Alterazione della funzione tiroidea, neoplasia tiroidea e PFAS:

LE POSSIBILI RELAZIONI

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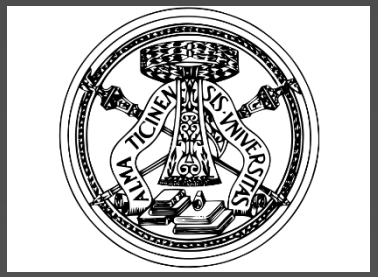


Dichiarazione di conflitti d'interesse

NESSUNO

Distruttori Endocrini

(*Endocrine Disrupting Chemicals o EDC)*

Sostanze esogene o miscele di sostanze esogene (*prevalentemente di origine industriale*) **che:**

(*interferendo con la produzione, il rilascio, il trasporto, il metabolismo, il legame, l'azione o l'eliminazione degli ormoni che nell'organismo mantengono l'omeostasi e regolano i processi di sviluppo*) **causano effetti avversi sulla salute di un organismo, oppure della sua progenie, o su sottopopolazioni**

European Workshop on the Impact of Endocrine Disrupters on Human Health and Wildlife, Weybridge (2-4/12/1996) e The World Health Organization, International Programme on Chemical Safety (IPCS/WHO 2002)

Sostanze naturalmente presenti nell'ambiente

- **Composti organici solforati (tiocianati, iso-tiocianati, goitrina, disulfidi):**
  - ***Cassava***, *miglio americano, fagioli di Lima, germogli di bamboo,* ***brassicacee****, aglio, cipolla, acque provenienti da particolari sottosuoli*
- **Flavonoidi e loro metaboliti (cianidina, vitexina, floretina):**
  - *Melissa officinalis, Lycopus europeus, miglio, sorgo*
- **Derivati fenolici e idrossi-fenolici:**
  - *Resorcinolo, sostanze umiche, derivati del carbone, argille*
- **Piridine:**
  - *Derivati del carbone, alcuni legumi tropicali*
- **Ftalati:**
  - *Argille, petrolio, alcuni funghi*
- **Fitoestrogeni:**
  - ***Ginesteina****, cumestrolo*
- **Idrocarburi policiclici aromatici**
  - *Metilcolantrene, metilantracene, derivati del carbone*

Sostanze volontariamente introdotte nell'ambiente

- **Diserbanti:**
  - *Amidi (ossiacetamide)*
  - *Triazine (atrazina, cianazina)*
  - *Triazoli (**aminotriazolo**), acetochlor, pronamide*
- **Insetticidi:**
  - *Carbamati (carbaryl, carbofuran)*
  - *Organocloruri (alachlor, DDT, endosulfan)*
  - *Organofosfati (dimetoato, malathion, metilparathion)*
  - *Piretroidi*
- **Fungicidi:**
  - ***Tiocarbamati** (mancozeb, maneb, zineb), tiourea (etilenetiourea)*
  - *Esaclorobenzene, Vinclozin*
- **Fertilizzanti:**
  - ***Perclorato**, nitrati*

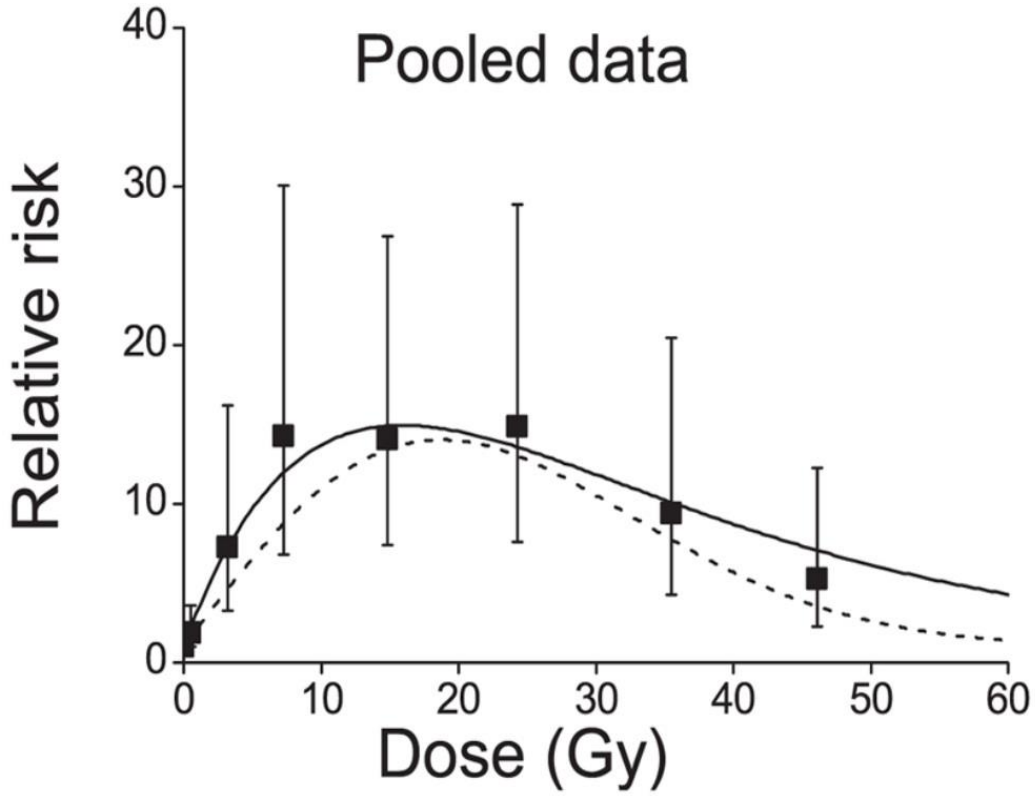
Sostanze «inevitabilmente, accidentalmente/illegalmente introdotte nell'ambiente

- **Poli-clorobifenili (PCB):**
  - *Fluido refrigerante di trasformatori e condensatori*
- **Diossine:**
  - *Sottoprodotti industriali, contaminanti di pesticidi e diserbanti, derivati di combustione negli inceneritori*
- **Derivati fenolici e idrossi-fenolici:**
  - *Sottoprodotti della lavorazione del carbone*
- **Plastiche e catalizzatori della plastica**
  - *Ftalati, **Bisfenolo A***
- **Idrocarburi policiclici aromatici:**
  - *Scarichi industriali, rifiuti urbani*
- **Metalli pesanti:**
  - *Piombo, cadmio, mercurio*
- **Sostanze radioattive (incidenti nucleari)**

Effetti degli EDC sulla fauna selvatica e sull'uomo

- Persistenza nell'ambiente (non biodegradabili)
- Accumulo in tessuti animali/umani
- Età al momento dell'esposizione (finestra temporale)
- Latenza dall'esposizione
- Effetti trans-generazionali
- Effetti epigenetici
- Miscele di EDC (effetto cocktail)
- Effetto non monotonico

NEOPLASIE TIROIDEE DA RADIAZIONI



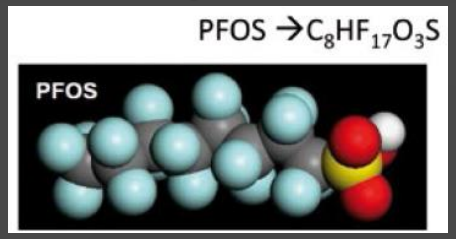
Rischio di neoplasia tiroidea in bambini sottoposti a radioterapia

- **Aumento del RR con la dose** (RR= 6.8 per dosi di 2-4 Gy, RR=14.9 per dosi di 5-9 Gy)
- **Plateau** per dosi di 10-30 Gy (RR=14.8 per dosi di 10-19 Gy, RR=15.2 per dosi di 20-29 Gy)
- Riduzione del rischio a dosi superiori, probabilmente a causa della **distruzione cellulare** (RR=9.3 per dosi di 30-39 Gy, RR=5.1 per dosi >40 Gy)

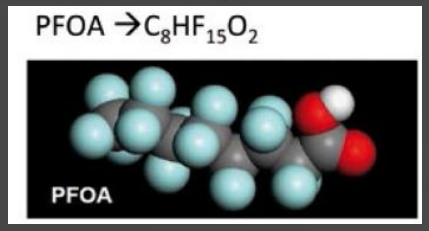
Veiga et al., *Radiation Res 2012; 178:365*

PFAS: Sostanze Alchiliche Perfluorate

PFOS = acido perfluoro ottan sulfonico



PFOA = acido perfluoro ottanoico



"Surface active agent"

- **Anfoteri**
- **bassa tensione superficiale**
- **resistenza al calore**
- **resistenza alla degradazione chimica e microbica**
- **elevata solubilità in acqua**

PFOA: iniziatore di catena per la produzione di fluoropolimeri (come il teflon)

