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Combining perfluoroalkane acid exposure levels for risk assessment

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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 polychlorinated 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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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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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 polychlorinated 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
<i>2-Generation rat studies</i>				
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	
<i>Rat developmental toxicity studies (GD 2–20 exposure for PFOS and GD 6–15 exposure for PFOA)</i>				
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%) ^c		
<i>Mouse developmental toxicity studies (GD 1–17 exposure for PFOA and PFOS; GD 6–15 exposure for PFDA)</i>				
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) ^e

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).

$$\text{Serum concentration} = 114.5 * \text{dose} + 20.48 * \text{dose}^2 \quad (2)$$

Exposure–response data were modeled using the EPA Benchmark dose program, version 1.4.1. All models available in the program were run, and the model with the lowest Akaike information criterion (AIC) was chosen for modeling. The same model was used for members of each pair of endpoints when possible.

Relative potencies of pairs of perfluoroalkane acids were evaluated in rat studies using scaling factors calculated as a ratio of benchmark doses or as a ratio of the doses producing half-maximal responses (ED₅₀s). Benchmark doses were calculated using a benchmark response of 1 control standard deviation and the lower bound of the 95% confidence interval around the benchmark dose (BMDL_{1SD}). The use of a ratio of ED₅₀s is comparable to the method described for the TEF system for dioxin-like

Table 2
Comparisons of perfluoroalkane acid potencies

Figure	Compounds	Design	Endpoint	Model	Ratio of BMDL _{1SD} s	Ratio of ED ₅₀ s	
1	PFBS ^a	PFOA ^b	2-Generation	F ₀ male absolute liver weight	Hill	Not calculable	164/1 = 164
2	PFBS ^a	PFOA ^b	2-Generation	F ₀ male relative liver weight	Hill	172/0.25 = 688	297/2.92 = 102
3	PFBS ^a	PFOA ^b	2-Generation	F ₁ male absolute liver weight	Hill	Not calculable	50/1.5 = 33
4	PFBS ^a	PFOA ^b	2-Generation	F ₁ male relative liver weight	Hill	327/0.27 = 1211	327/2.74 = 119
5	PFBS ^a	PFOA ^b	2-Generation	F ₁ preputial separation	Hill/linear	Not calculable	Not calculable
6	PFOA ^b	PFOS ^c	2-Generation	PND 1 pup weight	Hill	12/0.58 = 20.69	33.32/1.44 = 23.14
7	PFBS ^d	PFOS ^c	Developmental	Fetal body weight	Linear/linear	567/3.1 = 183	Not calculable
8	PFBS ^f	PFOS ^e	90-Day	Male relative liver weight	Hill/linear	218/0.32 = 681	Not calculable
9	PFOA ^b	PFOS ^c	2-Generation	F ₀ male terminal body weight	Hill	4.1/2.01 = 2	322,800/4.65 = 69,419

^a York (2003a).

^b Butenhoff et al. (2004b) and York (2002a).

^c Luebker et al. (2005).

^d York (2002b).

^e Thibodeaux et al. (2003).

^f York (2003b).

^g Goldenthal (1978).

