

Avian toxicity reference values (TRV) for perfluorooctane sulfonate (PFOS)

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Introduction

Perfluorinated chemicals (PFCs) have been widely used in commerce as surfactants, surface protectors in carpets, paper products, and as performance chemicals in products such as fire fighting foams, floor polishes and shampoos¹. Until recently little was known about their environmental fate and even less was known about their potential environmental effects. Since PFCs were reported to be widespread in wildlife there has been interest in determining the potential for effects of these compounds on wildlife. In particular, much of this interest has been focused on a single PFC, perfluorooctane sulfonate (PFOS), a predominant PFC found in many biota. The assessment of possible effects of PFCs to wildlife has been hampered by a limited understanding of the mode of action and by a lack of toxicological data for wildlife species. Here we summarize several toxicological studies available for perfluorinated compounds (PFCs) on two avian species. This toxicological information is then used to derive toxicity reference values, or benchmarks that are protective of avian populations. These benchmarks are then used in conjunction with environmental concentration data to evaluate the potential risk that this compound may pose to avian wildlife.

Studies of effects of PFOS to Birds

Several recent toxicological studies have examined the acute and chronic effects of a dietary exposure of PFOS on two avian species, Mallards (*Anas platyrhynchos*) and Northern bobwhite quail (*Colinus virginianus*)^{3,4}. In these studies, toxicological endpoints that were evaluated included mortality, altered behavior and appearance, body weight, growth, feed consumption, gross pathology and histopathology in adult birds. Reproductive endpoints included egg production, measures of egg fertility and hatchability, and survival, growth and health of the surviving offspring. PFOS concentrations were also measured in the liver and serum of adults and offspring at study termination and in eggs.

Acute dietary exposures.

In a dietary acute study, PFOS was acutely toxic to both juvenile quail and mallards³. The 8-Day LC50 for juvenile quail was 212 mg PFOS/kg, diet with a 95% confidence interval of 158 to 278 mg PFOS/kg, diet. The 8-Day LD50 was 61 mg PFOS/kg, bw/d with a 95% confidence interval of 48 to 77 mg PFOS/kg, bw/d based on estimates of average daily intake (ADI) of PFOS. Based on lethality, the NOAEL based was 70.3 mg PFOS/kg, diet (or 24 mg PFOS/kg, bw/d). For juvenile mallards, the 8-Day dietary LC50 was 603 mg PFOS/kg, diet with a 95% confidence interval of 431 to 938 mg PFOS/kg, diet. The 8-Day LD50 was 150 mg PFOS/kg, bw/d with a 95% confidence interval of 117 to 201 mg PFOS/kg, bw/d. For mallards, the NOAEL using lethality as an endpoint was 141 mg PFOS/kg, diet (or 61 mg PFOS/kg, bw/d). A comparison of the toxicity data for these two species indicates that quail were more sensitive than mallards.

Bobwhite Reproductive Study

In a reproductive study with northern bobwhites, birds were exposed to PFOS at nominal concentrations of 0, 10, 50, or 150 mg PFOS/kg in the diet⁴. However, due to overt signs of toxicity noted in adult birds from the 50 and 150 mg PFOS/kg treatments by Week 5, these treatment levels were terminated. No treatment-related mortalities were observed in the 10 mg PFOS/kg treatment, nor were there any significant alterations in body weight or feed consumption in adult birds. At study termination, the gross necropsy indicated that adult males had an increase in the incidence of small testes in the 10 ppm treatment. This increase in the incidence in small testes was not accompanied by any morphological change in spermatogenesis nor were there any indications of altered fertility noted in the study. It

was concluded that PFOS may have accelerated post-reproductive regression, a normal physiological process but based on the evidence, this phenomenon was not toxicologically significant. While no treatment related effects were noted on adult male livers, there was a statistically significant increase in female liver weight in the 10 mg PFOS/kg diet treatment. However, when liver weight was normalized to body weight, these differences were no longer significant. No other treatment-related lesions were noted in the study.

There were no effects on egg production in the 10 mg/kg diet treatment when compared to controls. However, there were slight, but not statistically significant reductions in several parameters including the number of viable embryos, live 3-week embryos, hatchlings, and 14-day old offspring survivors. There were also slight but not statistically significant, reductions in most of the normalized reproductive values. However, there was a significant reduction in the percentage of 14-day old survivors as number of eggs set ($p < 0.05$) from control levels. No treatment related effects were observed on offspring body or liver weights. Based on these results, the female and male LOAEL was determined to be 10 mg PFOS/kg diet (or 0.77 mg PFOS/kg, bw/d) while a NOAEL could not be determined. Female serum and liver PFOS concentrations corresponding to the LOAEL were 8.7 μg PFOS/ml and 4.9 μg PFOS/g, respectively. For males, the PFOS concentrations in serum and liver corresponding to the LOAEL were 140 μg PFOS/ml and 88 μg PFOS/g, respectively. PFOS concentration in egg yolk from the 10 mg/kg treatment averaged 62 mg PFOS/ml.