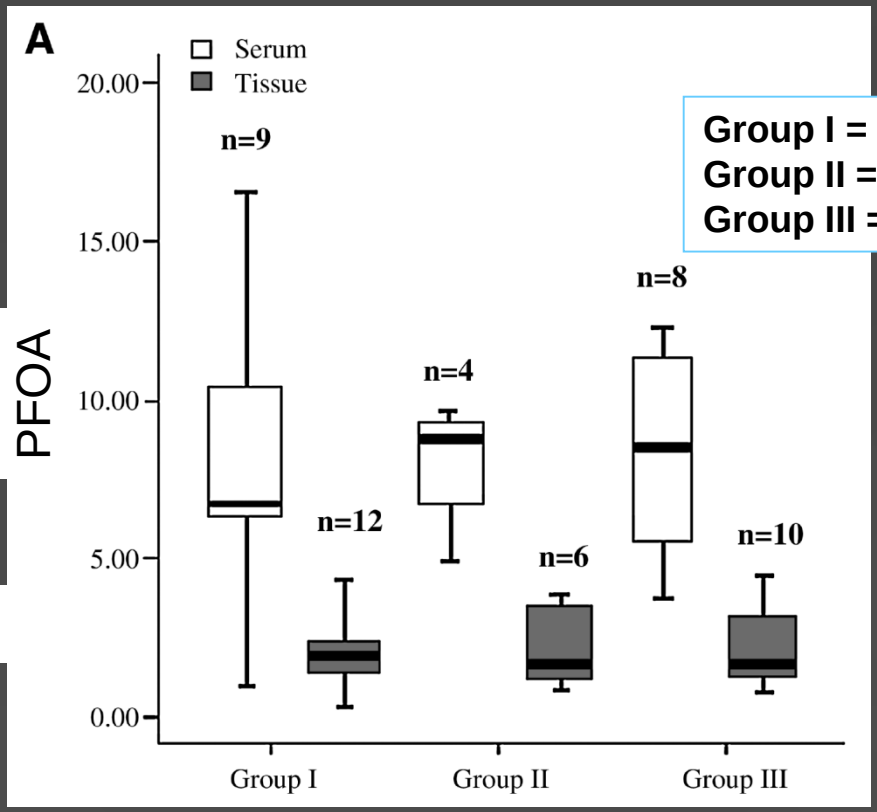
PFOS: trattamenti impermeabilizzanti di pelle e tessuti (rivestimento di carta e cartone, impermeabili, schiume anti-incendio, pitture e vernici, detergenti, industria fotografica)

- **Ratti = 90 giorni**
- **Scimmie 200 giorni**
- **Uomo = 3-6 anni**

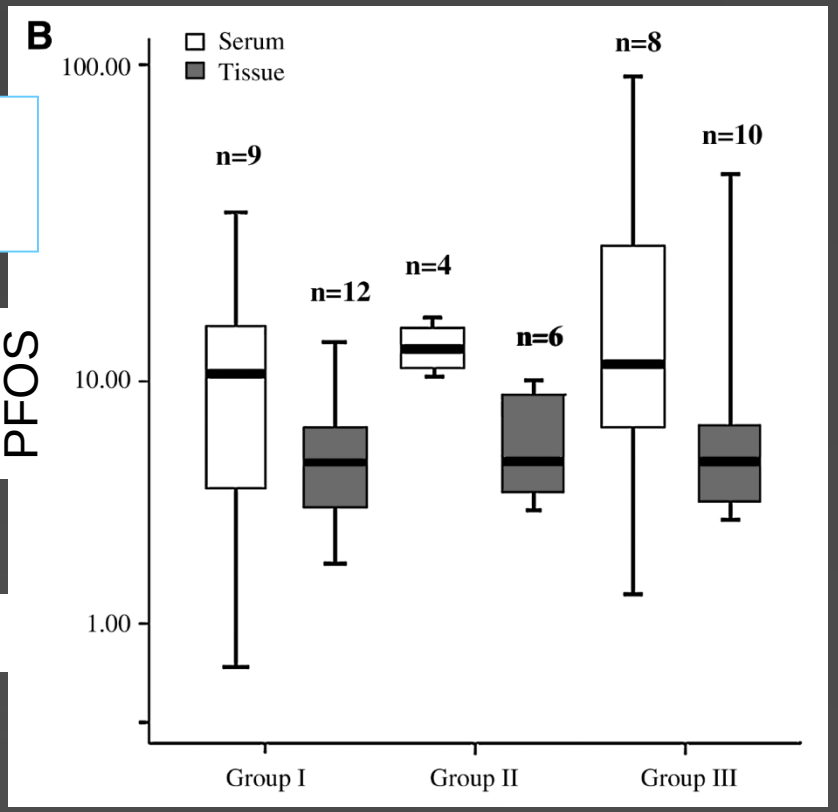
2005: EPA classifica PFOA e PFOS come *likely carcinogen*

Perfluorooctane Sulfonate and Perfluorooctanoic Acid in Surgical Thyroid Specimens of Patients with Thyroid Diseases

Pirali et al. Thyroid 2009



Group I = MNG
Group II = DTC
Group III =HT or GD



- Intra-thyroidal concentrations of PFOA and PFOS were similar in surgical specimens of patients with thyroid diseases compared with normal thyroid glands obtained at autopsy
- There was no relationship between the intrathyroidal concentrations of either PFOA or PFOS and the type of underlying thyroid disease
- A significant correlation between the serum and the tissue levels of PFOS was found in all patients.
- The serum concentrations of PFOA and PFOS were significantly higher than those in the correspondent surgical specimens.

Association between Serum Perfluorooctanoic Acid (PFOA) and Thyroid Disease in the U.S. National Health and Nutrition Examination Survey

David Melzer,[1] Neil Rice,[1] Michael H. Depledge,[2] William E. Henley,[3] and Tamara S. Galloway[4]

[1]Epidemiology and Public Health Group, and [2]Environment and Human Health Group, Peninsula Medical School, Exeter, United Kingdom; [3]School of Mathematics and Statistics, University of Plymouth, Plymouth, United Kingdom; [4]School of Biosciences, University of Exeter, Exeter, United Kingdom

Environmental Health Perspectives, 2010

- The NHANES-weighted prevalence of reporting any thyroid disease was 16.18% (n = 292) in women and 3.06% (n = 69) in men.
- In fully adjusted logistic models, women with PFOA ≥ 5.7 ng/mL were more likely to report current treated thyroid disease [odds ratio (OR) = 2.24; 95% confidence interval (CI), 1.38–3.65; p = 0.002] compared with PFOA ≤ 4.0 ng/mL (quartiles 1 and 2)
- Men with PFOS ≥ 36.8 ng/mL (quartile 4) versus ≤ 25.5 ng/mL (quartiles 1 and 2: OR for treated disease = 2.68; 95% CI, 1.03–6.98; p = 0.043) had a similar association

Higher concentrations of serum PFOA and PFOS are associated with current thyroid disease in the U.S. general adult population

US GENERAL POPULATION

Analyses of PFOA/PFOS versus thyroid function in the NHANES in 2007–2008 and in 2009–2010:

Coperchini et al. J Endocrinol Invest 2017

Geometric means (ng/ml) and 95% confidence interval (CI) PFOA = 4.15 (4.02–4.29) PFOS = 14.2 (13.59 –14.86) PFNA = 1.54 (1.48–1.59) PFHxS = 2.00 (1.89–2.11) In the full-sample PFCs: Higher in men than in women Different among ethnic groups Higher in individuals with more education Higher in older people	After weighting for sampling strategy, in women: A 1-U increase in natural Log-serum PFOA increased TT3 by 6.628 ng/dl ($P = 0.035$) A 1-U increase in natural log-PFHxS increased TT4 by 0.26 mcg/mL ($P = 0.002$) and TT3 by 4.074 ng/dl ($P = 0.001$) A 1-U increase in natural log-PFHxS decrease in natural log-FT4 by 0.016 ng/dl ($P = 0.019$) in men. In adjusted regression models, associations between: 1-U increase in natural log-serum PFOA, PFOS, PFHxS, and subclinical hypothyroidism in women (OR 7.41, 3.03, and 3.10, respectively) 1-U increase in natural log-serum PFOS was positively associated with subclinical hypothyroidism in men (OR 1.98) 1-U increase in natural log-serum PFHxS was positively associated with subclinical hyperthyroidism in women (OR 2.27) 1-U increase in natural log-serum PFOA was negatively associated with subclinical hyperthyroidism in men (OR 0.38)	Melzer et al. [64]

GENERAL POPULATION IN KOREA
(Siheung city)

PFOA/PFOS levels	Effect on thyroid function	References
Serum PFOS concentrations: Median = 7.96 ng/ml Range 5.58–12.10 ng/ml Serum PFOA concentrations: Median = 2.74 Range 2.04–3.64 ng/ml Serum PFTrDA concentrations: Median = 0.39 ng/ml Range 0.27–0.57 ng/ml	PFOS and PFOA not associated with TT4 or TSH PFTrDA associated: Negatively with TT4 Positively with TSH	Ji et al. [66]

Coperchini et al. J Endocrinol Invest 2017

OCCUPATIONALLY EXPOSED POPULATION

Employees of two perfluorooctanyl manufacturing facilities at Antwerp, Belgium and Decatur, Alabama (USA)

PFOA/PFOS levels	Effect on thyroid function	References
Mean serum concentrations in Decatur PFOS = 1.32 ppm (geometric mean 0.91, range 0.06–10.06 ppm) PFOA = 1.78 ppm (geometric mean 1.13, range 0.04–12.70 ppm) Mean concentrations 50% in Antwerp workers	After adjusting for potential confounding factors, no substantial changes in thyroid parameters in cross-sectional or longitudinal analyses Positive association between PFOS and TT3 in the longitudinal assessment, but deprived of any clinical relevance for this association	Olsen et al. [57]

Employees of three PFOA manufacturing facilities at Antwerp, Belgium; Cottage Grove, Minnesota and Decatur, Alabama (USA):

Serum PFOA concentrations Arithmetic mean = 2210 ng/ml Median = 1100 ng/ml Range 7–92,030 ng/ml	In analyses of all locations: PFOA No association with TSH or TT4 Negative association with FT4 Positive association with TT3 (all within the normal reference ranges)	Olsen and Zobel [58] **Coperchini et al. J Endocrinol Invest 2017**

NON-OCCUPATIONALLY EXPOSED POPULATION (Persons who had resided in the Little Hocking Water Association district for at least 2 years (water supplies contaminated with PFOA for many years)

Median PFOA = 354 ng/ml interquartile range 181–571 ng/ml	No significant positive relationships between serum PFOA and TSH Mean serum PFOA not increased in residents with a history of thyroid disease	Emmett et al. [59]

