Tossicità a valori guida delle sostanze perfluoroalchiliche: stato dell'arte

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Pubblicazioni scientifiche indicizzate *«peer reviewed»* su destino ambientale, ecotossicologia, tossicità ed esposizione umana a sostanze perfluoroalchiliche

Periodo 1960 – 2000: circa 300

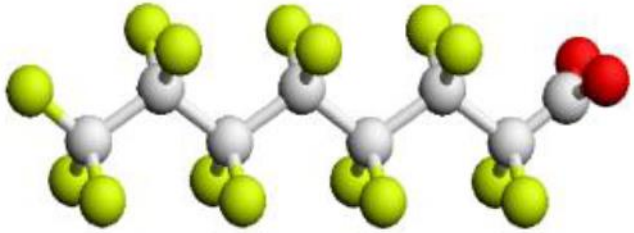
Periodo 2000 – 2012: >1800

Fonte: Lau, 2012

Acido perfluoroottanoico: profilo tossicologico

- Tossicocinetica: rapido assorbimento orale; non metabolizzato; si accumula nel fegato, reni, plasma; escrezione urinaria specie e sesso specifica (trascurabile nell'uomo, in cui l'emivita stimata è 3,8 anni).
- Genotossicità: non genotossico.
- Tossicità acuta: moderata (LD50 > 200 mg/kg pc).
- Tossicità (sub)cronica: a carico del fegato (NOAEL 0,06 mg/kg nel ratto).

Acido perfluoroottanoico: profilo tossicologico



- Cancerogenesi: ratto ♂ adenomi epatocellulari, tumori al pancreas esocrino (*acinar cells*) e testicolo (*Leydig ce*lls).
- Tossicità riproduttiva e dello sviluppo: effetti avversi sullo sviluppo del feto (NOAEL < 1 mg/kg pc).
- Studi sull'uomo (occupazionali): alterati parametri biochimici (↑colesterolo LDL, ↑ trigliceridi); evidenze inconclusive o negative per cancerogenesi.

J.E. Klaunig (2012) Mode of Action analysis of perfluorooctanoic acid (PFOA) tumorigenicity and Human Relevance. Reproductive Toxicology 33 (2012) 410–8

Rat liver tumors (human relevance: not relevant)

1.activation of PPARα receptor

2. cell growth gene expression

3. cell proliferqation/clonal expansio

Leydig cell tumors in rats (HR: unresolved)

1. 1.activation of PPARα receptor

2. hormonal unbalance

3. increased LC proliferation/clonal expansion

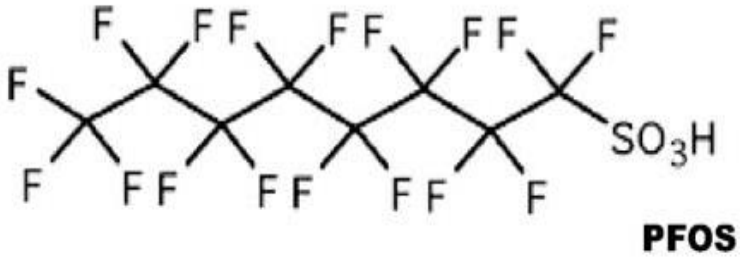
Pancreatic acinar cell tumors in rats (HR: not relevant)

1. 1.activation of PPARα receptor

2. cholestasis →increased CCK(cholecystokinin)

3.cell proliferation/clonal expansion

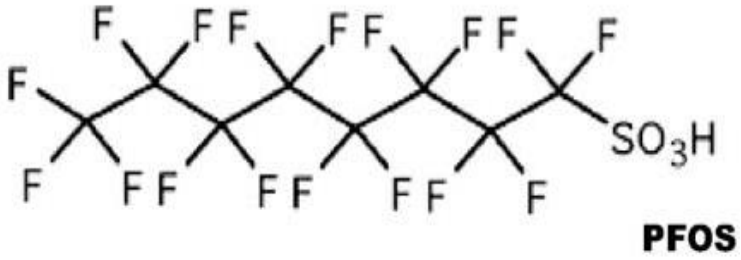
Acido perfluorooctansulfonico: profilo tossicologico



PFOS

- Tossicocinetica: rapido assorbimento orale; non metabolizzato; si accumula nel fegato, reni, plasma; escrezione urinaria specie e sesso specifica (trascurabile nell'uomo, in cui l'emivita stimata è ~ 5 anni).
- Genotossicità: non genotossico.
- Tossicità acuta: moderata (LD50 > 100 mg/kg pc).
- Tossicità (sub)cronica: a carico del fegato (NOAEL 0,4 mg/kg nel ratto), metabolismo lipidico, ormoni tiroidei (NOAEL 0,03 mg/kg in *Cynomolgus*).

