diffusion-limited distribution to tissues, TCDD-dependent increase in the maximal binding capacity of the Ah receptor, Ah receptor-mediated induction of the TCDD-binding protein CYP1A2, and Hill kinetics for hepatic metabolism of TCDD. The model also accounts for loss of TCDD from the liver consequent to cytotoxicity resulting from chronic exposure. This model was converted into a model for the mouse by replacing the physiological parameter values (tissue volumes and perfusion rates) with those for the mouse,[9] and other parameter values (see below) were estimated from the observed tissue TCDD distributions in orally dosed mice.[10] Bile and urine flow and GI tract transit rates were obtained from the literature[11] to represent excretion of metabolite(s) and unabsorbed gut lumen TCDD. The fat:blood partition coefficient was adjusted to 10 times the liver value.[12] Other partition coefficients and tissue permeabilities were unchanged.

As CYP1A2 is maximally induced to a four-fold higher concentration in mice than in rats,[10] the apparent K_m and V_{max} of induction in the rat model were adjusted to reflect this difference. In order to avoid over-prediction of hepatic TCDD at the highest doses, an inhibitory DNA binding site for the Ah-TCDD complex had to be assumed. The binding affinity of CYP1A2 for TCDD was adjusted to reproduce the observed ratio of liver:fat concentrations in mice given repeated oral doses 5 days/week for 90 days. The whole-body half-life of TCDD in mice is half of that in rats. The maximal rate of hepatic metabolism of TCDD was scaled to reproduce this lower half-life.

A variant of the above mouse model was created to represent dermal absorption of topically applied TCDD. The dose was painted on a 2 cm-square region on the mouse's back, accounting for 13% of the body surface, and a variable for TCDD at this site was added to the model. A pseudofirst-order rate constant for uptake into the skin at the site of application was estimated from experimental data[13] by formal optimization. TCDD at that site was treated as partitioning into the blood and distributed to the rest of the body. The skin:blood partition coefficient was estimated as twice that of rapidly perfused tissues.[14] The remaining parameter values were the same as in the oral dosing model.

Results and Discussion

The rate of hepatic induction of CYP1A2 was represented by the equation

$$v_{induction} = \frac{V_{\max}^{induction}}{\left(K_m / Ah.TCDD + 1\right) \cdot \left(Ah.TCDD / K_i + 1\right)}$$

where K_m and K_i are 5.5 and 8.5 nM, respectively, and the maximal induction rate is 19.3 nmole/g/day. The TCDD binding affinity of CYP1A2 was estimated as 0.2 □M. The maximal rate of TCDD metabolism was calculated to be 13.2 pmole/g/day. The optimal rate constant for absorption of topically applied TCDD into the adjacent skin was 0.067 day^{-1}.

These values produced the liver:fat concentration ratios in Table 1 for female $B6C3F_1$ mice given TCDD orally 5 days/week for 90 days.

Table 1. Liver:fat Concentration Ratios Following 90 Days Oral Dosing 5 Days/Week

Dose, ng/kg	Calculated Ratio	Observed Ratio[10]
1.5	0.45	0.37
4.5	0.46	0.50
15.0	0.58	1.3
45.0	1.1	2.2
150.0	2.9	2.5

The oral and skin dosing models were run with trial values of the applied dose to find those doses given by each route that would result in similar concentrations of TCDD delivered to the skin by the circulation of the blood. The results for oral and skin doses are given in Table 2 and Table 3, respectively. The doses in these tables are those that were actually used in the experiments.[15] Local skin is at the site of application; remote skin is tissue not adjacent to the applied TCDD. As remote skin is computed to achieve comparable burdens of TCDD by the two

routes, the mice in the cancer study were given oral doses in the range 0–1250 ng/kg or topical skin doses of 0–760 ng/kg to achieve comparable TCDD burdens in the skin from systemic delivery.

Table 2. Computed Tissue Concentrations (pmole/g) of TCDD Following Oral Gavage 5 Days/Week for 26 Weeks

Dose, ng/kg	Blood	Liver	Fat	Skin
105	0.0926	6.82	7.66	3.67
450	1.41	75.2	106	54.9
1250	6.62	224	498	255

The model predicts comparable skin TCDD burdens (at the site of application for skin dosing) at 105 and 5 ng/kg, 450 and 36 ng/kg, and 1250 and 166 ng/kg for oral and dermal doses, respectively. The disparity in the TCDD burdens of other tissues indicates that local skin is not in systemic equilibrium. For example, the computed liver TCDD burden is comparable at an oral and skin doses of 105 and 166 ng/kg, respectively.

Table 3. Computed Tissue Concentrations (pmole/g) of TCDD Following Topical Skin Application 3 Days/Week for 26 Weeks

Dose, ng/kg	Blood	Liver	Fat	Local Skin	Remote Skin
5	0.0186	0.0596	0.172	7.58	0.0823
17	0.0268	0.229	0.581	25.8	0.282
36	0.0379	0.612	1.25	54.7	0.616
76	0.0620	1.98	2.77	116	1.40
121	0.0932	4.60	4.70	184	2.44
166	0.130	8.36	6.90	253	3.67
355	0.374	31.3	20.2	546	11.7
760	1.42	85.7	76.5	1190	46.9

CYP1A2 is maximally induced in the liver at all three oral doses, but a topical dose of at least 166 ng/kg is required to reach the same level of induction.[15] The model predicts a liver concentration of this enzyme of 5.3 nmole/g at an oral dose of 105 ng/kg and 5.0 nmole/g at a skin dose of 166 ng/kg. These responses arise from similar computed concentrations of the hepatic Ah–TCDD complex—1.25 and 1.34 pmole/g for oral and skin dosing, respectively—and suggest the possibility that liver tumors might result after longer exposures. The successful conversion of an oral-dosing rat model to a skin-dosing mouse model demonstrates the utility of PBPK models for predicting responses across species, organs, and routes of exposure.

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