Coperchini et al. J Endocrinol Invest 2017

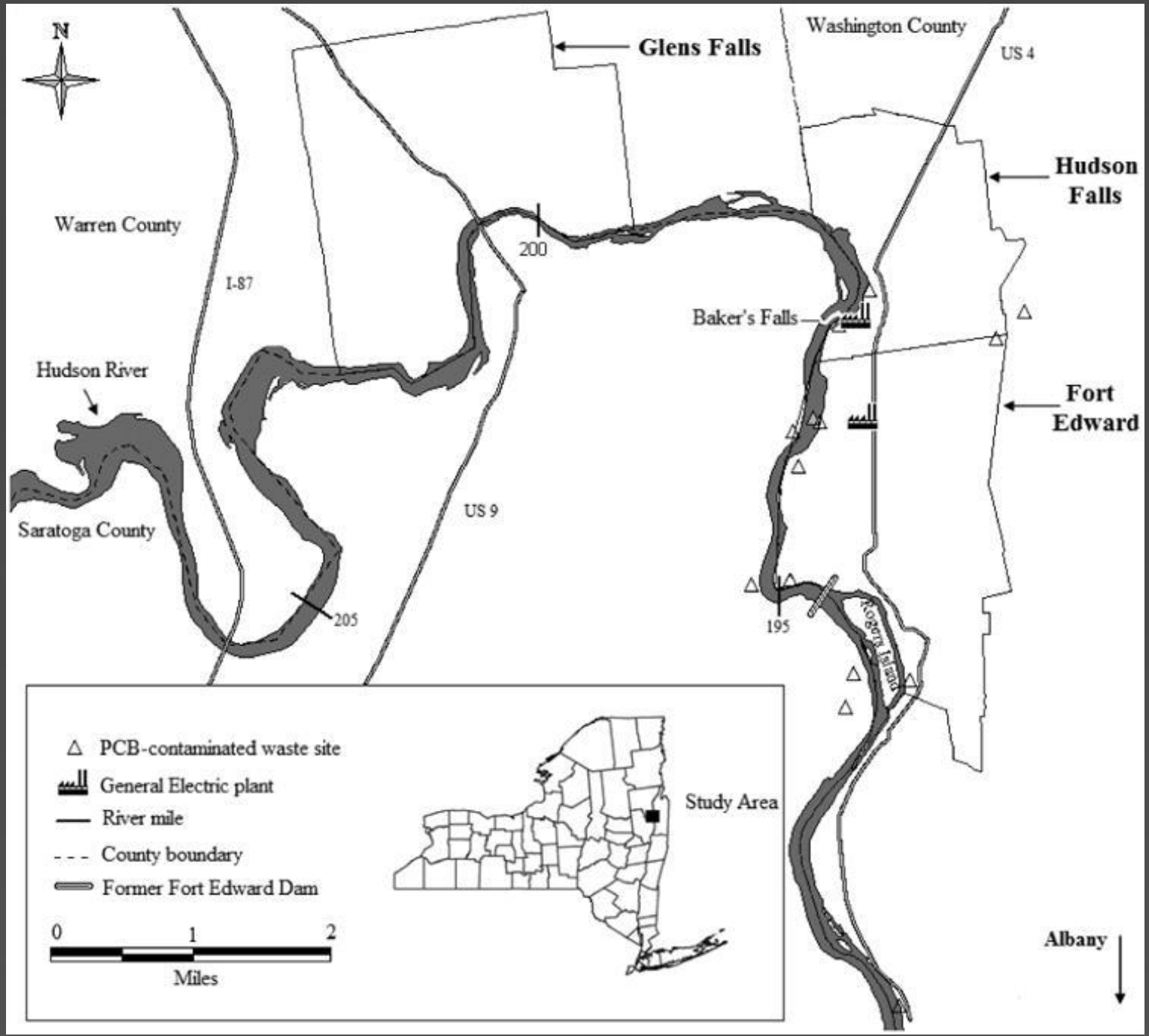
NON-OCCUPATIONALLY AND OCCUPATIONALLY EXPOSED POPULATION (Residents of the mid-Ohio River Valley exposed to PFOA-contaminated drinking water)

Mean (SD) PFOA serum concentrations Men 91.0 (261.5) ng/ml >50 Years = 124.3 (380.8) ng/ml Women = 52.6 (192.8) ng/ml >50 Years = 98.6 (230.2) ng/ml	PFOA and PFOS significantly associated with elevations of TT4 and reduction or T3 uptake in both men and women (a pattern suggesting an increased production of TBG, which was not measured)	Knox et al. [63]
Mean (SD) PFOS serum concentrations Men = 24.8 (14.3) ng/ml >50 Years = 29.1 (20.6) ng/ml Women = 17.3 (10.8) ng/ml >50 Years = 25.7 (17.5) ng/ml	No association with TSH	
Estimated serum PFOA concentrations: Community cohort by a multistage modeling procedure Plant workers by an occupational exposure model	HR for thyroid disease across cumulative exposure quintiles: Women = 1.00, 1.24, 1.27, 1.36, 1.37 ($P = 0.03$) Men = 1.00, 1.12, 0.83, 1.01, 1.05 ($P = 0.85$)	Winquist and Steenland [60]
Measured median PFOA serum concentration in 2005–2006 = 26.1 ng/ml (concentrations were higher in the late 1990s and early 2000s)	Women: increased HR for hyperthyroidism (retrospective analysis) and hypothyroidism Men: increased HR for hypothyroidism (prospective analysis)	**Coperchini et al. J Endocrinol Invest 2017**

NON-OCCUPATIONALLY EXPOSED POPULATION (Children 1–17 years of age living in the mid-Ohio River Valley USA)

PFOA/PFOS levels	Effect on thyroid function	References
Median concentrations of: Modeled in utero PFOA = 12 ng/ml Median measured in serum: PFOA = 29 ng/ml PFOS = 20 ng/ml PFNA = 1.5 ng/ml	Serum PFOA concentrations (2005–2006) positively associated with thyroid disease (mostly hypothyroidism) Serum concentrations of PFOS and PFNA, but not PFOA, positively associated with TT4 levels	Lopez-Espinosa et al. [68]

Coperchini et al. J Endocrinol Invest 2017


N
Glens Falls
Washington County
US 4
Hudson Falls
Warren County
200
I-87
Baker's Falls
Hudson River
Fort Edward
Saratoga County
US 9
205
195
Kaydeross Island
PCB-contaminated waste site
General Electric plant
River mile
County boundary
Former Fort Edward Dam
0
1
2
Miles
Study Area
Albany

NON-OCCUPATIONALLY EXPOSED POPULATION (Men and women 55–74 years old who lived in 3 Hudson River communities in New York State for ≥25 years, in the proximity to General Electric plants)

Serum concentrations (geometric mean) PFOS = 31.6 ng/ml PFOA = 9.2 ng/ml	PFOS: 1 interquartile range difference = 4 and 9% increases in FT4 and TT4, respectively PFOA: joint increases with age = 3 and 7% increases in FT4 and TT4, respectively Interactions between: PFOS and total PCBs for the effect on TT3 PFOA and total PBDEs for the effect on TSH All alterations subtle	Shrestha et al. [70]

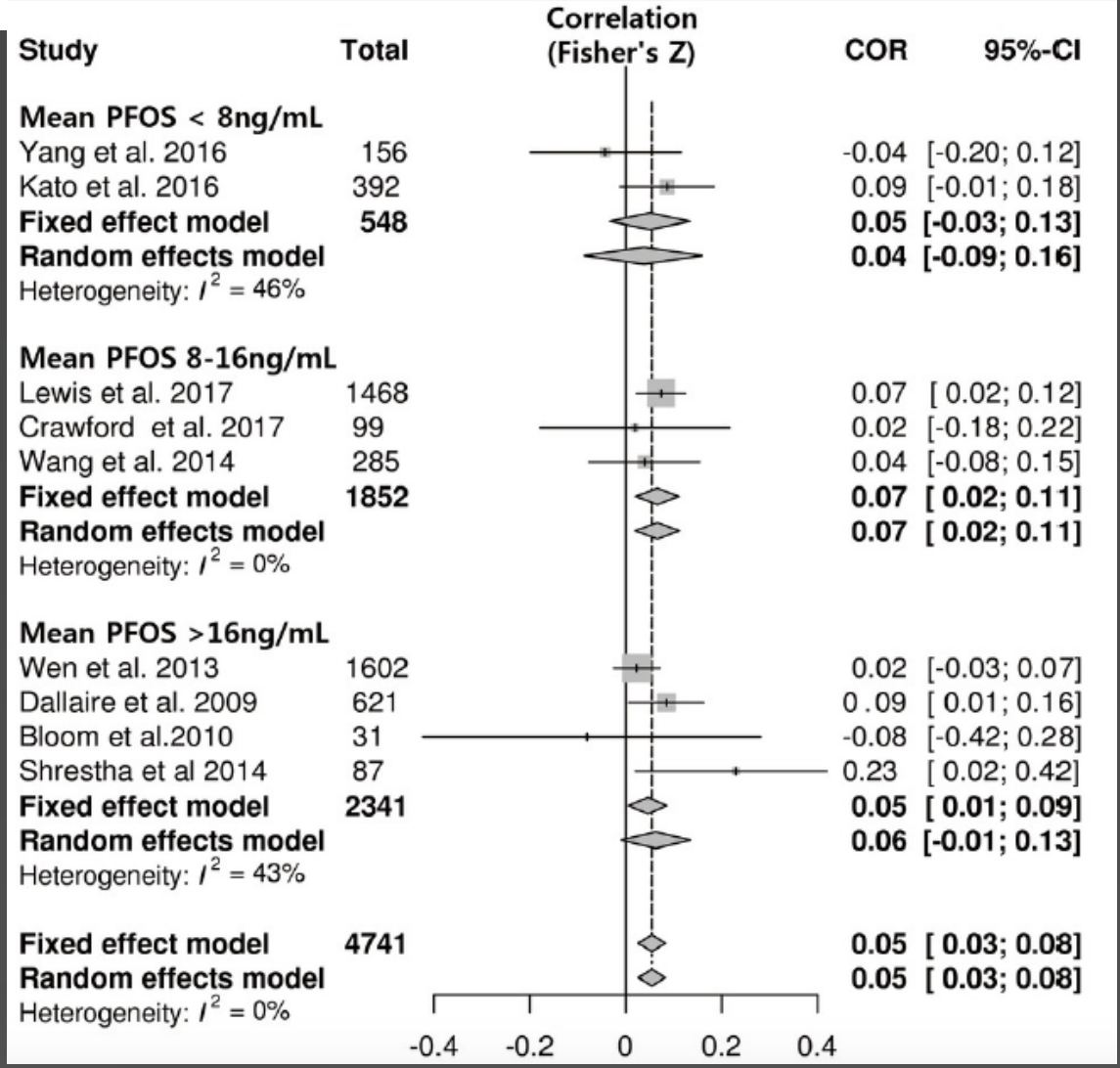
Coperchini et al. J Endocrinol Invest 2017