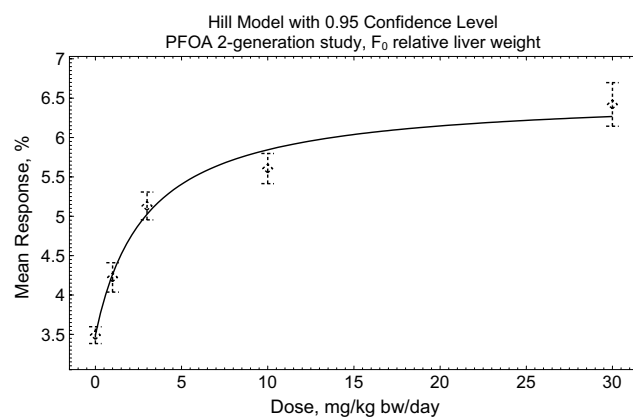
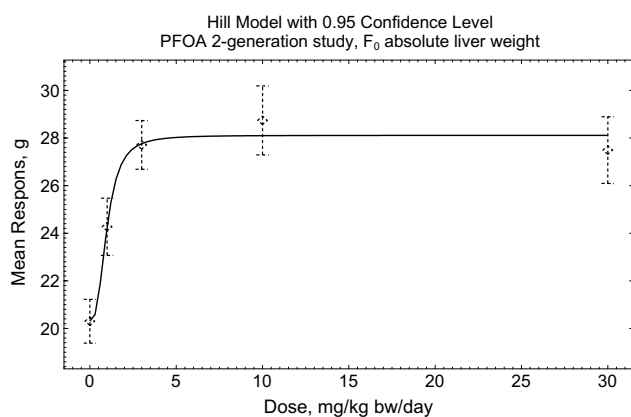
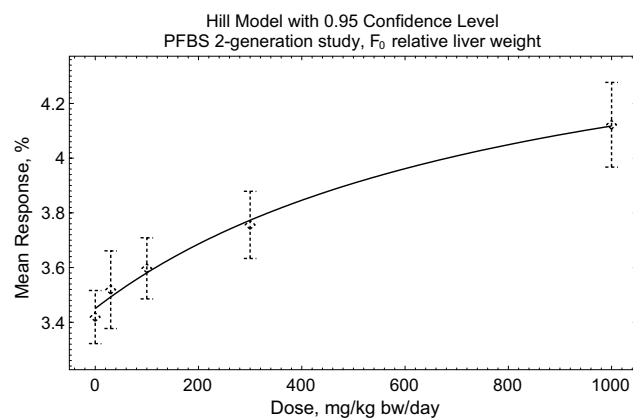
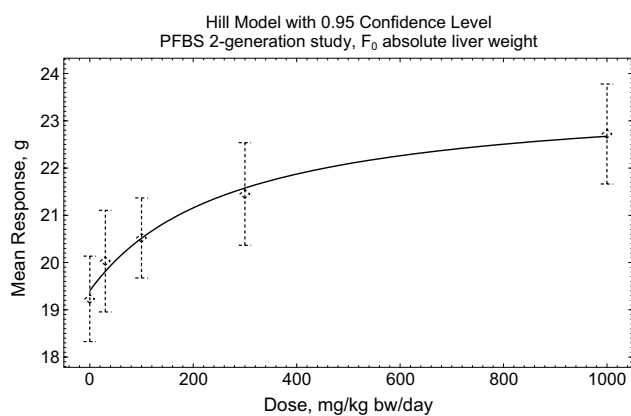


Fig. 1. Dose–response curves for F₀ absolute liver weight from 2-generation studies in rats. The top graph was drawn from York (2003a) and the bottom graph from Butenhoff et al. (2004b) and York (2002a).

Fig. 2. Dose–response curves for F₀ liver/body weight from 2-generation studies in rats. The top graph was drawn from York (2003a) and the bottom graph from Butenhoff et al. (2004b) and York (2002a).