Acido perfluorooctansulfonico: profilo tossicologico



PFOS

- Cancerogenesi: ratto ♂ adenomi e carcinomi epatocellulari.
- Tossicità riproduttiva e dello sviluppo: tossicità fetale e neonatale a dosi ≤ materno-tossiche (NOAEL 0,1 mg/kg pc).
- Studi sull'uomo (occupazionali): alterati parametri biochimici (funzionalità epatica, ↑colesterolo,↑ trigliceridi, ormoni tiroidei); evidenze inconclusive o negative per cancerogenesi.

Emivita di vari PFAS nel siero/plasma

	PFBS ♂/♀	PFBA ♂/♀	PFOS ♂/♀	PFOA ♂/♀
Ratto	4/4,5 h	1,5/9 h	60/42 gg	3h/4 gg
Scimmia	3,5/4 gg	1,7 gg		10/25 gg
Uomo	30 gg	3 gg	5,4 anni	2,3/3,8 anni

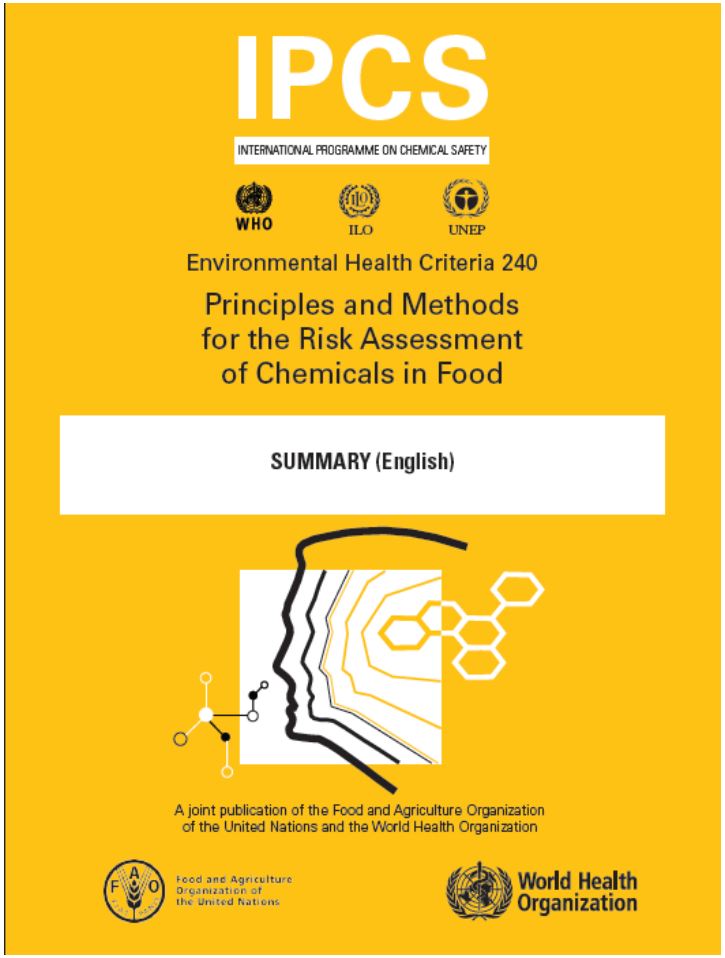
Valori parametrici per l'acqua potabile o livelli di esposizione orale tollerabile a PFOS e PFOA secondo diversi enti regolatori

	PFOA	PFOS
EFSA	1,5 µg/kg pc	0,15 µg/kg pc
UK COT	3,0 µg/kg pc	0,3 µg/kg pc
UK HPA	10 µg/L	0,3 µg/L
Trinkwasserkommission DE	0,1 µg/kg pc	0,1 µg/kg pc
U.S. EPA	0,4 µg/L	0,2 µg/L
New Jersey Dept.Env.Prot	0,04 µg/L	

L'approccio dell'EFSA per il Risk Assessment in campo alimentare

- Si basa essenzialmente sui criteri sviluppati dai comitati WHO/FAO su additivi e residui di pesticidi (JMPR):
- **ADI/TDI = NOAEL/BMDL:UFs**

ADI/TDI= dose giornaliera accettabile/tollerabile
NOAEL = No Observed Adverse Effect Level
BMDL = Benchmark Dose Level
UFs = Uncertainty Factors



Definizione di un livello tollerabile (TDI) di PFOS nella catena alimentare

The EFSA Journal (2008) 653, 7-131

Studio tossicologico critico: tossicità subcronica nel macaco (*Cynomolgus monkey*);

End-point: alterazioni biochimiche (metabolismo lipidi, ormoni tiroidei);

NOAEL: 0,03 mg/kg pc/die

UF: 200 (100x *default* inter-intraspecie; 2x durata dello studio < emivita);

