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ScienceDirect
Regulatory Toxicology and Pharmacology 49 (2007) 195–202
Regulatory Toxicology and Pharmacology
www.elsevier.com/locate/yrtph

Combining perfluoroalkane acid exposure levels for risk assessment

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Received 15 June 2007
Available online 24 August 2007

Abstract

Perfluoroalkane acids are present in biologic samples from >90% of people in the developed world. Because people may be exposed to multiple perfluoroalkane acids, it is reasonable to consider whether the exposure levels of these agents can be combined for risk assessment purposes. To investigate this possibility, we considered whether the literature on perfluoroalkane acids could be used to justify a scaling system analogous to the Toxic Equivalency Factor (TEF) system used for polychlorinated biphenyls, polychlorinated dibenzo-*p*-dioxins, and polychorinated dibenzofurans. We evaluated pairs of studies performed with different perfluoroalkane acids in the same species using the same design and found that endpoints for perfluorooctanesulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorobutanesulfonate (PFBS), and perfluorodecanoic acid (PFDA) could be discordant. We evaluated pairs of rat studies of PFOS, PFOA, and PFBS performed with the same design for which dose–response curves could be modeled for the concordant endpoints, but we were unable to identify a scaling system that gave values consistently within an order of magnitude for the same compounds. Currently available data do not support the combining of exposure levels of perfluoroalkane acids for risk assessment, although re-evaluation after additional data are available is recommended.
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Keywords: Perfluoroalkane acids; Perfluorooctanesulfonate; PFOS; Perfluorooctanoic acid; PFOA; Perfluorobutanesulfonate; PFBS; Perfluorodecanoic acid; PFDA; Toxic equivalency factors; Risk assessment

1. Introduction

Perfluorinated chemicals are present in the environment as a result of their use in a number of commercial applications. Some of these compounds have been found in the majority of blood samples tested in the US National Health and Nutrition Examination Survey (NHANES) (Calafat et al., 2006, 2007), in Washington County, MD (Olsen et al., 2005), in elderly subjects in Seattle, Washington (Olsen et al., 2004), and in American Red Cross blood donors (Olsen et al., 2003). Donated blood in South America, Europe, and Asia demonstrated detectable concentrations of perfluorinated chemicals in many samples, although the proportion of positive samples appeared lower in developing than developed countries (Kannan et al., 2004).

The elimination half-lives of two perfluorinated alkane acids, perfluorooctanoic acid (PFOA) and perfluorooctanesulfonate (PFOS), have been estimated from worker studies to be on the order of 4–5 years (Olsen et al., 2007). The apparent ubiquitous exposure to these compounds in developed countries and the long half-life have produced concern that continued environmental exposures may be associated with adverse effects on health.

Studies in experimental animals with some perfluorinated alkane acids have demonstrated adverse effects of treatment on the liver and on reproduction (reviewed below), although the dose levels required to produce toxicity were much higher than human exposure levels. Because environmental exposures may include multiple perfluorinated alkane acids, it is reasonable to ask whether the

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doi:10.1016/j.yrtph.2007.08.003

exposure levels to individual perfluorinated alkane acids can be combined in some manner for risk assessment purposes.

One method of combining exposure levels of structurally-related compounds is exemplified by the toxic equivalency factors (TEFs) for polychlorinated biphenyls, polychlorinated dibenzo-*p*-dioxins, and polychorinated dibenzofurans. Several such chemicals have been found to have toxicity similar to that of tetrachlorodibenzo-*p*-dioxin (TCDD). The TEF system for TCDD-like chemicals assigns an order of magnitude estimate for the toxicity of a compound relative to TCDD (reviewed by Van den Berg et al., 1998, 2006). There are three conditions that have been used to justify the use of TEFs for this group of compounds:

1. The compounds "have been shown to cause toxic responses similar to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin".
2. The mechanism of toxicity is understood to occur through interaction with a common receptor (the Ah receptor).
3. There is a substantial body of evidence from experiments showing that the effects of these agents are additive, within a factor of about 2.