Association between perfluoroalkyl substances exposure and thyroid function in adults: A meta-analysis

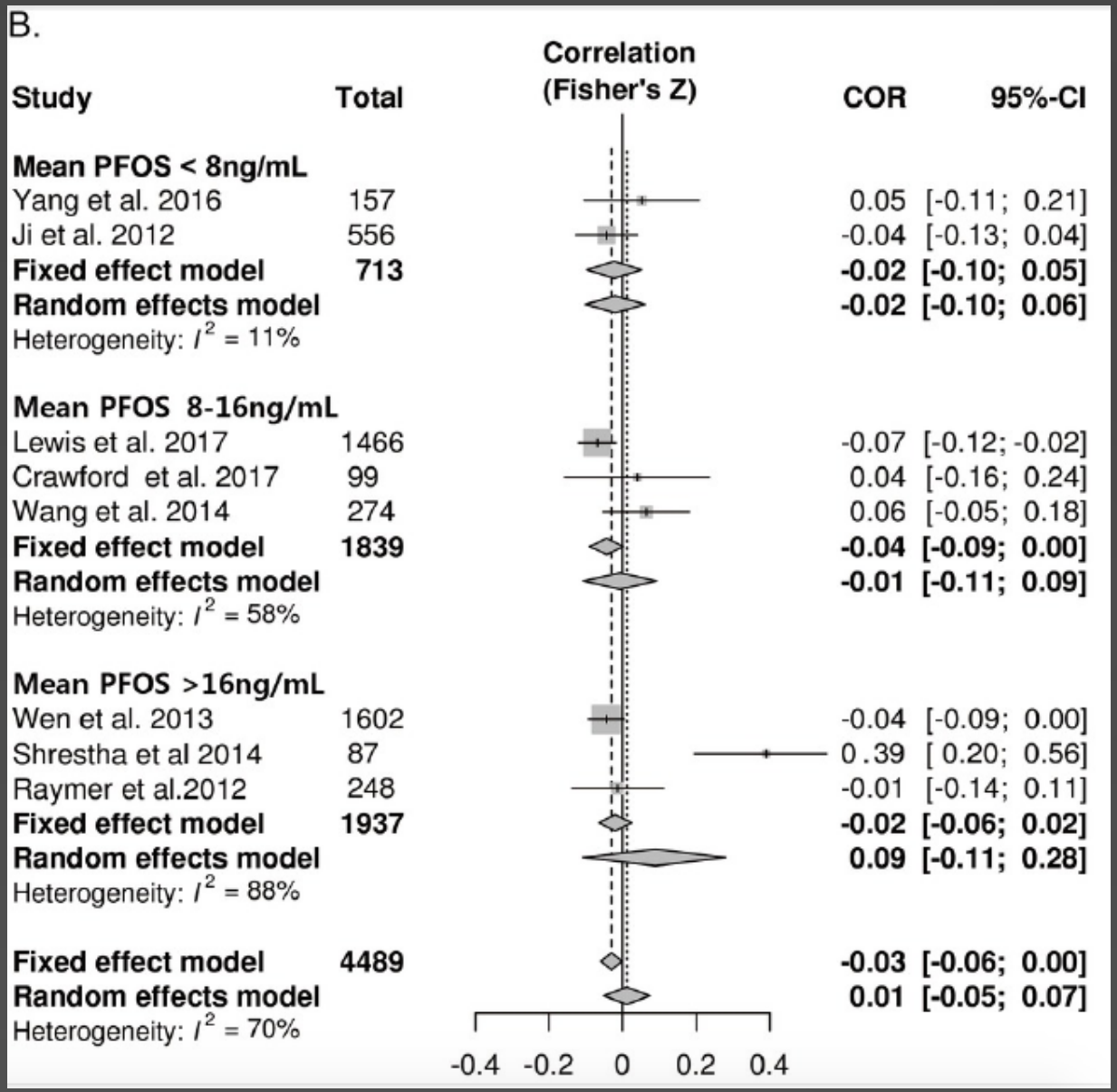
Min Joo Kim[1☯], Shinje Moon[2☯], Byung-Chul Oh[3], Dawoon Jung[4], Kyunghee Ji[5], Kyungho Choi[6], Young Joo Park[1]*

PFOS and freeT4

- **PFOS positivamente correlato con FT4**



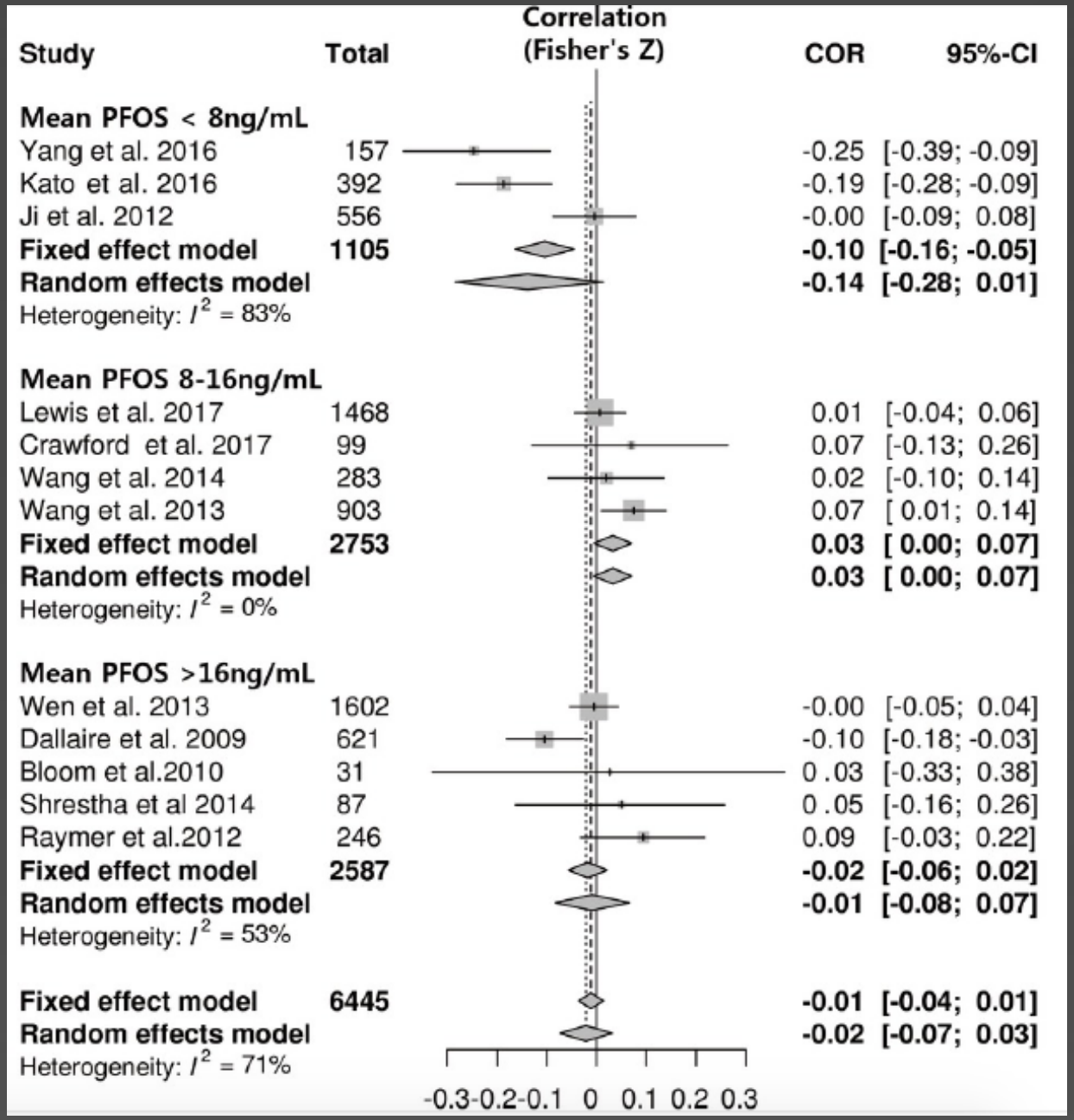
PFOS and total T4



- **PFOS era negativamente correlato al T4 totale**
- **Le analisi dei sottogruppi basate sulla concentrazione media di PFOS e sullo stato di gravidanza non hanno mostrato alcuna correlazione**