TDI: 150 ng/kg pc/die

(0,03 mg/kg : 200)

Definizione di un livello tollerabile (TDI) di PFOA nella catena alimentare

The EFSA Journal (2008) 653, 7-131

Studio tossicologico critico: tossicità sub-cronica nel ratto;

End-point: alterazioni biochimiche e istopatologiche nel fegato (diversi studi);

BMDL10: 0,3-0,7 mg/kg pc/die

UF: 200 (100x *default* inter-intraspecie; 2x cinetica dose interna);

TDI: 1,5 µg/kg pc/die

(0,3 mg/kg : 200)

WHO (2011) Guidelines for drinking-water quality

From TDI to Guideline Value (GV)

$$GV = (TDI^* \times bw \times P) : Vol$$

Bw (body weight) = 10 kg

P (% allocation) = 20 %

Vol (daily consumption) = 1 L

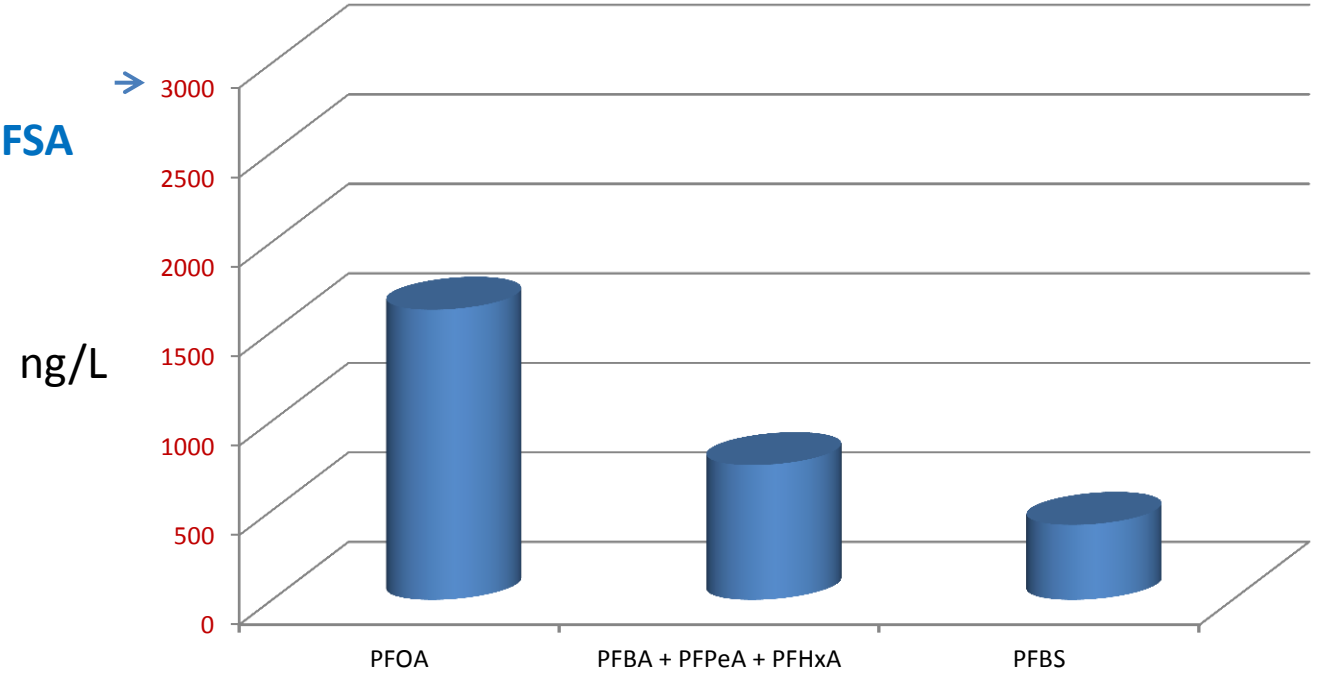
GV **PFOS = 0,3 µg/L** (150 ng/kg x 10 kg X 0,2)

GV **PFOA = 3 µg/L** (1,5 µg/kg x 10 kg x 0,2)

* *as established by EFSA (2008)*

Valori massimi di PFAS rilevati nell'acqua potabile dall'indagine IRSA-CNR

GV per PFOA derivato da EFSA TDI



Maximumm acceptable concentrations of PFOS and PFOA in drinking water (August 2007)

PFOS: 0.3 µg/L

10% of TDI (0.3 µg/kg pc) for one-year children (10 kg bw) consuming 1 L drinking water/day

PFOA : 10 µg/L

50% of TDI (3 µg/kg pc) for 0.75 L of drinking water consumed daily by a bottle-fed baby weighing 5 kg

German Ministry of Health – Drinking Water Commission (Trinkwasserkommission)