Our purpose in this study was to evaluate the experimental animal literature to determine whether these three conditions are met by mixtures of perfluorinated alkane acids.

2. Materials and methods

Relevant toxicology studies were located through literature searching, inspection of studies in Environmental Protection Agency (EPA) docket AR-226, and evaluation of the reference lists of papers that were retrieved. We identified studies in which different perfluorinated alkane acids were evaluated using the same or similar design in the same experimental species, resulting in the selection of several pairs of studies that appeared comparable in design. Data were obtained from original study reports and published versions of these studies. We recorded the dose–response data for endpoints common to studies within each pair. Endpoints for which toxicity was demonstrated in one but not the other study in a pair were taken to be discordant and not considered further. Acute toxicity testing and studies with primarily biochemical endpoints were also not considered.

Administered dose was used in all cases; in addition, associated serum or plasma concentrations were considered when available. PFOA undergoes rapid renal elimination in female but not male rats, probably due to sexually dimorphic organic anion transporter expression (Kudo et al., 2002). The excretion of PFOA by female rats is virtually complete within a day. It has been recommended that PFOA serum concentrations be approximated in female rats by dividing the area under the time–concentration curve by 24 to give a time-weighted serum concentration over the course of a daily (24 h) dosing period (Butenhoff et al., 2004a). We used the formula derived from Butenhoff et al. (2004a) to make this calculation:

$$\text{Time-weighted serum PFOA concentration(mg/L)} = 2.63 * \text{Administered dose(mg/kg/day)} \quad (1)$$

PFOS serum concentrations in pregnant (gestation day 21) female rats were obtained from Luebker et al., 2005. Serum concentrations were measured after daily administration of PFOS of 0.1, 0.4, 1.6, or 3.2 mg/kg/day. We entered the serum concentrations in GraphPad Prism version 2.01 (GraphPad Software, San Diego, CA) and estimated the best-fit equation ($R^2 = 0.9966$) describing the data as:

Table 1
Discordant results in developmental toxicity testing of perfluoroalkane acids

Endpoint	Effect levels (mg/kg bw/day)			
	PFOS	PFOA	PFBS	PFDA
2-Generation rat studies				
Decreased gestation duration, implantation sites, liveborn pups; increased preweaning pup death	Affected at 3.2 (maternal bw gain ↓42% GD 0–7 and 14% GD 0–21)[a]	No effect at 30 (maternal bw ↓5% on GD 10; bw gain not affected GD 0–21)[b]	No effect at 1000 (maternal bw not affected)[c]	
Decreased pup weight at weaning	Affected at 1.6 (maternal bw ↓8% on PND 1)[a]	No effect at 30 (maternal bw ↓4–6% on PND 15)[b]	No effect at 1000 (maternal bw ↓5% on PND 8)[c]	
Rat developmental toxicity studies (GD 2–20 exposure for PFOS and GD 6–15 exposure for PFOA)				
Increased malformations	Affected at 5 (maternal bw gain from ~GD 2–20 ↓~10%)[d]	No effect at 100 (maternal body weight gain from GD 6–21 ↓14%)[e]		
Mouse developmental toxicity studies (GD 1–17 exposure for PFOA and PFOS; GD 6–15 exposure for PFDA)				
Increased malformations	Affected at 15 (maternal body weight gain decreased at 20)[d]	Affected at 3 (no effect on maternal body weight gain)[f]		No effects at 12.8 (maternal body weight loss from GD 6–18)[g]

Bw, body weight, ↓, statistically significant decrease.
[a] Luebker et al. (2005).
[b] Butenhoff et al. (2004b) and York (2002a).
[c] York (2003a).
[d] Thibodeaux et al. (2003).
[e] Staples et al. (1984).
[f] Lau et al. (2006).
[g] Harris and Birnbaum (1989).

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