Kim et al., PLOS ONE 2018

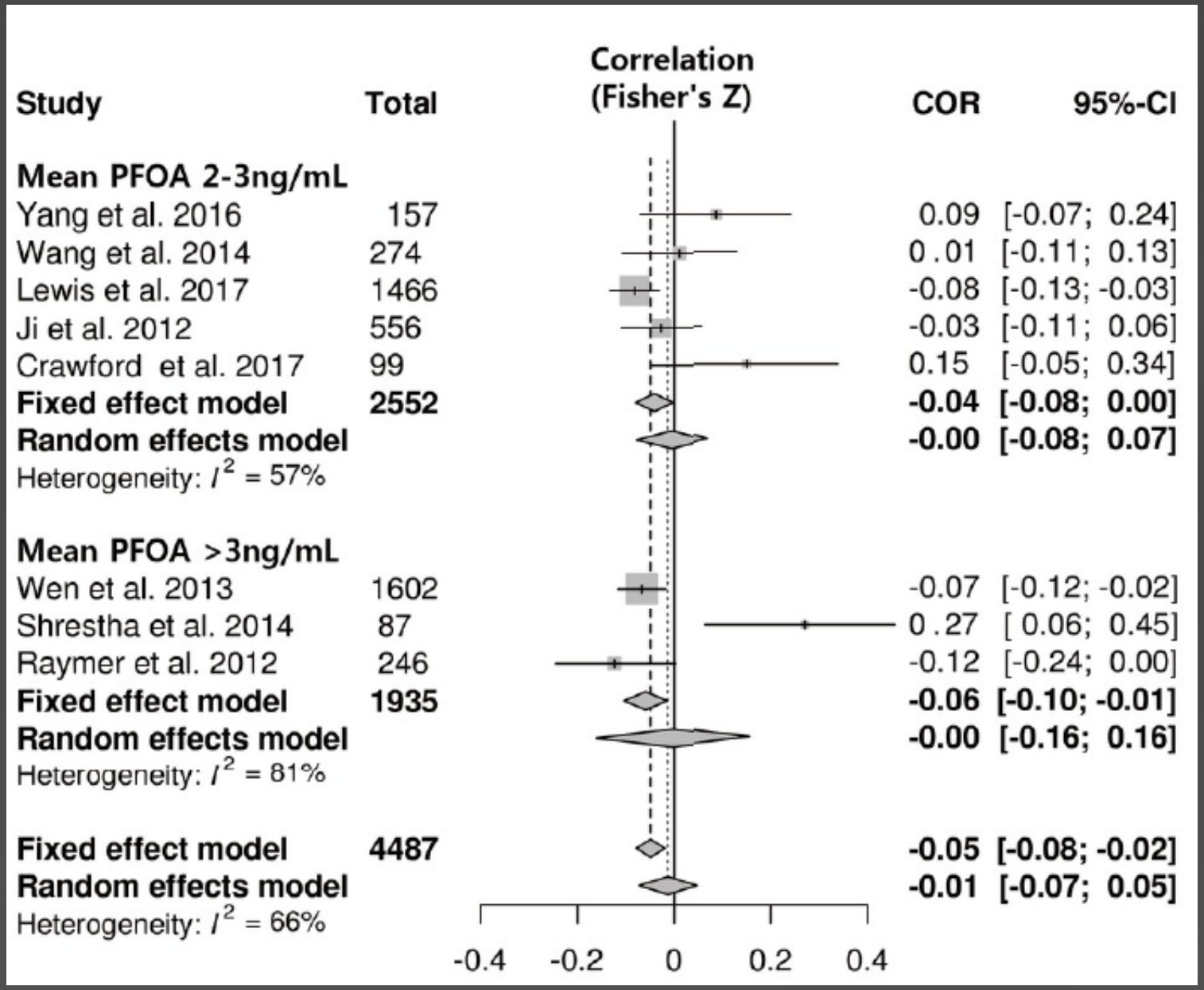
PFOS and TSH



Nell'analisi dei sottogruppi stratificata per concentrazione media di PFOS, è emersa una correlazione positiva statisticamente significativa tra PFOS e TSH nel gruppo intermedio

Kim et al., PLOS ONE 2018

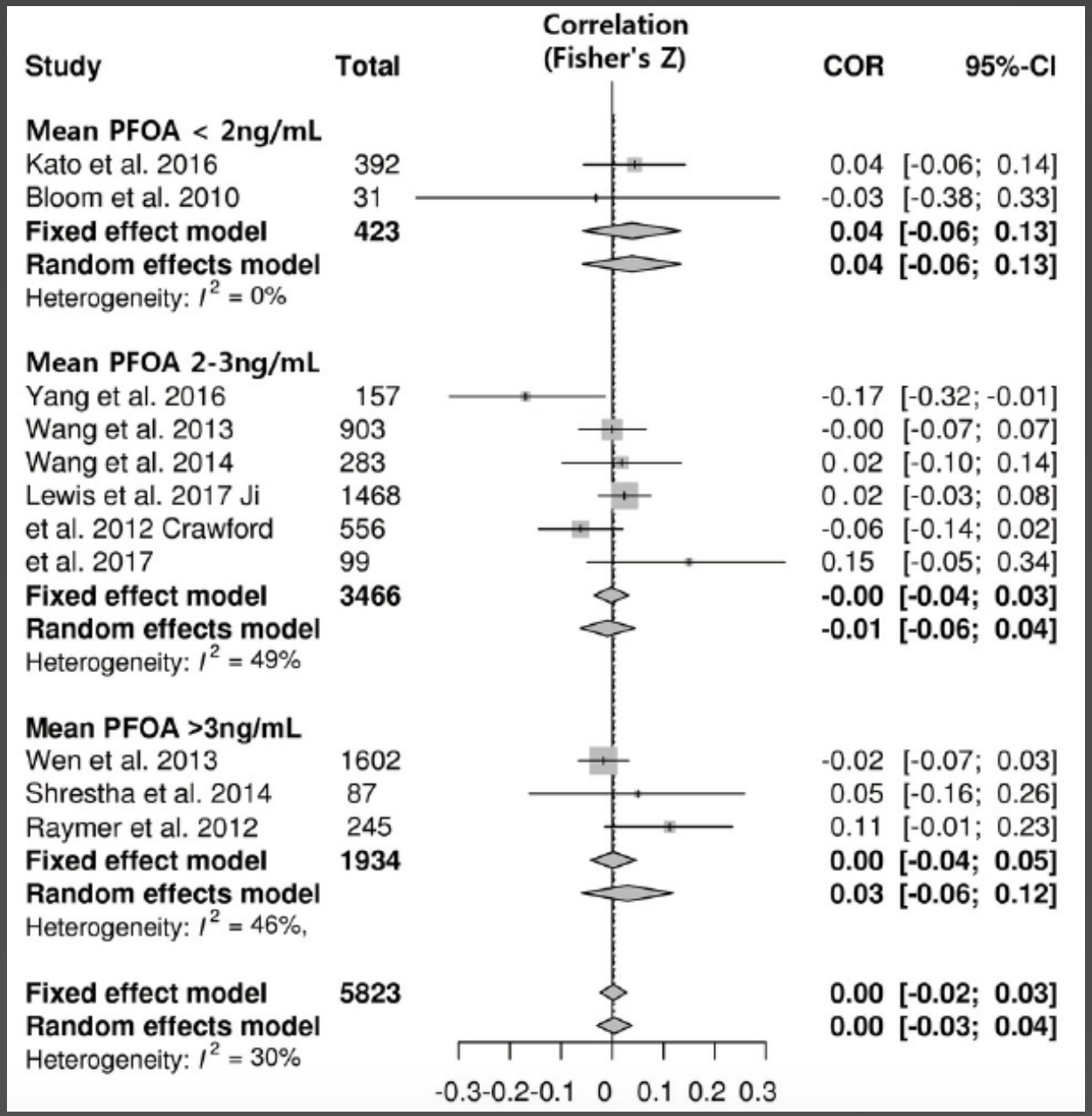
PFOA and total T4



Il pooled z value tra PFOA e T4 totale ha mostrato una modesta correlazione negativa

Kim et al., PLOS ONE 2018

PFOA and TSH



Nessuna correlazione significativa tra esposizione a PFOA e TSH

Kim et al., PLOS ONE 2018

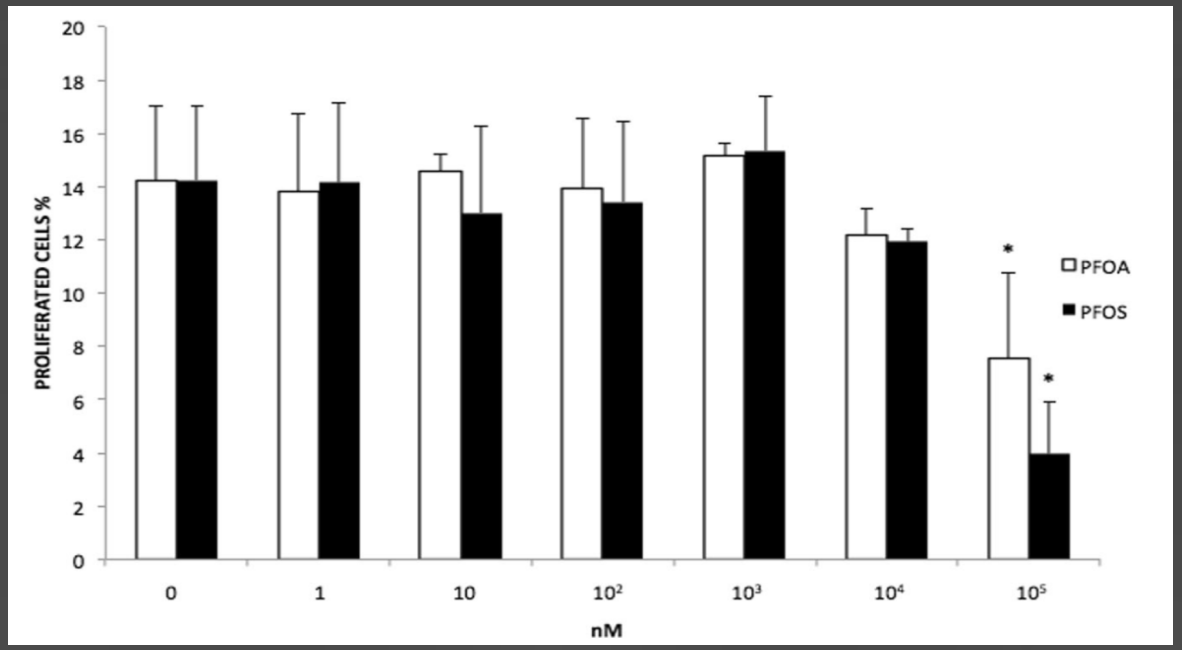
Thyroid disruption by perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA)