Admissible health based precautionary values (HPV) for PFOA and perfluorocarbons in drinking water (2006):

«the HPV of **0,1 µg/L*** for non- or low potency genotoxic substances also applies to PFOA, PFOS and other perfluorocarbons»

* Lifetime exposure; ≤ 0,5 µg/L max 10 years; ≤ 5 µg/L max 1 year

Provisional Health Advisories for PFOA and PFOS (2008)

PFOA

Pivotal study: Lau et al, 2006 (developmental toxicity study in mice)

Most sensitive end-point: increased maternal liver weight

PoD: BMDL10 = 0,46 mg/kg bw/day

PFOS

Pivotal study: Seacat et al 2002 (subchronic toxicity in Cynomolgus monkey)

Most sensitive end-point: ↑ TSH, ↓T3 and HDL

PoD: NOAEL = 0,03 mg/kg bw/day

Provisional Health Advisories for PFOA and PFOS (2008)

$$GV = \frac{(NOAEL/BMDL) \times bw \times \% \text{ allocation}}{UF \times \textit{extrapolation factor}^{*} \times Vol}$$

CL animal/CL human = 80,7 PFOA and 13,1 PFOS

$$\frac{0{,}46 \times 10 \times 0{,}2}{10 \times 3 \times 81} = \textbf{0,4 µg PFOA/L}$$

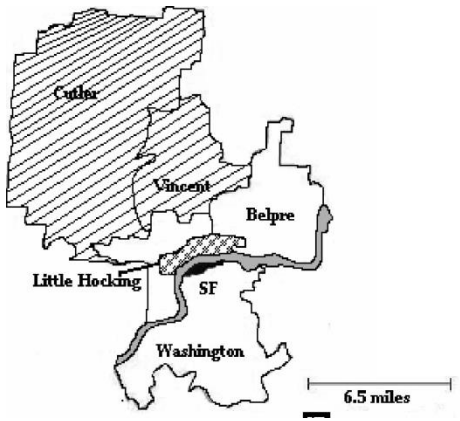
$$\frac{0{,}03 \times 10 \times 0{,}2}{10 \times 3 \times 13} = \textbf{0,2 µg PFOS/L}$$

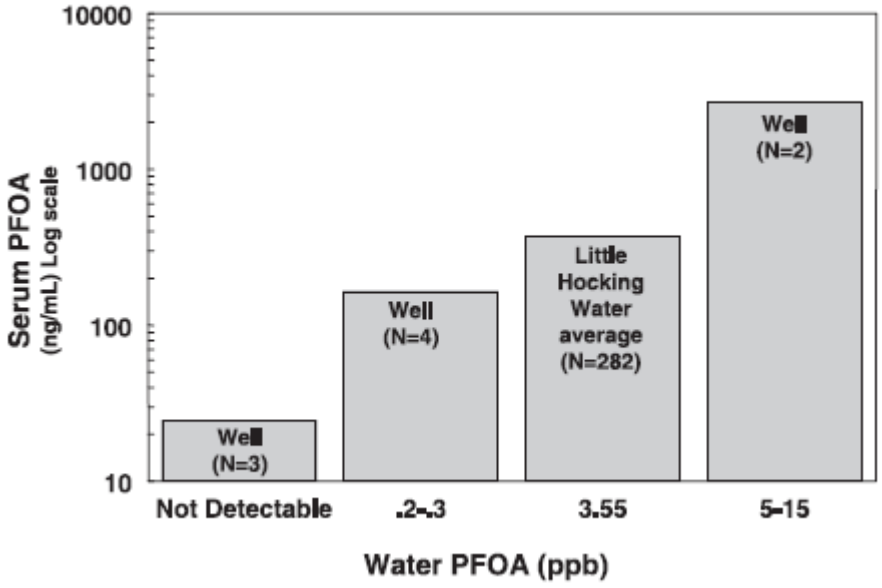
Updated statement on the tolerable daily intake for perfluorooctanoic acid COT (July 2009)

… the critical difference between the three assesments [USEPA, EFSA and HPA] was the uncertainty factor used for interspecies toxicokinetics. The USEPA used 81 compared with uncertainty factors of 4 and 8 used by COT and EFSA, respectively.

...we regard the USEPA approach as unsatisfatory because it makes too many assumptions that cannot be supported robustly by the available data… in addition on-going work has estimated a shorter half life for PFOA than proposed by the EPA, which introduces additional uncertainty.