Mallard Reproductive Study

In a reproductive study with mallards, birds were exposed to PFOS at nominal concentrations of 0, 10, 50, or 150 mg PFOS/kg in the diet⁴. However, due to overt signs of toxicity noted in both 50 and 150 mg PFOS/kg treatments by Week 5, these treatment were terminated and only the control and 10 ppm treatments were maintained until the end of the study. No treatment-related mortalities or alterations of body weight or feed consumption were observed in adult male or female birds from the 10 mg PFOS/kg dietary treatment. Gross necropsy results at study termination indicated no treatment related effects in adult females but that there was a greater incidence of small testes in the treated males. The presence of small testes was accompanied by some alteration in spermatogenesis. However, the proportion of birds with small testes that also exhibited altered spermatogenesis was similar between the control and treated groups. As a result, the increase in small testes in treated birds is suggestive of an accelerated post-reproductive regression of testes that is commonly observed at the end of reproduction cycles. No treatment related effects were noted on liver weights in either sex. There were also no treatment-related effects on any reproductive parameter or on offspring survival, body or liver weight. Based on these results, the female LOAEL was determined to be 50 ppm in the diet (or 6.4 mg PFOS/kg, bw/d) while the NOAEL was determined to be 10 ppm in the diet (or 1.5 mg PFOS/kg body weight /day). For males, the LOAEL was not determined in this study while the NOAEL was found to be 10 mg PFOS/kg diet (or 1.5 mg PFOS/kg, bw/d). Female serum and liver PFOS concentrations corresponding to the NOAEL were 17 μg PFOS/ml and 11 μg PFOS/g, respectively. For males, the PFOS concentrations in serum and liver corresponding to the LOAEL were 87 μg PFOS/ml and 61 μg PFOS/g, respectively. PFOS concentration in egg yolk averaged 53 μg PFOS/ml.

Avian Risk Assessment

TRV Calculation

In a global monitoring study of PFOS residues in biota, fish-eating water birds were found to have some of the greatest liver and serum PFOS concentrations⁵. Top avian aquatic predators such as eagles and cormorants accumulated the greatest concentrations of PFOS when compared to other lower trophic level bird species. To be protective of all avian species, an avian TRV for PFOS was derived based on the characteristics of trophic level 4 fish-eating birds^{6,7}.

TRVs were developed from the laboratory studies by applying uncertainty factors to toxicity data a based on an approach outlined in the USEPA Great Lakes Initiative (GLI)⁸. In this approach, three categorical uncertainties were delineated and included: [1] Uncertainty with LOAEL to NOAEL extrapolation (UF_L), [2] Uncertainty related to duration of exposure (UF_S), and [3] uncertainty related to inter-taxon extrapolations (UF_A). Uncertainty factors for each category are assigned values between 1 and 10 that are based on available scientific findings and best professional judgment. Based on the quail reproduction study and the characteristics of a Level 4 avian predator, uncertainty factors were assigned as follows:

Table 1. Assignment of uncertainty factors for the calculation of a generic Trophic Level 4 avian predator toxicity reference value (TRV) for PFOS. ^a

Uncertainty Factors	Notes
Intertaxon extrapolation (UF _A)	The laboratory study used to determine a threshold dose was from northern bobwhite quail. Since this species belongs to the same taxonomic class but different order, UF_A = 6
Toxicological Endpoint (UF _L)	The quail study determined a LOAEL but not a NOAEL based on multiple endpoints that included reproduction. Furthermore, the difference between the LOAEL and control was less than 20% for the effected reproductive endpoints. Taken together with other study data, the UF_L = 2
Exposure duration (UF _S)	The quail reproductive study was conducted for 20 weeks and evaluated several important life stages including embryonic development and offspring growth and survival, so UFs = 3
* Overall UF for TRV	UF = 6*2*3 = 36

^a Selection of uncertainty factors based on the Great Lake Initiative (USEPA, 1995)

TRVs were calculated using the LOAELs taken from the bobwhite quail reproduction study.

$$\text{TRV} = \frac{\text{Test Dose or LOAEL}}{\text{Overall UF}}$$

Dietary and tissue-specific (liver and serum) TRV values were determined for both male and females birds (Table2). Since sex-specific differences in adult serum and liver concentrations were observed. TRVs were derived that integrated the differences between sexes and reproductive condition. This was accomplished by first calculating the geometric mean for pre- and post-reproductive female serum PFOS concentrations and then a geometric mean between the latter mean and that for males. For liver, the geometric mean of male and female liver PFOS concentrations was used. Based on this approach, the TRVs for serum and liver were 1.7 µg PFOS/ml and 0.6 µg PFOS/g, ww, respectively. A comparison to benchmark values calculated using EC guidelines⁹ indicate that the TRV calculated by the GLI methodology results in values are approximately 1.7-fold greater than corresponding PNEC values. The basis for this difference was the application of an assessment factor of 30 to the chronic avian data and the use of an additional correction factor of 2 that is applied to a LOEL if a NOEL is not available.

Table 2. PFOS TRV values for a generic Trophic Level IV predator based on dietary, liver, and serum toxic doses. ^a

	Male		Female	
	LOAEL	TRV ^b	LOAEL	TRV ^b
ADI (mg PFOS/kg/d) ^d	0.77	0.021	0.77	0.021
Liver (µg PFOS/g, ww)	88	2.4	4.9	0.14
Serum (µg PFOS/ml)	141	3.9	8.7	0.24
Egg Yolk (µg PFOS/ml)			62	1.7

^a LOAEL values based on bobwhite quail definitive study

^b TRV estimated with total uncertainty factor of 36 using the USEPA GLI protocol.

^c ADI= Average daily intake (mg PFOS/kg bw/d); estimates were based on pen averages .

Summary

Results from global monitoring programs have shown that concentrations of PFOS in birds vary depending on location

and species. In most circumstances, the concentrations of PFOS found in bird tissues do not seem to pose a significant threat based on the results of this hazard assessment. Since much of the production of PFOS was voluntarily ceased in 2000, concentrations of PFOS are expected to decrease from current levels.

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