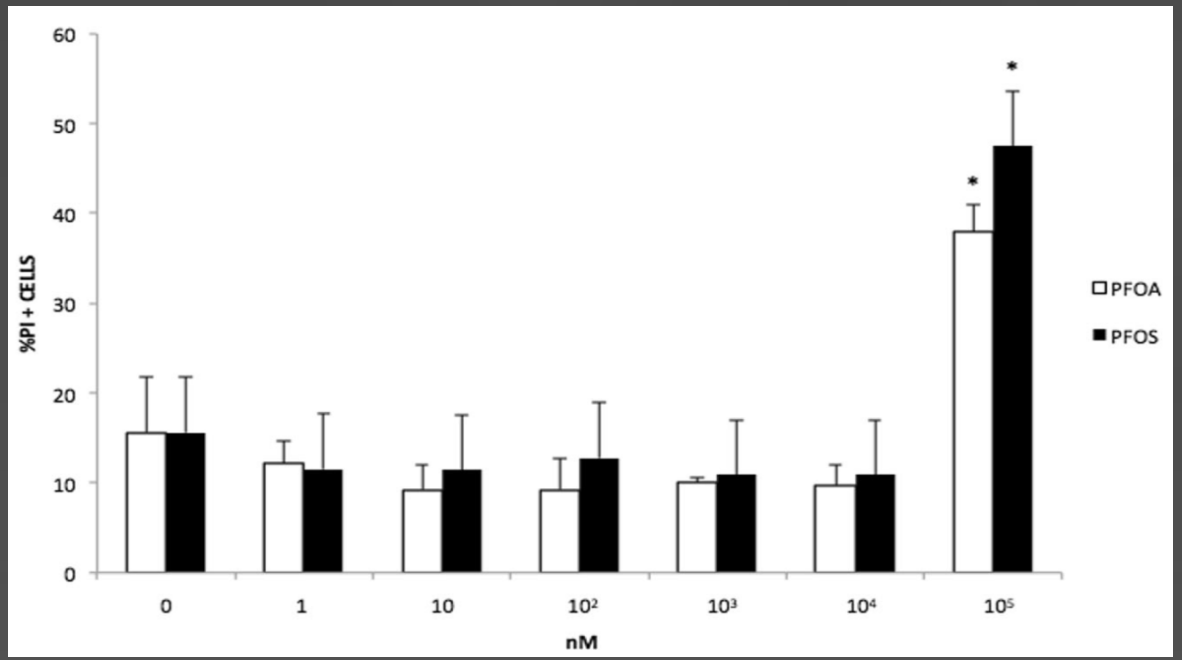
J Endocrinol Invest 2017

F. Coperchini[1] · O. Awwad[2] · M. Rotondi[1] · F. Santini[3] · M. Imbriani[4] · L. Chiovato[1]

PFOS e PFOA riducono i livelli di ormoni tiroidei in animali esposti a una dieta contenente tali composti, principalmente incrementando la loro clearance metabolica:

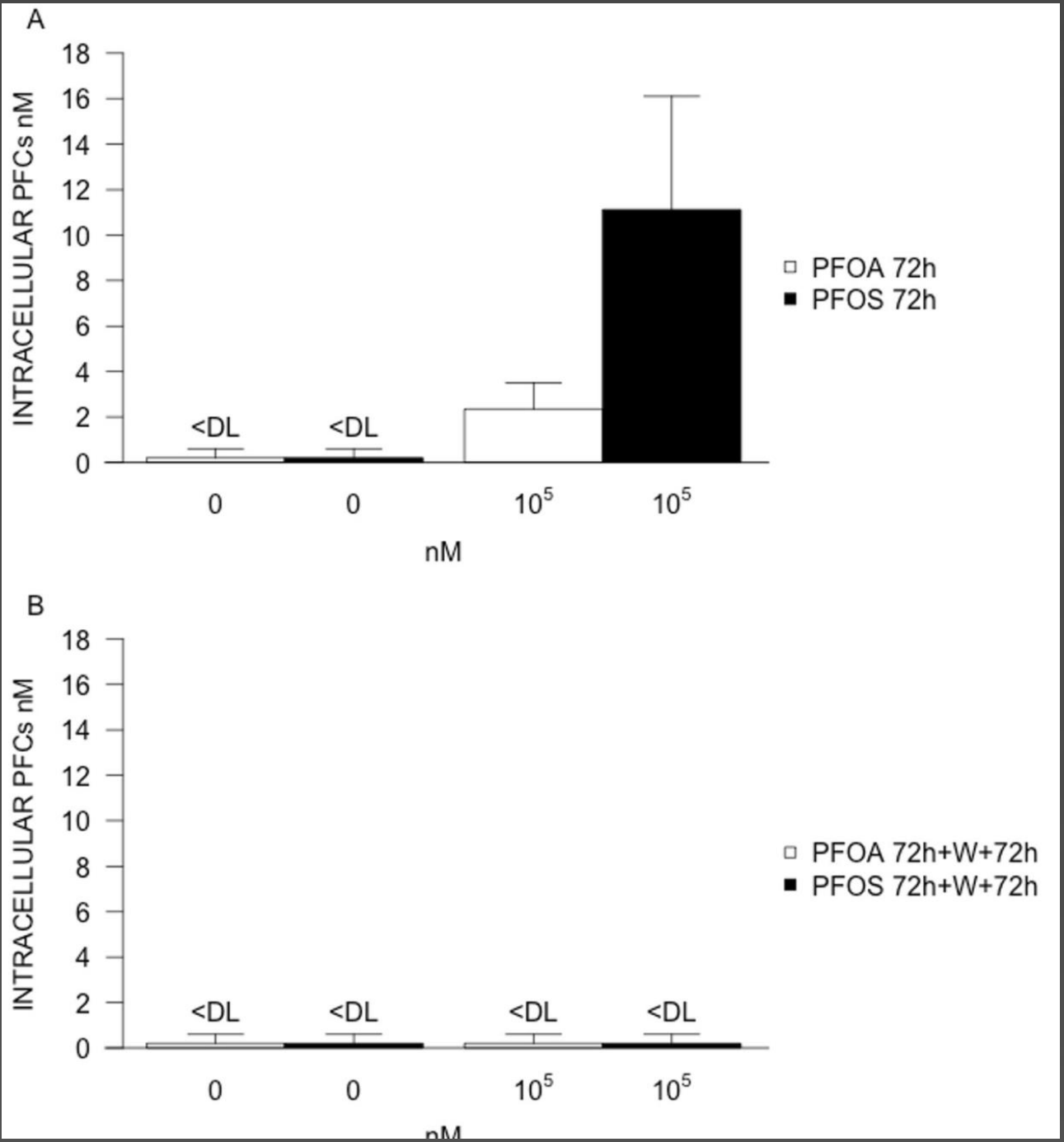
- Aumentando le proteine epatiche che accelerano la captazione di T4 e il suo efflusso dal fegato
- Inducendo l'enzima epatico UDP-glucuronoil-transferasi (UGT1a1), che incrementa la glucuronazione e la conseguente escrezione di T4 dal fegato
- Stimolando WY 14643, PPARα agonista, nel potenziare la degradazione epatica dell'ormone tiroideo
- Aumentando l'enzima desiodasi-1 DIO-1
- Legandosi in modo competitivo a TTR e spiazzando il legame di circa il 15% degli ormoni tiroidei





PFOA or PFOS at in vitro concentrations ranging from 1 to 10^4 nM do not affect cell viability and/or proliferation in a strain of differentiated rat thyroid cells (FRTL5), while a cytotoxic effect was found at a concentration of 10^5 nM of both PFCs

Coperchini et al.
Environ Sci Pollut Res 2014



The recovery rates, calculated as percentages of the concentration of either compound in the culture medium, were 0.0023 % for PFOA
and 0.0111 % for PFOS, respectively