Emmett MA et al (2006) Community Exposure to Perfluorooctanoate: Relationships Between Serum Concentrations and Exposure Sources. JOEM • Volume 48, Number 8, 759-770





«an approximately **100:1 ratio** is observed between concentration of PFOA in serum and drinking water»

TABLE 3. PFOA Levels in Drinking Water and Serum in Communities in Ohio and West Virginia

water district	PFOA levels reported by water district (μg/L) (*32*)	median serum PFOA level (μg/L) (*33*)
Little Hocking, OH	1.7–4.3	224
Lubeck, WV	0.4–3.9	70
Tuppers Plains, OH	0.25–0.37	35
City of Belpre, OH	0.08–0.13	37
Mason County, WV	0.06–0.1	12
Village of Pomeroy, OH	0.06–0.07	12

NJ Dept Envir Protect – Derivation of a health-based drinking water concentration for PFOA (October 2009)

Pivotal study: oral chronic toxicity in ♀ rat

Critical end-point: ↓ body weight, hematology

PoD: NOAEL 1.6 mg/kg bw/day (30 ppm)

Animal serum level at NOAEL: 1800 µg/L

Uncertainty factor: 100x (?)

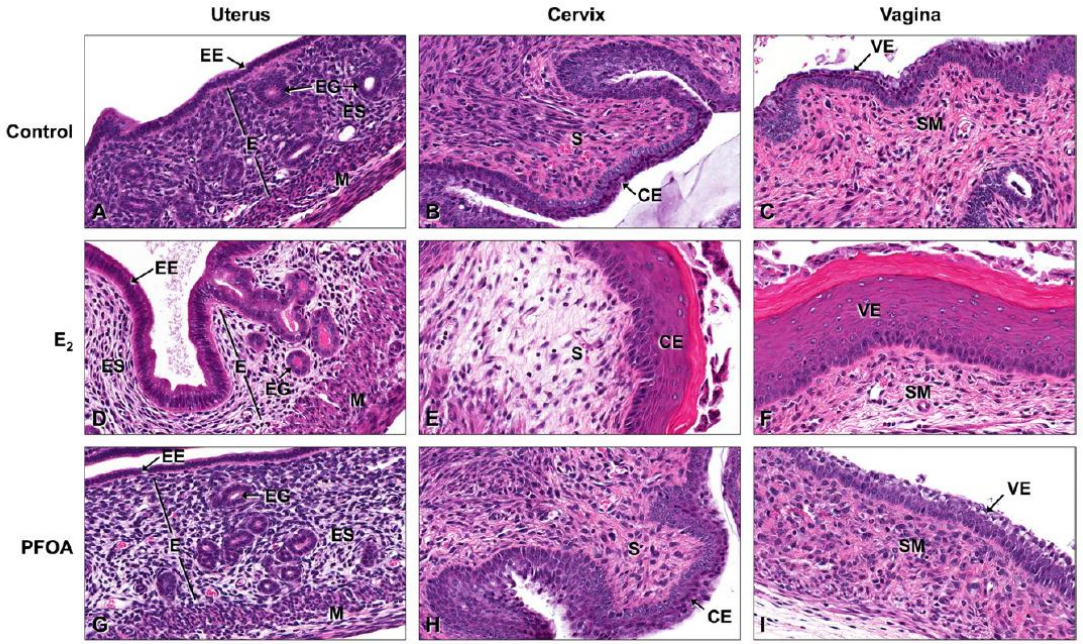
Target human serum level: 18 µg/L

Target contribution of drinking water (20%): 4 µg/L

Health-based drinking water concentration: **0.04 µg/L**

Recenti studi sperimentali su PFOA e sostanze perfluoroalchiliche

D. Dixon et al. (2012) Histopathologic changes in the uterus, cervix and vagina of immature CD-1 mice exposed to low doses of perfluorooctanoic acid (PFOA) in a uterotrophic assay. Reproductive Toxicology 33, 506-12



LOAEL 0,01 mg/kg

M.B.Macon et al. (2011) Prenatal Perfluorooctanoic Acid Exposure in CD-1 Mice: Low-Dose Developmental Effects and Internal Dosimetry. Toxicol. Sci. 122, 134-45

