Alliance for Risk Assessment (*ARA*)
Range of the PFOA Safe Dose

The Steering Committee of the Alliance for Risk Assessment (*ARA*, 2022) endorsed the formation of an international collaboration on determination of the range of the PFOA safe dose. The results shown below summarize the consensus of findings from 3 teams of scientists working independently over 6 months regarding PFOA's underlying mode of action for various effects, its likely critical effect(s), the extrapolation of experimental or human data to the presumed sensitive subgroup, and other tasks as appropriate.

The range of the PFOA safe dose is estimated to be 0.01 to 0.07 ug/kg body weight-day based on points of departure and uncertainty factors from the following studies.

Monkey: Point of Departure = 19 ug/ml from Green and Crouch (2019) based on a serum PFOA benchmark concentration (BMC) for *increased liver weight* in the Butenhoff et al. (2002).

- Monkey to human toxicokinetic factor = 1, factor is not needed since BMC is based on serum concentration.
- Monkey to human toxicodynamic factor = 2.5 (IPCS default) or 3 (EPA default)
- Human toxicodynamic factor = 3 [default of IPCS (2005) and EPA (2014)]
- Human toxicokinetic factor = 8.4 [0.79 ml/day/kg arithmetic mean clearance of average group from Zhang et al. (2013, Table 2) ÷ 0.094 ml/day/kg arithmetic 95% lower bound clearance of sensitive group from Zhang et al. (2013, Table 2)]
- Database uncertainty factor = 1, although it could be argued that the small number of animals in the study justifies an additional uncertainty factor; the counter-argument is that these are primates.

- RfD serum concentration = 0.25 ug/ml [19 ug/ml ÷ (1 x 3 x 3 x 8.4 x 1) = 0.25]
- RfD = 0.06 ug/kg-day [0.25 ug/ml x 0.23 ml/day/kg (geometric mean clearance from Zhang et al. (2013, Table 2) assuming steady state][1]

Mouse: Point of Departure = 1 mg/kg-day or 23 µg/ml No Observed Adverse Effect Level (NOAEL) for *dose-dependent growth deficits* in the Lau et al. 2006 for gestation days 1-17

- Mouse to human toxicokinetic factor = 1, factor is not needed since BMD is based on serum concentration.
- Mouse to human toxicodynamic factor = 2.5 (IPCS default) or 3 (EPA default)
- Human toxicodynamic factor = 3 [default of IPCS (2005) and EPA (2014)]

[1] If folks want to compare equivalent serum levels amongst species, which is usually based on average values, then this comparison should be made prior to the use of either the human toxicodynamic and toxicokinetic factors. Note that the serum RfD is in effect the biomonitoring equivalent of the RfD.

- Human toxicokinetic factor = 8.4 [0.79 ml/day/kg arithmetic mean clearance of average group from Zhang et al. (2013, Table 2) ÷ 0.094 ml/day/kg arithmetic 95% lower bound clearance of sensitive group from Zhang et al. (2013, Table 2)]
- Database uncertainty factor = 1, although it has been argued that a number of problems with this study might justify an additional uncertainty factor; counter-argument is that US EPA uses a value of 1.

- RfD serum concentration = 0.3 ug/ml [23 ug/ml ÷ (1 x 3 x 3 x 8 x 1) = 0.3]
- RfD = 0.07 ug/kg-day [0.3 ug/ml x 0.23 ml/day/kg (geometric mean clearance from Zhang et al. (2013, Table 2) assuming steady state]

Notes:

- It could be argued that the fetal toxicity is secondary to disruption of lipid metabolism in the dam, as evidenced by the increased maternal liver weight at all doses.

- Several authorities consider the 1 mg/kg/d dose to be a LOAEL, but effects at the lowest dose were only observed in dams. Resulting US State RfDs range from 0.005 – 0.020 ug/kg-day (Post et al., 2021).

Mouse: Point of Departure = 4.35 µg/ml based on a serum PFOA benchmark concentration by New Jersey/New Hampshire (Post et al., 2021) for *lipid parameters/relative liver weight* in male mice from Loveless et al. (2006)

- Rat to human toxicokinetic factor = 1, factor is not needed since BMD is based on serum concentration.
- Rat to human toxicodynamic factor = 2.5 (IPCS default) or 3 (US EPA default)
- Human toxicodynamic factor = 3 [default of IPCS (2005) and US EPA (2014)]
- Human toxicokinetic factor = 8.4 [0.79 ml/day/kg arithmetic mean clearance of average group from Zhang et al. (2013, Table 2) ÷ 0.094 ml/day/kg arithmetic 95% lower bound clearance of sensitive group from Zhang et al. (2013, Table 2)]
- Database uncertainty factor = 1

- RfD serum concentration = 0.058 ug/ml [4.35 ug/ml ÷ (1 x 3 x 3 x 8.4 x 1) = 0.058]
- RfD = 0.01 ug/kg-day [0.058 ug/ml x 0.23 ml/day/kg (geometric mean clearance from Zhang et al. (2013, Table 2) assuming steady state]

Notes:

- It could be argued that a toxicodynamic UF of 0.1 could be applied for rodent to human differences in response to PPAR activation.