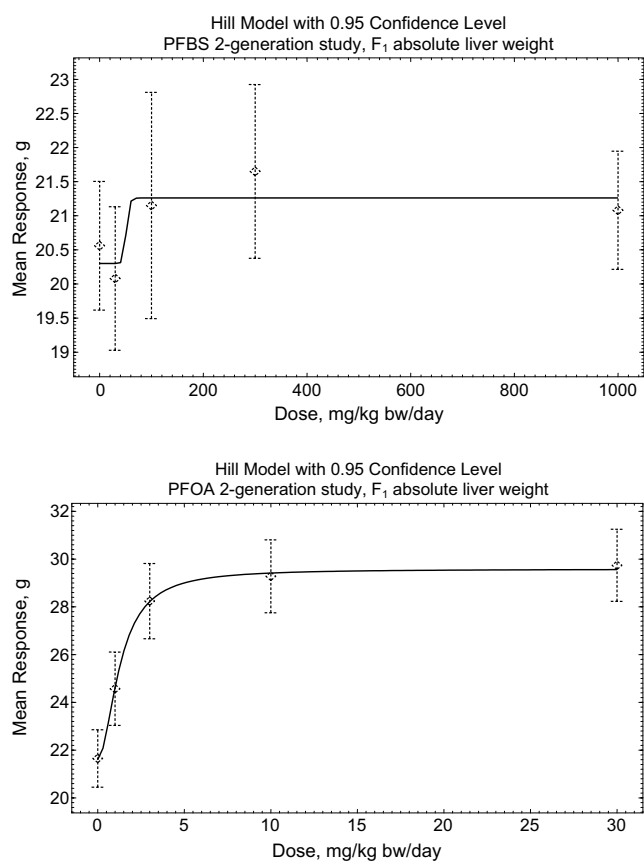


Fig. 3. Dose–response curves for F_1 absolute liver weight from 2-generation studies in rats. The top graph was drawn from York (2003a) and the bottom graph from Butenhoff et al. (2004b) and York (2002a).

compounds (Van den Berg et al., 1998). When an effect plateau was demonstrated in the experimental data, the half-maximal response was taken as the midpoint between the control response and the plateau response. When the modeled dose–response curve tended towards an asymptote as dose became very large, the half-maximal response was taken as the midpoint between the control response and the asymptote.

Scaling factors were evaluated for the perfluoroalkane acids to determine if these factors were consistent within an order of magnitude across studies and across endpoints.

3. Results

Evaluation for discordance was possible in rats and mice for PFOS, PFOA, perfluorobutanesulfonate (PFBS), and perfluorodecanoic acid (PFDA). Table 1 summarizes the lowest effect level for studies showing developmental effects and the highest tested exposure level for studies not showing effects. Maternal weight response is given as a further comparator. For endpoints with discordant results, no finite scaling factor can be developed.

Pairs of rat studies with scalable endpoints are shown in Table 2 and the underlying dose–response curves, using administered dose, are shown in Figs. 1–9. There were sufficient endpoints in pairs of studies for evaluation of PFOA, PFOS, and PFBS. In some cases, the dose–response curves were markedly dissimilar. For example,

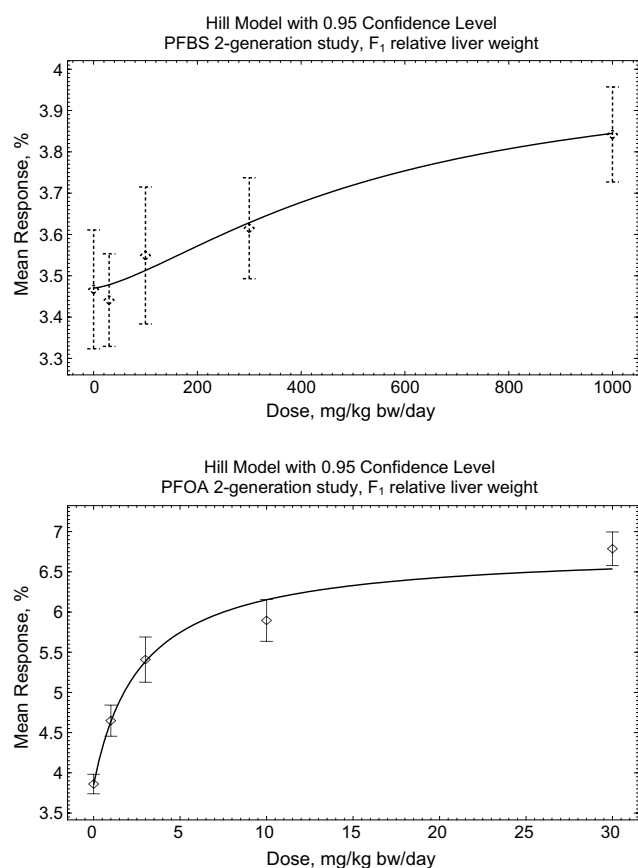


Fig. 4. Dose–response curves for F_1 liver/body weight from 2-generation studies in rats. The top graph was drawn from York (2003a) and the bottom graph from Butenhoff et al. (2004b) and York (2002a).