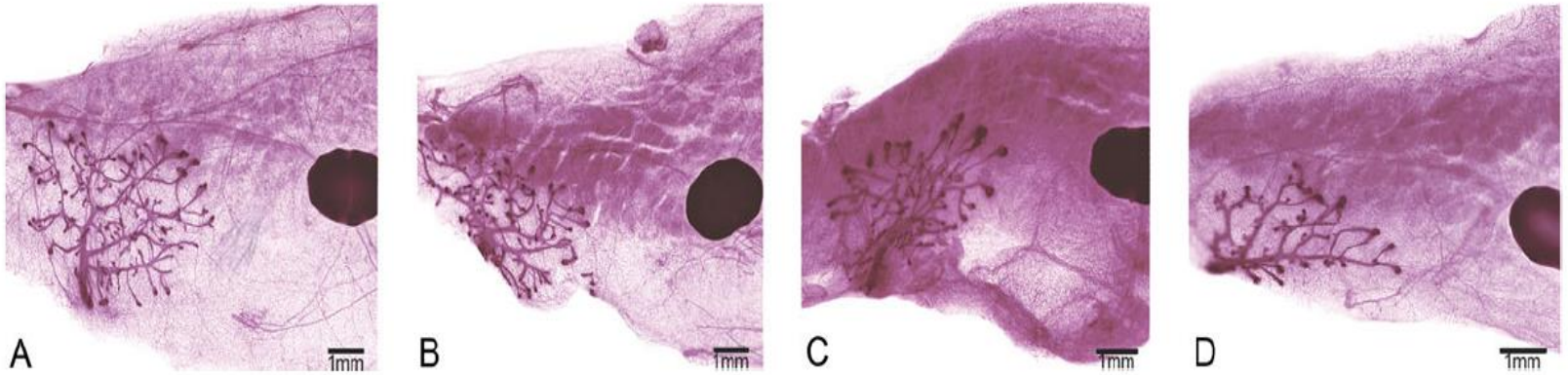


FIG. 4. Female offspring mammary gland whole mounts at PND 21 in the late-gestation study from (A) controls, (B) 0.01 mg/kg, (C) 0.1 mg/kg, and (D) 1.0 mg/kg. Glands pictured are representative of the mean score for each treatment group; $n = 3–5$. PFOA-exposed glands were smaller in size, displayed poor branching patterns, and had fewer TEBs relative to controls. All PFOA-treated mammary glands received significantly lower developmental scores compared with controls ($p < 0.05$).

LOAEL 0,01 mg/kg

White S.S. et al. (2011) Gestational and Chronic Low-Dose PFOA Exposures and Mammary Gland Growth and Differentiation in Three Generations of CD-1 Mice. Environ. Health Pespect. 119, 1070-6

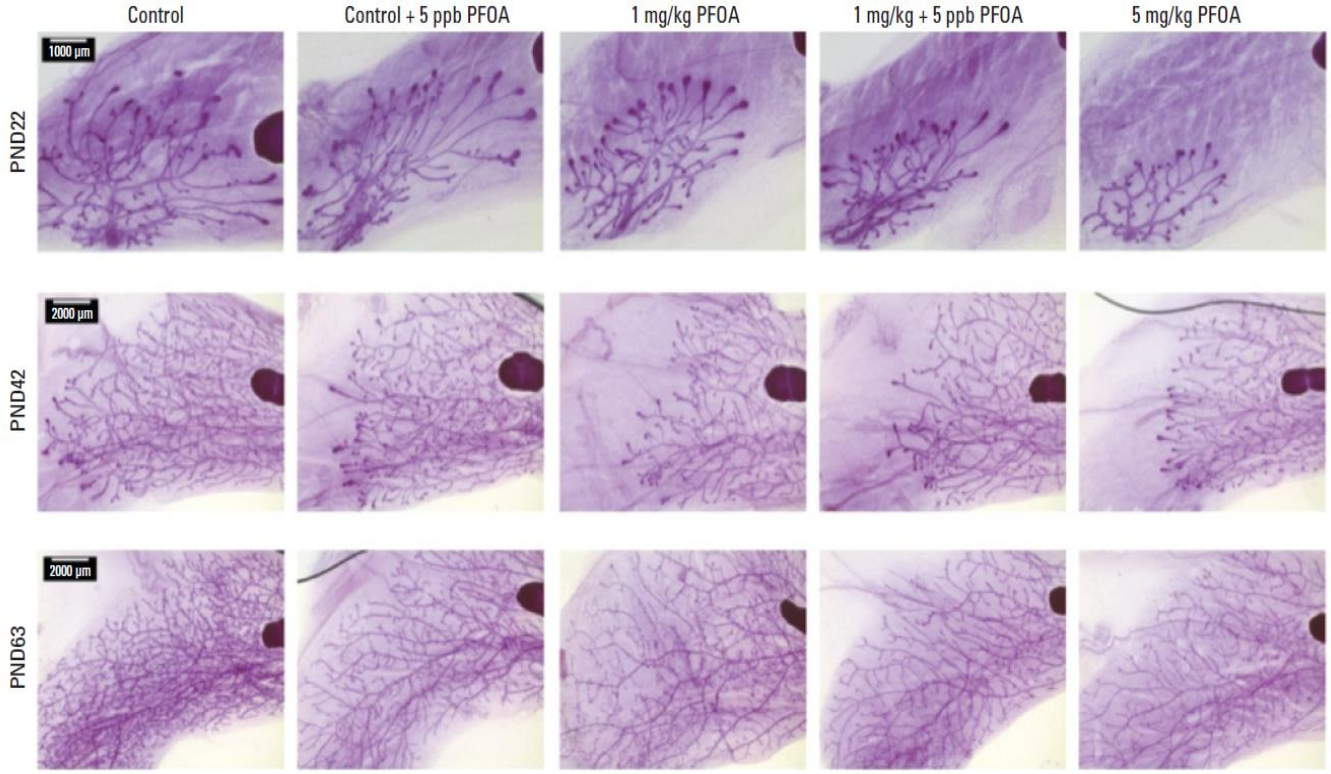


Figure 1. F_1 female mammary gland development. Mammary whole-mounts illustrate morphology representative of treatment groups at PNDs 22, 42, and 63 (n = 6–7 females/treatment/age). Bars = 1,000 µm for PND22 and 2,000 µm for PND42 and PND63.