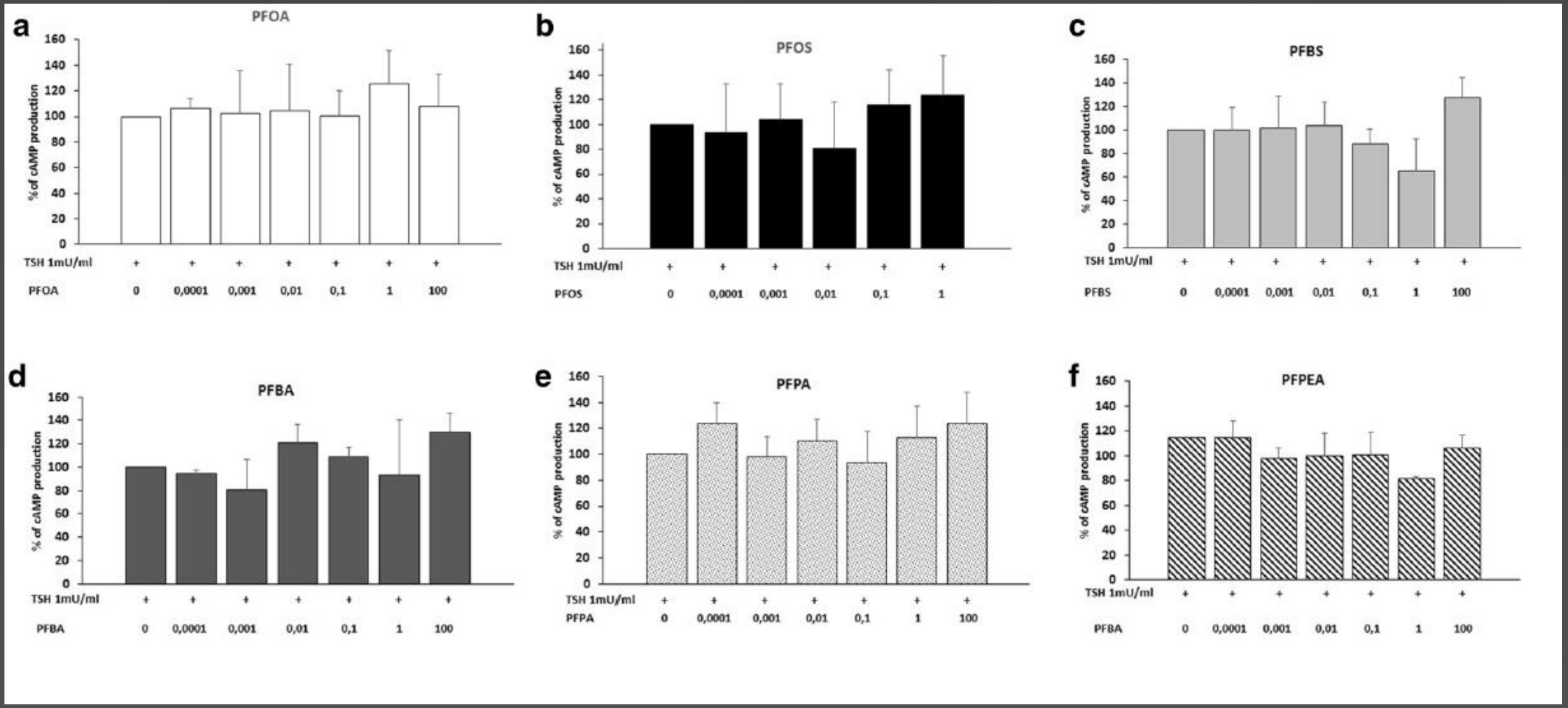
PFOA and PFOS 10^5 nM penetrate the cellular membrane of rat thyroid cells (FRTL-5) and human thyroid cells, likely by a passive diffusion mechanism

Coperchini et al.
Environ Sci Pollut Res 2014

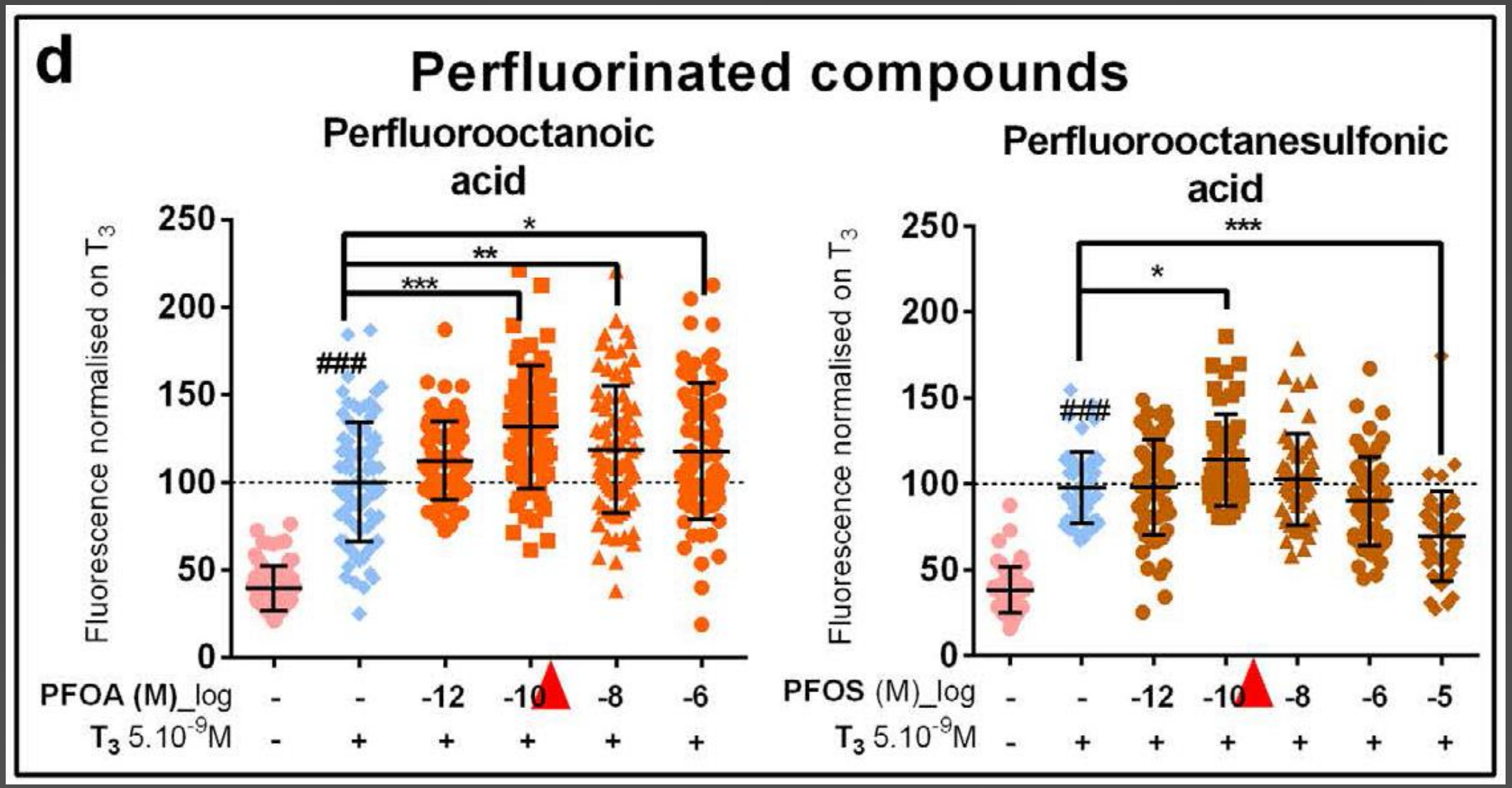
Effect of long- and short-chain perfluorinated compounds on cultured thyroid cells viability and response to TSH

J Endocrinol Invest 2019

L. Croce[1,2] · F. Coperchini[1] · M. Tonacchera[4] · M. Imbriani[5] · M. Rotondi[1,3] · L. Chiovato[1,3]



Thyroid disrupting activity of molecules measured in humans with the Xenopus Embryonic Thyroid Assay (XETA)



Fini et al., Sci Rep 2016

PFAS e tumore della tiroide

- Studio di alimentazione di 2 anni con PFOS o PFOA a concentrazioni fino a 20 ppm nella dieta in ratti maschi Sprague-Dawley
- Nel gruppo di recupero" (cioè esposti a PFOS solo per le prime 53 settimane dello studio) aumento statisticamente significativo dell'incidenza di adenomi a cellule follicolari tiroidee (Butenhoff et al. 2012)
- Questo risultato è stato considerato un falso positivo alla luce dell'assenza di qualsiasi risposta nel gruppo corrispondente che è stato esposto a 20 ppm PFOS per l'intero periodo di 2 anni
- In sperimenti simili, PFOA ha indotto adenomi epatici benigni, adenomi a cellule di Leydig e tumori delle cellule acinose del pancreas nei ratti. (Butenhoff et al. 2012aButenhoff JL, Kennedy GL Jr, Chang SC, Olsen GW 2012, Sibinski, 1987)

Perfluorooctanoic Acid Enhances Invasion of Follicular Thyroid Carcinoma Cells Through NF-κB and Matrix Metalloproteinase-2 Activation