PFBS in a 2-generation rat study delayed preputial separation with a clear plateau, but the effect of PFOA on the same parameter showed no evidence of a plateau (Fig. 5). A comparison of the effects of PFOS and PFOA on F_1 pup weight in a 2-generation rat study (Fig. 6) suggested a plateau for PFOS but not for PFOA. The Hill function used to generate Fig. 6 identified an asymptote for PFOS at a dose level well above the experimental range. Although this asymptote was used to estimate a half-maximal value, animal death would likely preclude the corresponding dose level from being reached.

It was not possible to develop consistent scaling factors based on a comparison of ED_{50} s. For example, taking the potency of PFOA arbitrarily as 1, the potency of PFOS from line 9 of Table 2 would be 69,419. Line 6 of Table 2, however, suggests that the potency of PFOS should be 23. The discrepancy may be due to an unrealistic ED_{50} estimate for PFOA in line 9 of Table 2. Because of the very gradual approach of this function to its calculated asymptote, the half-maximal response was estimated to occur at a dose level of 322,800 mg/kg bw/day. As an alternative, it was assumed that the highest dose level tested (30 mg/kg bw/day) produced the maximal response. Under that assumption, the ED_{50} would be 10.2 mg/kg bw/day, and the scaling factor for PFOS would fall to 2.2. This factor

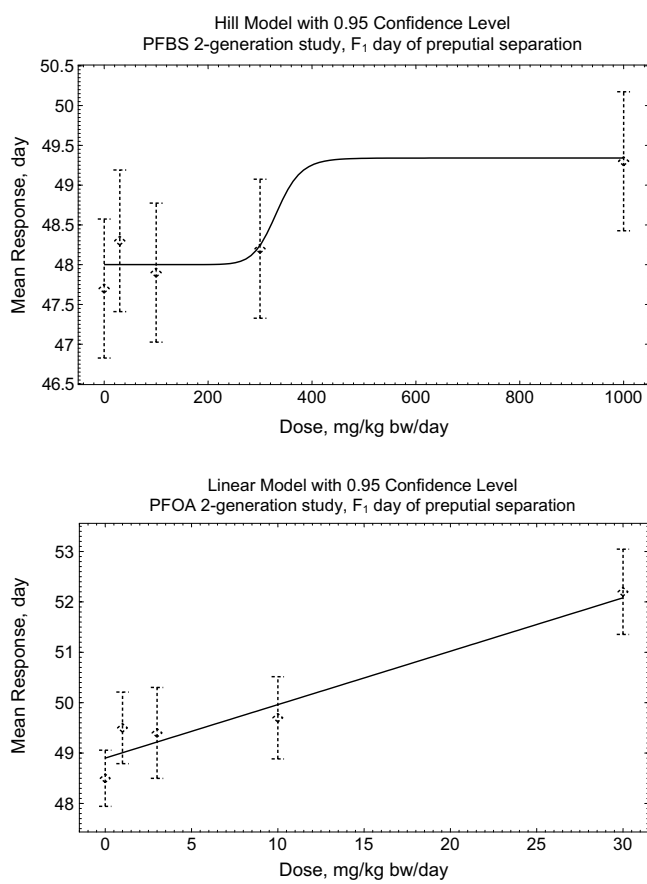


Fig. 5. Dose–response curves for F_1 day of preputial separation from 2-generation studies in rats. The top graph was drawn from York (2003a) and the bottom graph from Butenhoff et al. (2004b) and York (2002a).

