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Endocrine disruptors and carcinogenic effects

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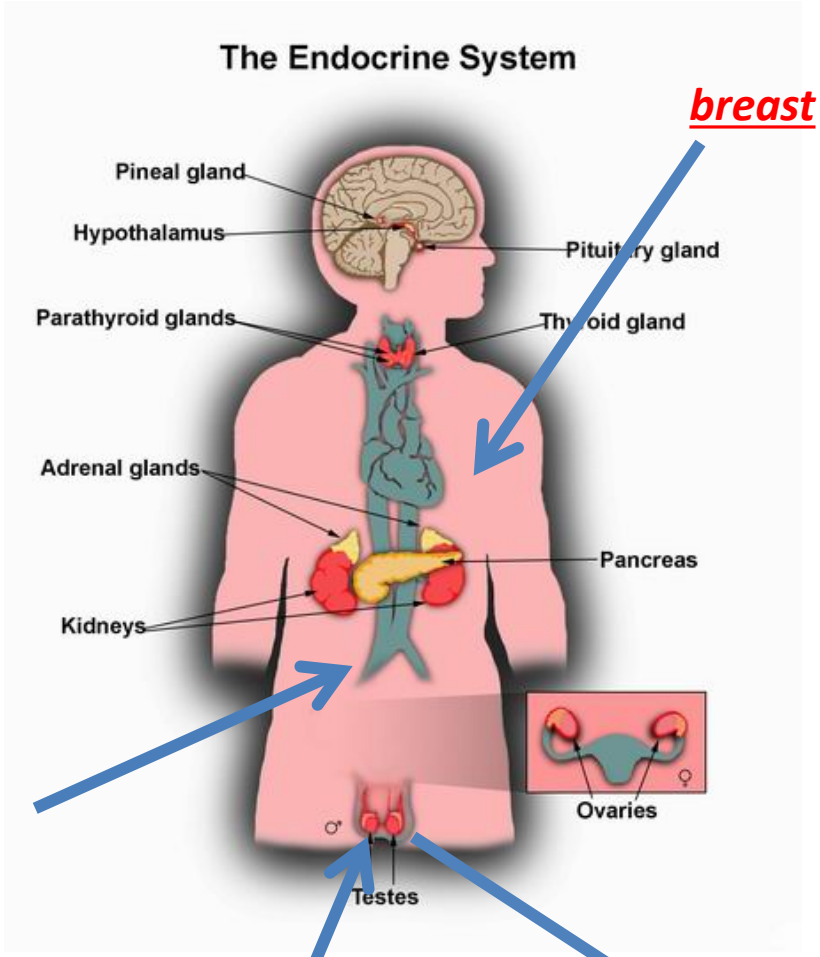
Introduction



breast

uterus

prostate

testes

Definiton: An ED

WHO (2002)

alters function(s) of the endocrine system

and consequently causes adverse health effects

Endocrine Society (2012)

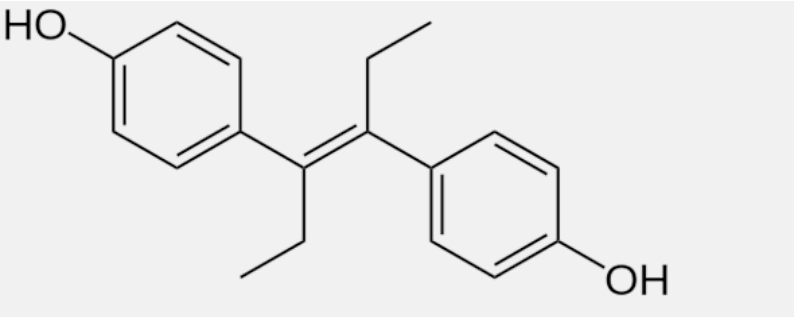
interferes with any aspect of hormone action

Why is ‚endocrine disruptors and cancer' a topic?

The history of diethylstilboestrol (DES)

In 1971, it was shown that DES intake during pregnancy caused clear cell carcinoma, a rare vaginal tumor, in girls and women who had been exposed to this drug in utero because their mothers were treated with this substance to avoid miscarriage.

