EFFECTS OF EXPOSURE ROUTE ON ABSORPTION, DISTRIBUTION, AND ELIMINATION OF ^{3}H-TCDD IN RATS

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Polychlorinated dibenzo-*p*-dioxins (PCDDs) and polychlorinated dibenzofurans (PCDFs) are ubiquitous environmental contaminants. Whereas human exposure to these compounds in the general population occurs mainly through the food chain, workers involved in the production, use, or destruction of materials containing these compounds or their precursors may receive relatively high exposures. In addition, high exposures have occurred through industrial accidents (e.g. Seveso, Italy in 1976) and improper disposal of industrial waste (e.g. Times Beach Missouri, 1982). For these higher risk sub-populations, inhalation and dermal routes of exposure are of primary concern. In evaluating human health risks to dioxin, it is necessary to effectively predict tissue levels consequent to exposure by all important routes. Route-to-route extrapolation may aid such predictions only if it is based upon sound understanding of the relationships between the various routes for the compound of interest or analogues. Therefore, the key issues of absorption across the lung, gut, and skin barriers in the body as well as the effects of route of entry on distribution and excretion must be addressed.

The objective of this study was to quantitate systemic absorption of an equimolar dose of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) through the lung and gut by comparing pulmonary and oral absorption to a completely absorbed intravenous dose. These results were then compared to results from a previous study in our laboratory evaluating dermal absorption of an equimolar

dose[1]. The approach of the present study was to administer ^{3}H-TCDD by intracheal instillation (it), by oral gavage (po), or by intravenous injection (iv) to male Fischer 344 rats and to follow disposition for three days after dosing. Intratracheal instillation was used as a surrogate for inhalation, allowing accurate determination of the delivered dose to the lung. Absorption, tissue distribution, and elimination of TCDD following exposure by different routes were then compared.

Non-labelled TCDD was obtained from Chemsyn Science Laboratories (Lenexa, KS) with a chemical purity of 98% by GC/MS. [1,6-^{3}H]-TCDD was synthesized by Chemsyn Science Laboratories (Lenexa, KS) with a chemical purity of ≥98% by HPLC and a specific activity of 39 Ci/mmole. The dose for all treatment groups was 1 nmol/kg (0.32 μg/kg) in an aqueous solution of 1:1:3::Emulphor®:ethanol:water. The treatment groups included intratracheal instillation, gavage, and intravenous injection; dosing volumes were 1, 5, and 1 ml/kg, respectively.

Male Fischer 344 rats (Charles River Breeding Labs, Raleigh, NC) were ~3 months old (~250 gms); three or four rats were used for each treatment group. Animals were housed four days prior to dosing in individual metabolism cages, provided food and water *ad libitum*, and maintained at constant temperature and humidity. After dosing, rats were returned to their metabolism cages and housed for 3 days; urine and feces were collected daily. At 72 hours after treatment, animals were euthanized by CO_2 asphyxiation and tissues were collected. Tissues and excreta were analyzed for total radioactivity.

Three days after iv, it, and po dosing, elimination of TCDD-derived radioactivity was 19, 25, and 33% in feces and 2.2, 1.3, and 1.4% in urine, respectively. For all routes approximately 4% of the dose was excreted in the feces by day 3. An additional 2% of the dose was found in the large intestinal contents, indicative of the amount to be excreted by day 4 in the feces. The absorbed dose (it, po) was defined as 100% minus (% total intratracheal or oral dose in feces on day 1 and 2 minus % total intravenous dose in feces on day 1 and 2). Transpulmonary (it) absorption was ~94% while oral absorption was ~86%; in our previous study, dermal absorption was ~40%[1].

For all routes major tissue depots for TCDD-derived radioactivity were liver and adipose tissue, with skin and muscle as secondary depots. Liver to adipose tissue ratios of total dose per gram of tissue for iv, it, and po exposures were 5.6, 6.8, and 3.0, respectively. Liver to adipose tissue ratios of total dose per organ for iv, it, and po were 1.8, 2.3, and 0.9, respectively. The body burden was defined as 100% minus (% total dose excreted in feces and urine). The body burdens at 3 days post dosing for iv, it, po, and dermal exposures were approximately 79, 75, 66, and 79%, respectively. Intravenously and intracheally treated rats had ~47 and 44% of the

absorbed dose body burden in liver and ~26 and ~19% in adipose tissue; oral exposure resulted in a shift to ~37% in liver and ~42% in adipose tissue. Dermally treated rats, by contrast, had ~57% and ~24% of the body burden in liver and adipose tissue, respectively[1].

This study quantitated pulmonary and oral absorption of an equimolar dose of TCDD. Pulmonary (it) absorption of TCDD was nearly complete--as compared to intravenous injection--and was slightly greater than oral absorption; dermal absorption appears to be about half that of oral absorption. These results for the absorption disposition of TCDD from an aqueous solution (it and po) or as neat compound (dermal) may be compared with previous studies for absorption of TCDD from mixtures or matrices. Pulmonary absorption of TCDD from TCDD-contaminated gallium oxide particles, as measured by hepatic enzyme induction, appears comparable to our results for pulmonary absorption of TCDD from an aqueous dosing solution--as measured by tissue levels of TCDD-derived radioactivity[2]. Other studies have indicated that matrix can modulate absorption by oral and dermal routes; oral and dermal bioavailability of TCDD from environmentally contaminated soil particles collected from different sites appears to be much less than TCDD bioavailability in our studies using aqueous (po) and neat (dermal) preparations [3,4,5,6]. Thus, bioavailability of dioxins depends not only on route of exposure but also on the exposure medium.

In conclusion, oral, pulmonary, and - to a lesser extent - dermal routes must all be considered as important routes of systemic exposure to TCDD, although in each case risk may be attenuated by specific conditions of exposure (e.g. matrix, duration). Moreover, the similarity in disposition of TCDD following absorption by the various routes suggests an assumption of additive body burden. Given that many environmental exposures occur by more than one route, this may be of particular importance to the assessment of human health risk resulting from exposure to TCDD and related compounds.
(This abstract does not necessarily reflect EPA policy.)

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