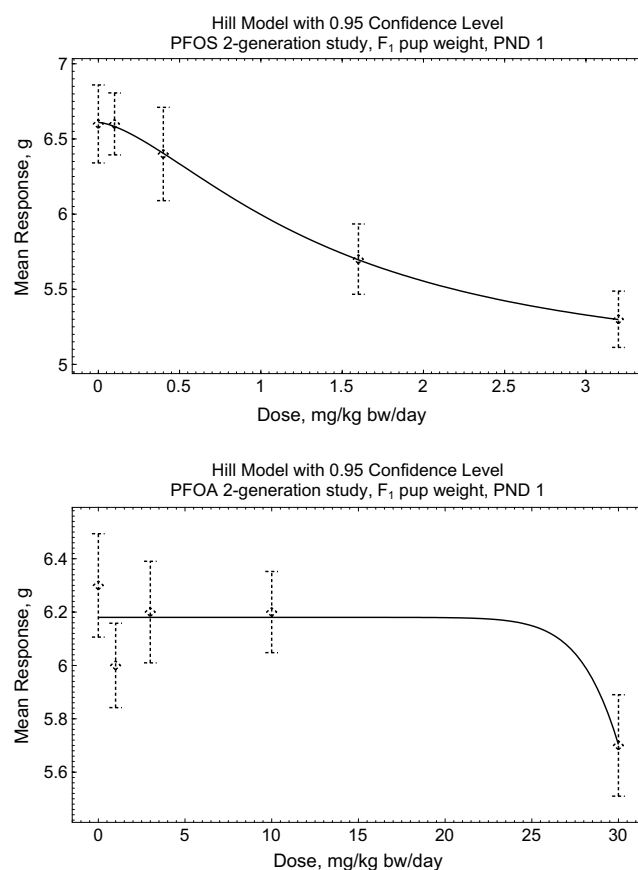


Fig. 6. Dose–response curves for F_1 pup weight on PND 1 from 2-generation studies in rats. The top graph was drawn from Luebker et al. (2005) and the bottom graph from Butenhoff et al. (2004b) and York (2002a).

is slightly more than an order of magnitude lower than the factor of 23 suggested by line 6.

A comparison of $BMDL_{1SDS}$ was also unsuccessful at demonstrating consistent scaling factors. Again defining PFOA potency as 1, line 9 of Table 2 suggests a PFOS scaling factor of 2, but line 6 suggests a PFOS factor of 21. If the PFOS scaling factor is taken to be 2, lines 7 and 8 give a PFBS scaling factor of 0.01 and 0.003, which are more than an order of magnitude apart. Line 2 of Table 2 suggests that the PFBS scaling factor should be 0.0014, which is one-third of an order of magnitude lower than the PFBS factor derived from line 8. Line 4 suggests a PFBS scaling factor of 0.0008, which is somewhat more than half an order of magnitude less than the PFBS factor derived from line 8. If the PFOS scaling factor is 21, lines 7 and 8 suggest PFBS scaling factors of 0.115 and 0.031, both of which are inconsistent with the PFBS scaling factors of 0.0014 and 0.0008 suggested by lines 2 and 4.

Serum concentration data were unavailable for PFBS (York, 2002a,b) and for males given PFOS in the 2-generation study (Luebker et al., 2005). Serum concentrations could be estimated in the 2-generation studies for PFOS (Luebker et al., 2005) and PFOA (Butenhoff et al., 2004b), permitting us to modify line 6 of Table 2 as follows:

The ratio of PFOA/PFOS $BMDL_{1SDS}$ of 12/0.58 converts to a serum ratio of $15.75/73.30 = 0.21$, and the ratio of ED_{50} s of 33.32/1.44 converts to $43.74/207.35 = 0.21$. Both calculations suggest that if PFOA has a scaling factor of 1, PFOS has a scaling factor of 0.21. This factor is more consistent with factors derived from other lines of Table 2; however, the other lines of Table 2 were developed using administered dose, not serum concentration.