The mechanism was thought to be due to oestrogenic action.



Adenocarcinoma of the vagina. Association of maternal stilbestrol therapy with tumor appearance in young women.

Daughters with adenocarcinoma

DES was given to **pregnant women** in the mistaken belief it would reduce the risk of pregnancy complications and losses.

Case No.	Age at 1st Symptoms (Yr)	Yr of Birth
1	20	1949
2	15	1951
3	14	1950
4	15	1950
5	19	1949
6	16	1951
7	18	1949
8	22	1946

Case No.	Maternal Age (Yr)		Estrogen Given in This Pregnancy	
	Case	Mean of 4 Controls	Case	Control
1	25	32	Yes	0/4
2	30	30	Yes	0/4
3	22	31	Yes	0/4
4	33	30	Yes	0/4
5	22	27	No	0/4
6	21	29	Yes	0/4
7	30	27	Yes	0/4
8	26	28	Yes	0/4

Herbst AL, Ulfelder H, Poskanzer DC.
N Engl J Med. 1971 284(15):878-81.

Adverse health outcomes in women exposed in utero to diethylstilbestrol

Table 2. Hazard Ratios for Adverse Health Outcomes in Women with and Those without Diethylstilbestrol (DES) Exposure.*

Adverse Outcome	Exposed Women	Unexposed Women	Hazard Ratio (95% CI)†
	no./total no.		
Infertility	1144/3769	252/1654	2.37 (2.05 to 2.75)
Spontaneous abortion‡	916/2690	328/1291	1.64 (1.42 to 1.88)
Ectopic pregnancy‡	255/2692	36/1293	3.72 (2.58 to 5.38)
Loss of second-trimester pregnancy‡	201/2692	35/1293	3.77 (2.56 to 5.54)
Preterm delivery§	624/2385	100/1238	4.68 (3.74 to 5.86)
Preeclampsia§	216/2412	80/1159	1.42 (1.07 to 1.89)
Stillbirth§	54/2385	16/1239	2.45 (1.33 to 4.54)
Neonatal death§	57/2383	7/1238	8.12 (3.53 to 18.65)
Early menopause	181/3993	49/1682	2.35 (1.67 to 3.31)
Cervical intraepithelial neoplasia, grade ≥2	208/4120	40/1785	2.28 (1.59 to 3.27)
Breast cancer at ≥40 yr	61/3693	21/1647	1.82 (1.04 to 3.18)
Clear-cell adenocarcinoma	4/4652	0/1926	∞ (0.37 to ∞)

Hoover RN, Hyer M, Pfeiffer RM, Adam E, Bond B, Cheville AL, Colton T, Hartge P, Hatch EE, Herbst AL, Karlan BY, Kaufman R, Noller KL, Palmer JR, Robboy SJ, Saal RC, Strohsnitter W, Titus-Ernstoff L, Troisi R.
N Engl J Med. 2011 365(14):1304-14.

DES exposure and urogenital abnormalities in sons born to mothers exposed to DES during pregnancy

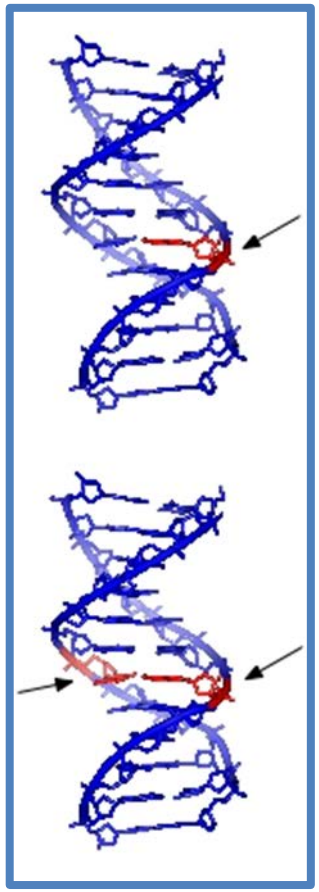
Table 1: DES exposure in relation to urogenital abnormalities