5 µg/L in drinking water

Recenti studi epidemiologici su PFOA e sostanze perfluoroalchiliche

V.M. Vieira (2013) Perfluorooctanoic Acid Exposure and Cancer Outcomes in a Contaminated Community: A Geographic Analysis. Environ. Health Perspect. 121, 318-23*

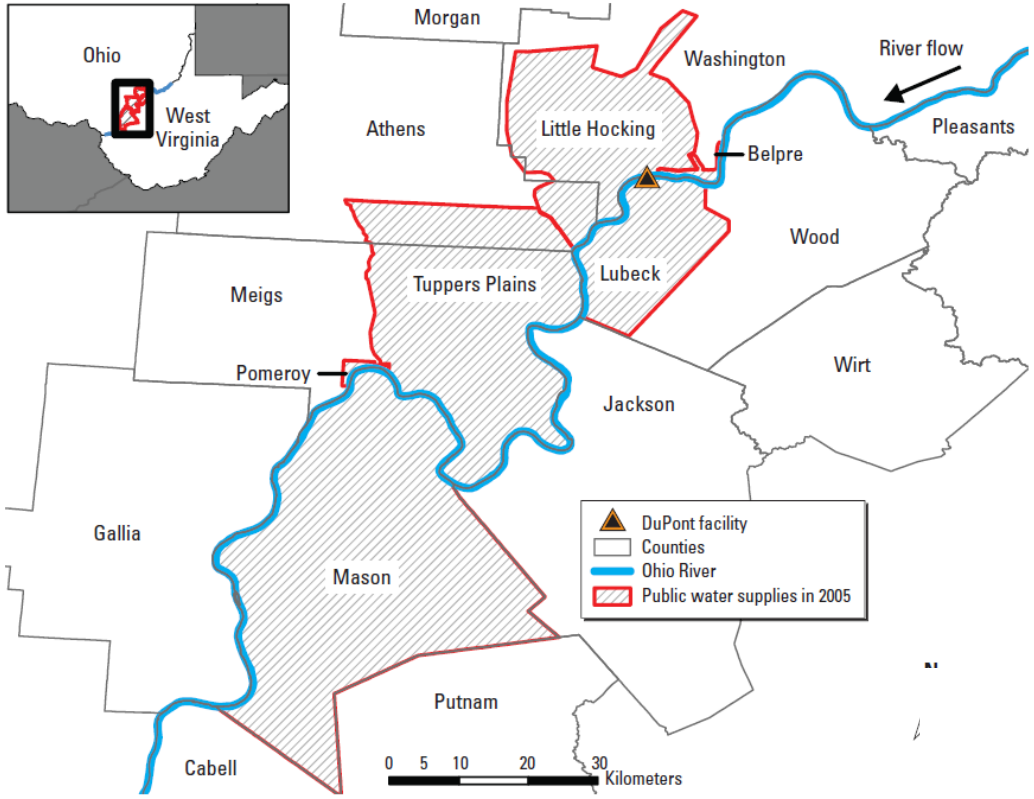
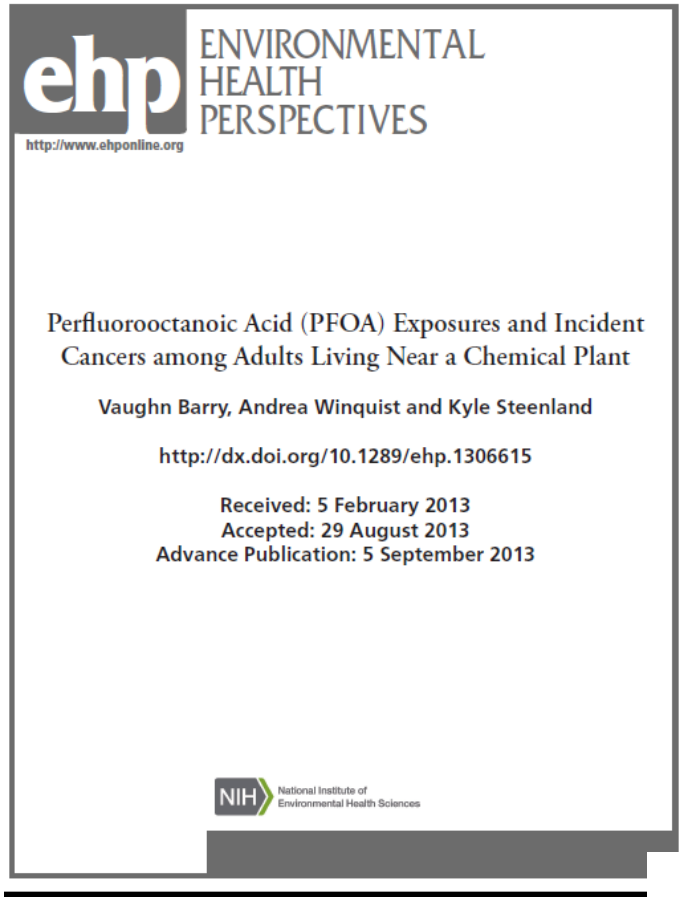


