

Consistency in the direction of association across studies with different exposure sources (and subsequent different sources of bias) reduces the likelihood that observed associations between PFOA and ALT can be fully explained by confounding across PFAS.

Evaluating health effects of highly correlated chemicals like PFAS is complicated by the potential for confounding by different substances in the same chemical class. As part of a systematic review of the hepatic effects of perfluorooctanoic acid (PFOA), we considered the sources and directions of bias in studies with varying exposure scenarios. For this example, we focused on studies of alanine aminotransferase (ALT) in adult participants.

Strengths

- PFOA exposure predominates, so little concern for confounding by other PFAS
- Well conducted, no serious validity concerns

Limitations

- Some potential for selection bias (away from the null) due to heightened awareness of exposure and potential lawsuits
- Fewer studies available

| Reference | Design | Population | Median exposure (ng/mL) in serum | Association with ALT β (95% CI) |
|-------------------------|--------|--|-------------------------------------|--|
| Gallo et al. (2012) | CS | C8 Health Project; 47,092 adults | 28 | 1.10 (1.07, 1.13)* |
| Darrow et al. (2016) | CS | C8 Health Project; 30,723 adults | 17 (model estimate) | 0.012 (0.008, 0.016)*; monotonic across quintiles |
| Emmett et al. (2006) | CS | Little Hocking Water District; 371 all ages | 345 | 0.00 (p=0.65) |

β represents In-unit (ng/mL) change in PFOA for C8, unit change for Emmett.

Table shading indicates finding that supports a positive association between PFOA and ALT. *p<0.05; C=cohort; CS=cross-sectional

Combining these data with findings for other hepatic outcomes from epidemiology studies and with animal and The views expressed in this poster are those of the author(s) and do not necessarily represent the views or the policies of the U.S. Environmental Protection Agency. mechanistic evidence can further increase certainty.

Using triangulation to assess confounding by co-exposures to multiple per- and polyfluoroalkyl substances (PFAS)

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Positive associations in studies:

- With/without concern for confounding across PFAS
- With potential selection bias towards/away from the null
- At exposure levels observed in the general population

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• PFOA exposure predominates, so little concern for confounding by other PFAS

• Potential for selection bias (primarily towards the null) due to healthy worker bias • Potential for other sources of confounding (e.g., variables such as smoking that may not be available)

| Population | Median or mean exposure (ng/mL) in serum | Association with ALT β (95% CI or SE) |
|--|--|--|
| Fluorochemical plant workers; 56 men | 11,900 | 0.116 (0.054, 0.177)* |
| Fluorochemical plant workers; 288 men | 6,800 | 2.77 (1.27)* in 1997, stronger with BMI<30 |
| Fluorochemical plant workers; 506 adults | 2,200 | Antwerp: 0.025 (0.013); Decatur: 0.08 (0.034)* |
| Workers with PFOA exposure; 1,025 adults | 494 | 0.023 (0.015) |
| Fluorochemical plant workers; 231 adults | 1,130 | 0.54 (-0.46, 1.54) |
| Fluorochemical plant workers; 179 adults | 881 | -0.0097 (0.005) per unit change in PFOA exposure from baseline |
| Fluorochemical plant workers and near-by residents, 132 adults | 1,636 (workers) | Residents: -0.1 (-0.19, 0.0) Workers: 0.04 (-0.06, 0.15) |

β represents change in PFOA: In-unit in Olsen 2007 (µg/mL), unit in Costa (µg/mL), Olsen 2000 (ppm), Sakr a/b (ppm). In Wang β is In-unit change in ALT.

- Well conducted, no serious validity concerns
- Exposure levels relevant to typical environmental exposures

Participants are exposed to a mixture of PFAS; it is difficult to disentangle effects.

Correlations across PFAS reported in Nian et al. (2019), Salihovic et al. (2018) indicated moderate associations (r=0.3-0.5) with some other PFAS, suggesting confounding cannot be ruled out. One study (Lin et al., 2010) adjusted for 3 other PFAS and found no attenuation.

| Reference | Design | Population | Median exposure (ng/mL) in serum | Association with ALT |
|-------------------------|--------|--|-------------------------------------|---|
| Lin et al. (2010) | CS | NHANES 1999-2000, 2003-04; 2,216 adults | 4.5 | β (SE): 1.86 (0.62)* |
| Jain et al. (2019) | CS | NHANES 2011-14; 2,883 adults | 4.0 | Nonobese β (p value): 0.0056 (0.8) Obese β (p value): 0.071 (<0.01)* |
| Nian et al. (2019) | CS | 1,605 adults | 6.2 | % change (95% CI): 7.4 (3.9, 11.0)* |
| Salihovic et al. (2018) | С | 1,002 elderly adults | 3.8 (plasma) | β (95% CI): 0.04 (0.03, 0.06)* |

β represents In-unit (ng/mL) change in PFOA for Nian, log-unit change for Lin and Jain, unit change for Salihovic.