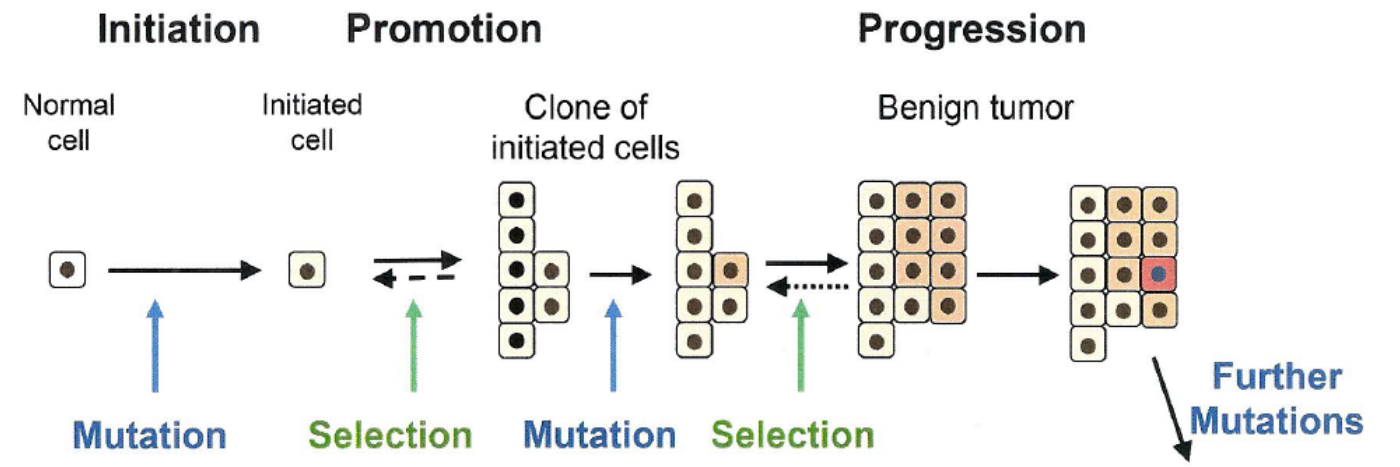
	DES-Exposed (N = 1197)	Unexposed (N = 1038)		
	Cases	Cases	Risk ratio*	95% Confidence interval
Urogenital abnormalities				
Cryptorchidism	38	17	1.9	1.13.4
Epididymal cyst	55	19	2.5	1.54.3

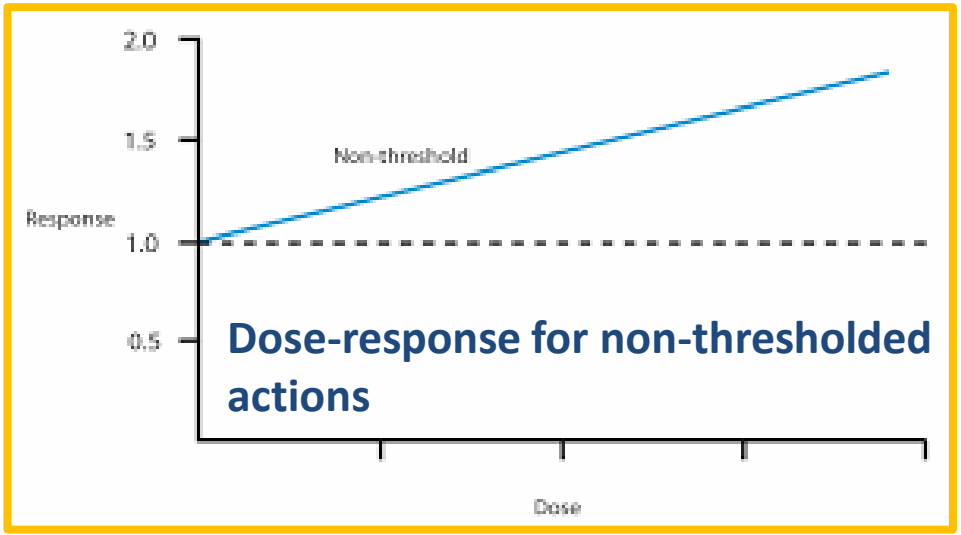
Cryptorchism is a risk factor for testicular germ cell tumors