Figure 1. Study area of 13 counties encompassing six contaminated water districts.

…our results *suggest* that higher PFOA serum leves *may be* associated with increased cancer at several sites…

Supported by the C8 Class Action



V. Barry et al. (2013) PFOA exposure and incident cancers among adults living near a chemical plant. Env.Health Perspect. e-pub 5 Sept. 2013 *

Objective: examine cancer incidence in mid-Ohio valley residents exposed to PFOA in drinking water due to chemical plant emission

Results: cumulative serum, PFOA positively associated with cancers… findings must be interpreted with caution

* Supported by the C8 Class Action

ENVIRONMENTAL HEALTH

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P.Grandjean & E.Budtz-Jørgensen (2013) Immunotoxicity of perfluorinated alkylates: calculation of benchmark doses based on serum concentrations in children.

«Current drinking water limits need to be reconsidered in the light of the observed immunotoxicity associated with PFCs exposure.»

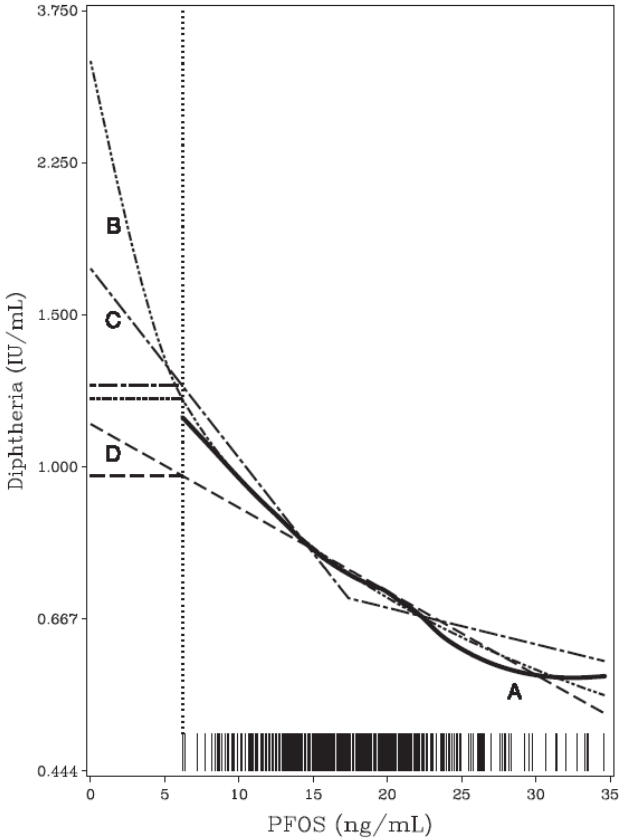

Figure 1 Estimated dose–response functions for the relationship between PFOS and the diphtheria-antibody

Conclusioni.1

- Enti regolatori diversi hanno proposto nel recente passato differenti dosi tollerabili per PFOA e PFOS, o valori guida nell'acqua potabile, anche partendo dagli stessi dati sperimentali.

- Tali divergenze rispecchiano le difficoltà insite nel *risk assessment* dei composti perfluoroalchilici, per le loro non comuni caratteristiche chimiche e biologiche.

- Sulla base delle conoscenze attuali il TDI proposto dall'EFSA costituisce un riferimento pragmaticamente utile e scientificamente valido.

Conclusioni.2

- Tutti i valori guida proposti sono comunque stati ottenuti con approcci conservativi, e vanno dunque interpretati come livelli massimi cautelativamente da non superare piuttosto che come *cut-off* per effetti tossici.

- La continua produzione di nuove evidenze scientifiche suggerisce l'opportunità di una periodica rivalutazione della tossicità dei PFAS e della congruità dei valori guida eventualmente proposti.