4. Discussion

Our attempt to develop a scaling system for perfluoroalkane acid toxicity was not successful because of a lack of consistency in scaling factors derived from data presented in different studies. This finding suggests that the relative toxicity of these compounds may vary with the endpoint being investigated. It is possible that the use of serum or plasma concentrations rather than administered dose will permit scaling factors that can be applied to different endpoints. Serum concentrations were available for too few of the studies in our investigation to evaluate this possibility. The rapid renal elimination of PFOA in female rats suggests that an estimate of internal dose such as serum concentration will be important in making comparisons

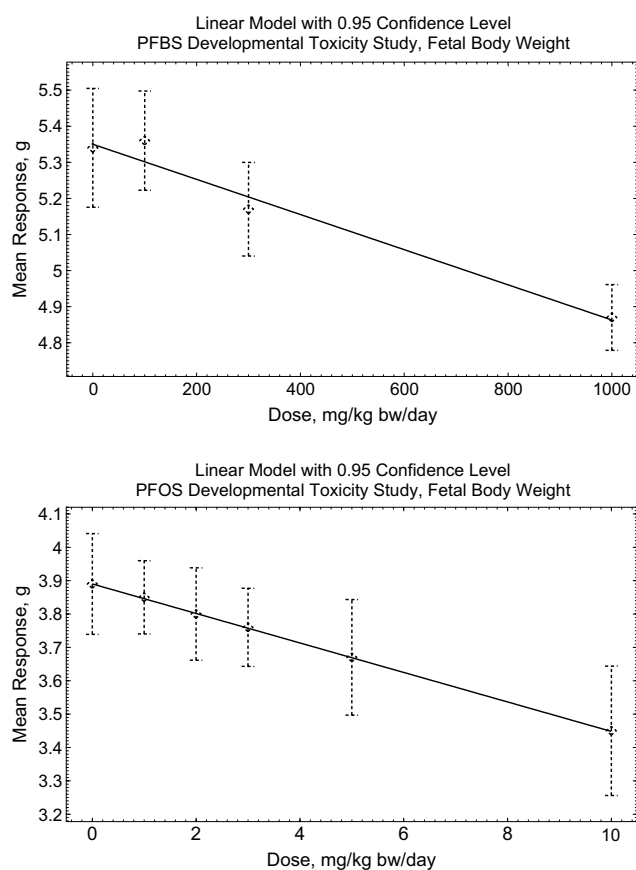


Fig. 7. Dose–response curves for fetal body weight from developmental toxicity studies in rats. The top graph was drawn from York (2002b) and the bottom graph from Thibodeaux et al. (2003).

between PFOA and other carboxylic acids to PFOS and other sulfonic acids, which are rapidly excreted by female rats. An alternative would be the use of a model such as the mouse, in which rapid renal excretion of the perfluoroalkane carboxylic acids does not occur in either sex (Hundley et al., 2006).

Criteria for the use of TEFs for TCDD-like compounds include the production of similar toxic responses by compounds considered eligible for assignment of a TEF. Our investigation of the similarity of toxic responses was limited by the diverse study designs that have been used to evaluate perfluoroalkane acids. Of the many studies we evaluated, few could be paired with a study of similar design. The most consistently similar designs were for studies evaluating developmental endpoints. As summarized in Table 1, we found several developmental endpoints for which results were discrepant. Developmental toxicity results for perfluoroalkane acids appeared to be compound specific; however it was not possible to draw firm conclusions about compound discordance because of differences in study design details and degrees of maternal toxicity achieved.