Macon et al. (2011) was not used because the statistics in this study appeared to be based on pups and not the maternal experimental animal. Using pups as the basis of the assessment is not in accordance with US EPA (1991) guidelines.

Neither Onischenko et al. (2011) nor Koskela et al. (2016) were used because of the few animals and limited doses used in these studies, and furthermore, the statistics appeared to be based on pups and not the maternal experimental animal. The use of these studies for risk assessment is not in accordance with multiple US EPA guidelines.

Mouse: Point of Departure = 0.3 mg/kg-day (10.4 ug/ml) No Observed Adverse Effect Level (NOAEL) for *neonatal survival* found in Abbott et al. (2007)

- Mouse to human toxicokinetic factor = 1, factor is not needed since BMD is based on serum concentration.
- Mouse to human toxicodynamic factor = 2.5 (IPCS default) or 3 (EPA default)
- Human toxicodynamic factor = 3 [default of IPCS (2005) and EPA (2014)]
- Human toxicokinetic factor = 8.4 [0.79 ml/day/kg arithmetic mean clearance of average group from Zhang et al. (2013, Table 2) ÷ 0.094 ml/day/kg arithmetic 95% lower bound clearance of sensitive group from Zhang et al. (2013, Table 2)]
- Database uncertainty factor = 1

- RfD serum concentration = 0.14 ug/ml [10.4 ug/ml ÷ (1 x 3 x 3 x 8.4 x 1) = 0.14]
- RfD = 0.03 ug/kg-day [0.14 ug/ml x 0.23 ml/day/kg (geometric mean clearance from Zhang et al. (2013, Table 2) assuming steady state]

Mouse: Point of Departure = 0.94 mg/kg-day (no serum values available) No Observed Adverse Effect Level (NOAEL) for *immune suppression* found in DeWitt et al. (2016).

Based on Lau et al. 2006, the serum level associated with in the mouse repeated dosing at 1 mg/kg-day is 23 µg/ml. Therefore, dosing at 0.94 mg/kg/d is estimated to be associated with a serum level of 22 µg/ml.

- Mouse to human toxicokinetic factor = 1, factor is not needed since BMD is based on serum concentration.
- Mouse to human toxicodynamic factor = 2.5 (IPCS default) or 3 (EPA default)
- Human toxicodynamic factor = 3 [default of IPCS (2005) and EPA (2014)]

- Human toxicokinetic factor = 8.4 [0.79 ml/day/kg arithmetic mean clearance of average group from Zhang et al. (2013, Table 2) ÷ 0.094 ml/day/kg arithmetic 95% lower bound clearance of sensitive group from Zhang et al. (2013, Table 2)]
- Database uncertainty factor = 1

- RfD serum concentration = 0.29 ug/ml [22 ug/ml ÷ (1 x 3 x 3 x 8.4 x 1) = 0.29]
- RfD = 0.07 ug/kg-day [0.29 ug/ml x 0.23 ml/day/kg (geometric mean clearance from Zhang et al. (2013, Table 2) assuming steady state]

A publishable manuscript is being developed from the deliberations of this effort. In the mean time, we welcome comments on these findings from interested colleagues. Comments can be directed to members of the Advisory Committee shown here:

Lyle Burgoon with Raptor Pharm & Tox, Ltd, USA
Harvey Clewell with Ramboll, Global
Tony Cox with Cox Associates, USA
Michael Dourson with TERA, USA
Tamara House-Knight with GHD, Global
Ravi Naidu with CRC CARE, Australia
Paul Nathanail with LQM, United Kingdom
James S. Smith with US DoD, USA
Nitin Verma with Chitkara University, India

Advisory Committee for International Collaboration on the PFOA/S Safe Dose

—Alliance for Risk Assessment (*ARA*), building a risk assessment community
Hallmarks: Open, collaborative, frugal, timely and erudite

---It is the mark of an instructed mind to rest satisfied with the degree of precision which the nature of the subject permits and not to seek an exactness where only an approximation of the truth is possible. Aristotle

References

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