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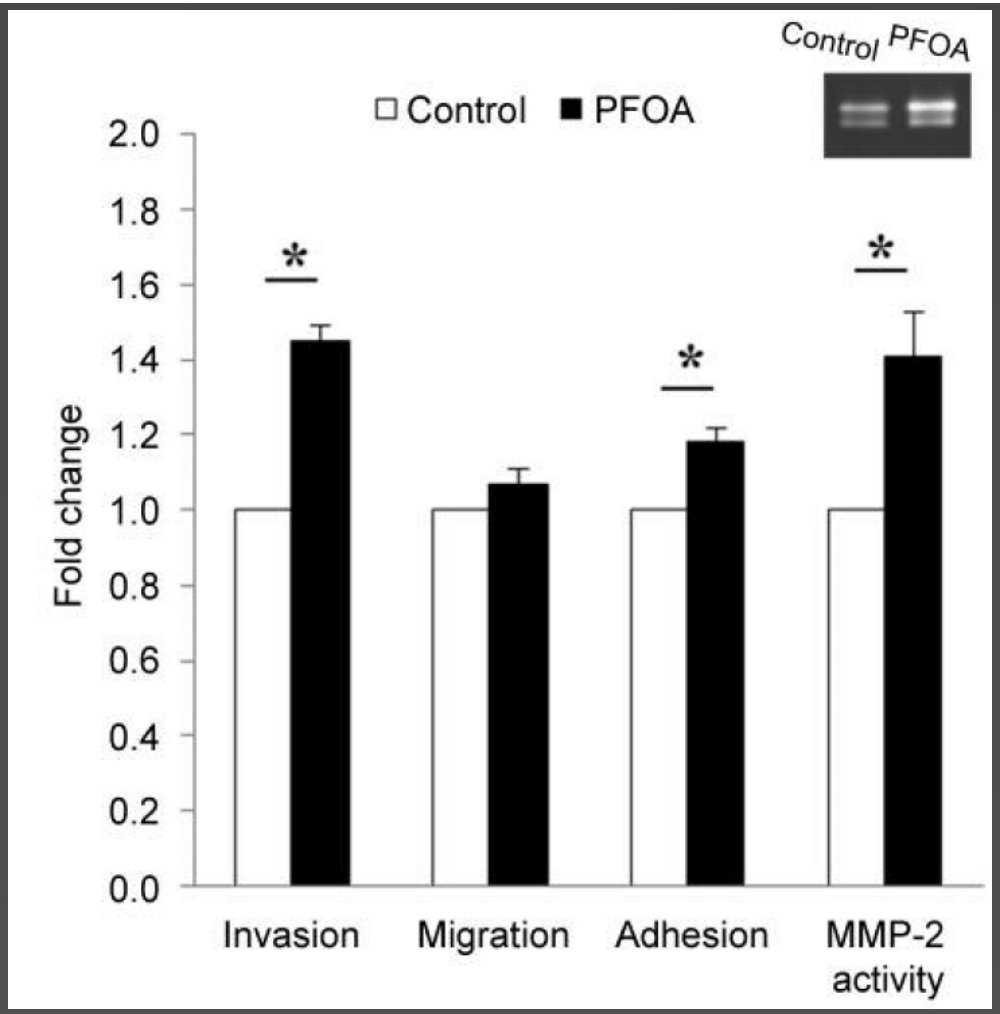
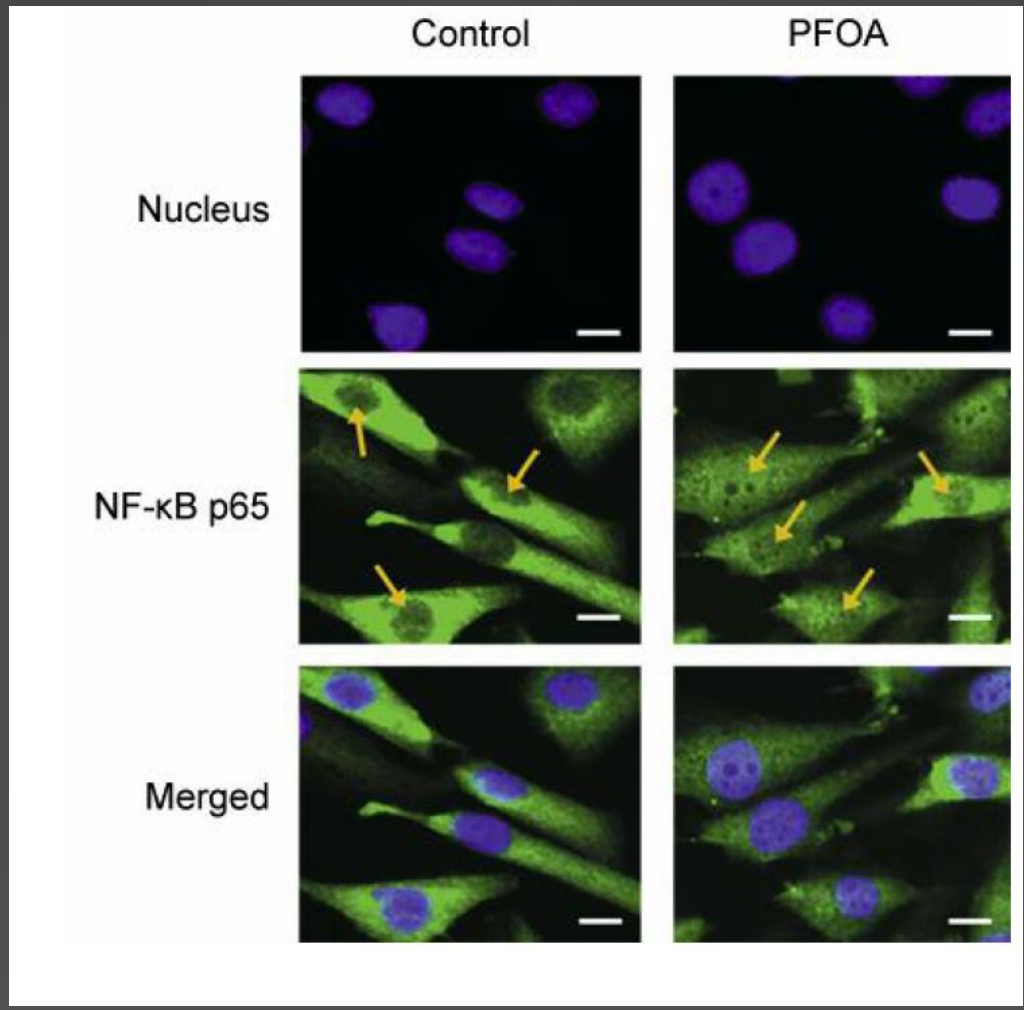
ANTICANCER RESEARCH *39*: 2429-2435 (2019)
doi:10.21873/anticanres.13360





OCCUPATIONALLY EXPOSED POPULATION

Occupationally exposed population to Parkersburg, West Virginia, USA Retrospective cohort mortality study Mean follow-up = 26 years men; 16 years women:

Median = 580 ng/ml (range 160–2880 ng/ml) Steenland and Woskie [31] No exposure–response gradient analysis	Excess mortality from thyroid and other endocrine gland cancers, compared only with the DuPont reference cohort	Leonard et al. [30] Steenland and Woskie [31]

Occupationally exposed population Parkersburg, West Virginia, USA Retrospective cohort mortality study Mean follow-up = 30 years:

Job exposure matrix in combination with serum PFOA data from 1308 workers in 1979–2004. (Median = 580 ng/ml) (range 160–2880 ng/ml) Mean estimated cumulative exposure = 7800 ng/ml-years	Thyroid cancer mortality not mentioned (presumably no significant relation) for any quartile of estimated cumulative PFOA exposure	Steenland and Woskie [31]

Occupationally exposed population (Cottage Grove, Minnesota, USA) Retrospective cohort mortality Follow-up 1947–1997, to 2002; mean = 31.3 years (29.3 years for definitely exposed, 31.6 years for probably exposed:

Semiquantitative job exposure matrix with 3 levels (definite, probable, or no/minimal)	Non-excess mortality for thyroid cancer	Lundin et al. [29]

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COMMUNITY STUDY AMONG RESIDENTS IN MID-OHIO VALLEY

Cancer-registry-based case–control study

Median PFOA serum levels in contaminated water districts Little Hocking = 125.0 ng/ml, Lubeck = 65.8 ng/ml, Tupper Plains = 23.9 ng/ml, Belpre = 18.7 ng/ml, Pomeroy = 10.7 ng/ml, Mason = 5.3 ng/ml PFOA exposure estimated based on residential water district at the time of diagnosis. Patients were geocoded to their street address at diagnosis. PFOA exposure was evaluated based on a model that estimated individual serum PFOA levels using linked environmental, exposure, and pharmacokinetic models	Higher PFOA serum levels may be associated with testicular, kidney, prostate, and ovarian cancers and non-Hodgkin lymphoma, but not with thyroid cancer	Vieira et al. [32]

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COMMUNITY STUDY AMONG RESIDENTS IN MID-OHIO VALLEY

Cohort cancer incidence study Self-reported cancers by questionnaire validated through medical records and cancer registry review:

Exposure to PFOA	Effect	References
Estimated median annual PFOA serum level = 19.4 (range 2.8–9217) ng/ml in community members and =174.4 (range 5.2–3683) ng/ml in workers PFOA exposure estimated similarly to Vieira et al. [32] Occupational PFOA exposure based on the job exposure matrix Steenland and Woksie [31]	Estimated cumulative serum PFOA concentrations positively associated with kidney and testicular cancer. No significant association with thyroid cancer For thyroid cancer, no significant exposure–response trend After stratification twofold excess of thyroid cancer among workers with no lag, but not after a 10-year lag or in community members When exposure was categorized into quartiles, positive exposure–response trends for thyroid cancer only in the workers cohort	Barry et al. [33]

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CONCLUSIONI (1)

- Negli ultimi decenni, è cresciuta la consapevolezza della diffusa esposizione ambientale ai PFC e ai loro potenziali effetti sulla funzione tiroidea nell'uomo e in altre specie
- PFOS e PFOA e PFAS riducono i livelli circolanti degli ormoni tiroidei negli animali esposti con la dieta, principalmente aumentando la loro clearance metabolica
- Il trasposto intracellulare di PFOS e PFOA avviene passivamente per gradiente di concentrazione. Nelle cellule tiroidee è stato osservato un effetto citotossico ma solo dopo l'esposizione a concentrazioni estremamente elevate di questi composti
- Nelle comunità con esposizione ambientale e nella popolazione generale, l'effetto più coerente dell'esposizione a PFOA e, in misura minore, a PFOS, è l'insorgenza di ipotiroidismo

CONCLUSIONI (2)

- Donne, bambini e adolescenti sono maggiormente a rischio di sviluppare insufficienza tiroidea lieve
- Le donne in gravidanza con anticorpi anti-tiroidei circolanti sono a rischio per lo sviluppo di ipotiroidismo subclinico, principalmente se esposti ad alte dosi di PFOS
- I rischi relativi per il carcinoma tiroideo nelle persone esposte a PFOA e PFOS erano bassi e basati su pochi casi. Non ci sono risultati coerenti in tutti o addirittura nella maggior parte degli studi.
- Tuttavia, a causa della loro lunga persistenza nell'ambiente e nel corpo umano, gli effetti oncogeni e sulla funzione tiroidea di PFOA e PFOS richiedono monitoraggio e studi futuri

Grazie per l'attenzione

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