A second criterion for development of TEFs is the action of the group of compounds through a common mechanism or receptor. The mechanisms of toxicity of per-

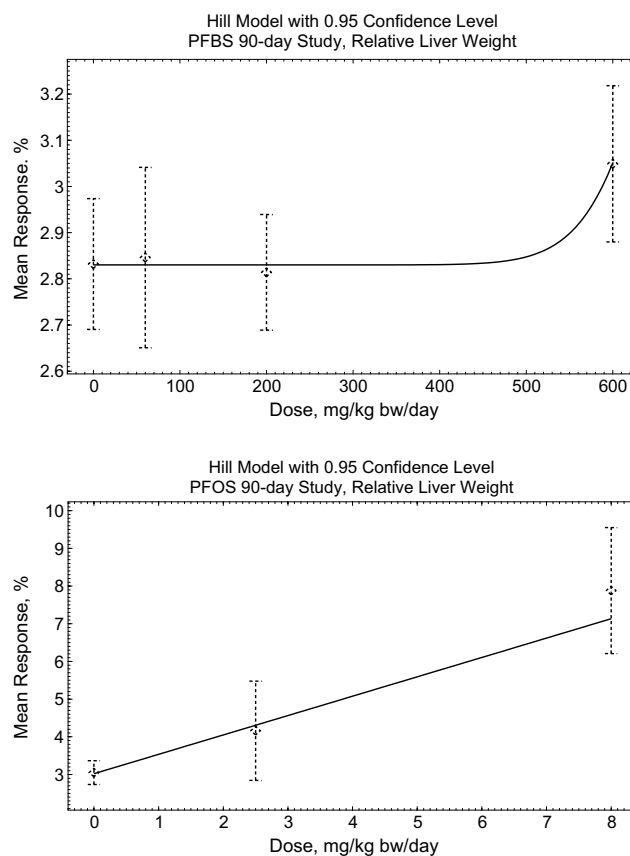


Fig. 8. Dose–response curves for liver/body weight in male rats from 90-day studies. The top graph was drawn from York (2003b) and the bottom graph from Goldenthal (1978).

fluoroalkane acids are unknown. These agents activate peroxisome proliferator-activated receptor- α (PPAR α) in rodents, and it is possible that some of the effects of these compounds are mediated through this receptor activation. The PPARs are members of a superfamily of nuclear receptors and are important in the regulation of lipids and glucose (reviewed by Li and Glass, 2004). The hepatic enlargement noted in rodents after treatment with PFOA and PFOS may be due in part to peroxisome proliferation secondary to activation of PPAR α .

It appears unlikely, however, that PPAR α activation mediates all the manifestations of perfluoroalkane acid toxicity. PFOA is a more potent activator of PPAR α than is PFOS (Vanden Heuvel et al., 2006; Takacs and Abbott, 2007); however, PFOS appears to be more potent than PFOA when endpoints common to both compounds are examined (Table 2, lines 6 and 9). In addition, although some PFOA developmental toxicity in experimental animals is attributable to PPAR α activation, other toxicity is PPAR α independent. Abbott et al. (2007) used pregnant PPAR α knockout mice treated with PFOA and showed that PPAR α was required for a PFOA-induced decrease in neonatal survival but not for PFOA-induced full litter resorption.

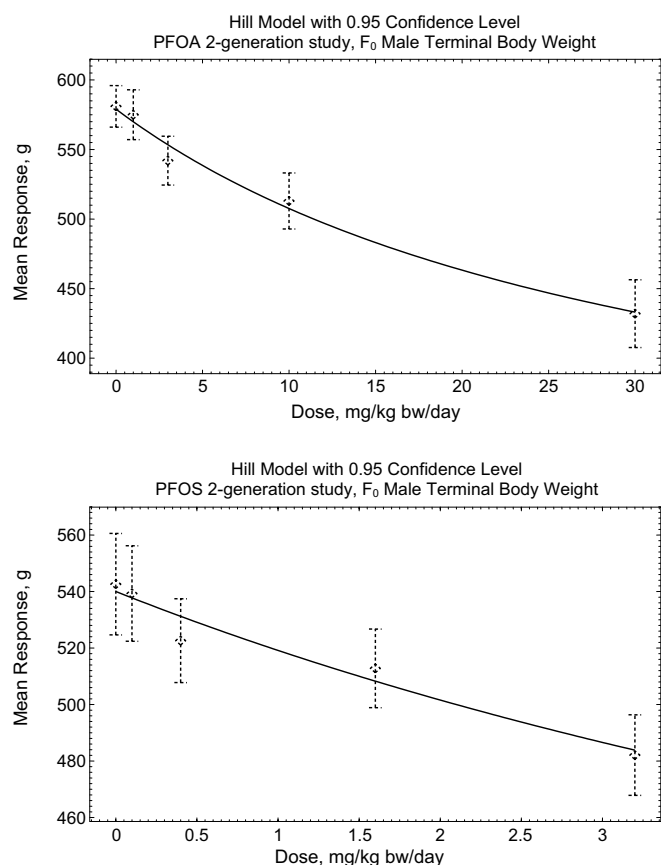


Fig. 9. Dose–response curves for F_0 male terminal body weight from 2-generation studies in rats. The top graph was drawn from Butenhoff et al. (2004b) and York (2002a) and the bottom graph from Luebker et al. (2005).

Even if PPAR α mediates some perfluoroalkane acid toxicity endpoints in rodents, the relevance of this mechanism to human risk assessment is not clear. PFOA exposure of transfected cells produced less activation of human than of mouse PPAR α receptor. Exposure of transfected cells to PFOS in some experiments showed little activation of human PPAR α (Takacs and Abbott, 2007), while other experiments have shown the human receptor to be activated (Shipley et al., 2004). Studies in transfected cells do not consider receptor densities in normal tissues and may not evaluate coactivators and other modifiers of the receptor–ligand interaction. Biochemical evidence of peroxisome proliferation has been reported in rats to be similar after single-dose treatment with PFOS and PFOA (Berthiaume and Wallace, 2002).

Another possible mechanism of perfluoroalkane acid toxicity is alteration of lipid membranes based on the surface active properties of these compounds. For example, interference with the pulmonary alveolar membrane transport of surfactant has been proposed as a mechanism of PFOS-associated neonatal death in rodents (Grasty et al., 2005), and induction of proton leaks in the mitochondrial membrane with impairments of mitochondrial respiration

has been suggested as a cause of wasting in rodents treated with perfluoroalkane acids (Starkov and Wallace, 2002).

The possibility that different perfluoroalkane acids produce different kinds of toxicity by different mechanisms may explain our finding that consistent scaling factors could not be developed for PFOA, PFOS, and PFBS. We restricted our evaluation to pairs of studies using the same designs, and we used only one species (rat) for our quantitative analysis to avoid species-related sources of variation. We chose the rat because number of studies using rats permitted comparison of scaling factors for different endpoints. We used two methods of scaling, one based on the ED₅₀ and one based on the BMDL_{1SD}. It is possible that the choice of another point on the dose–response curve would have given more consistent results.

The TEF system for TCDD-like compounds applies only to endpoints mediated through activation of the aryl hydrocarbon (Ah) receptor (Van den Berg et al., 1998). It is possible that a scaling factor could be developed for those endpoints of perfluoroalkane acid toxicity that are mediated through activation of a particular receptor, but at this time there is inadequate information to identify which endpoints might be included and which receptor should be evaluated.

One of the features used to justify the use of TEFs for TCDD-like compounds is a body of evidence from experiments showing that the effects of these agents are additive. There is no such body of evidence with respect to perfluoroalkane acids. Our inability to identify scaling factors that could consistently be applied to PFOA, PFOS, and PFBS, even within an order of magnitude, suggests that additivity should not be assumed for risk assessment purposes in the absence of additional experimental support. The available data for these compounds does not permit the conclusion that a TEF system is not possible, and the question should be reconsidered when additional data are available.

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