Palmer JR, Herbst AL, Noller KL, Boggs DA, Troisi R, Titus-Ernstoff L, Hatch EE, Wise LA, Strohsnitter WC, Hoover RN. Urogenital abnormalities in men exposed to diethylstilbestrol in utero: a cohort study. Environ Health. 2009 18;8:37

Mode of Action - non-thresholded genotoxic cancerogen

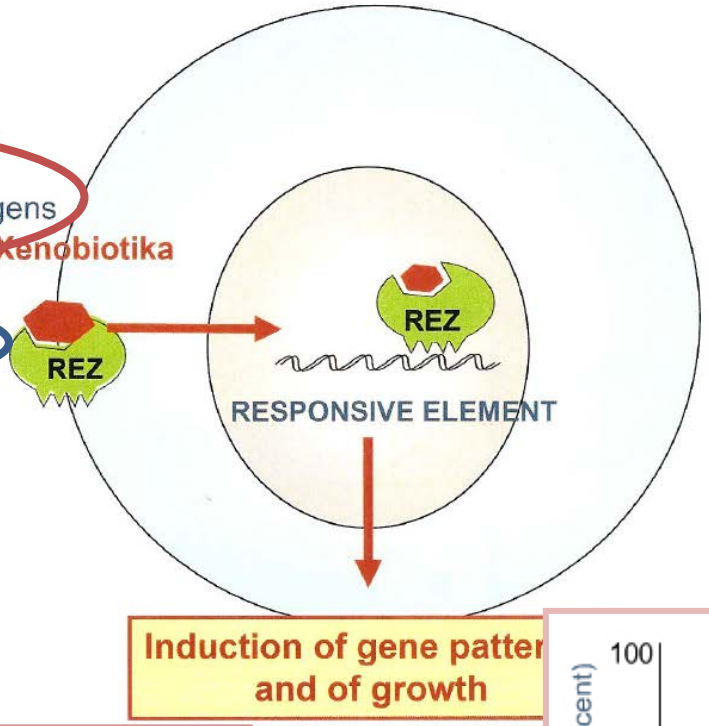






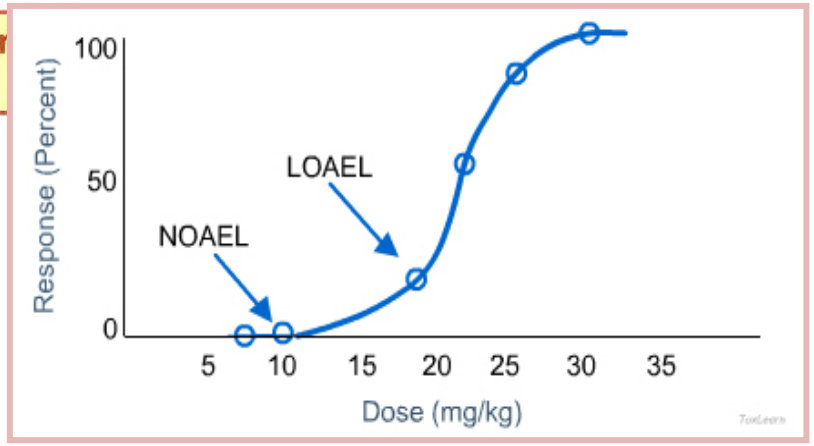
Non-genotoxic (thresholded) actions
Induction of Cell Growth via Receptor mediated Signalling

Proteinkinase C
TPA
Hormone Receptors:
Estrogens, Gestagens, Androgens
Thyroid Hormones
PPAR-Receptors:
Hypolipidemics, Phthales
Dioxin-Receptor:
Dioxin, PAH
Constitutive Androstan Rec./
Pregenolon-X-Receptor:
many chemical compounds

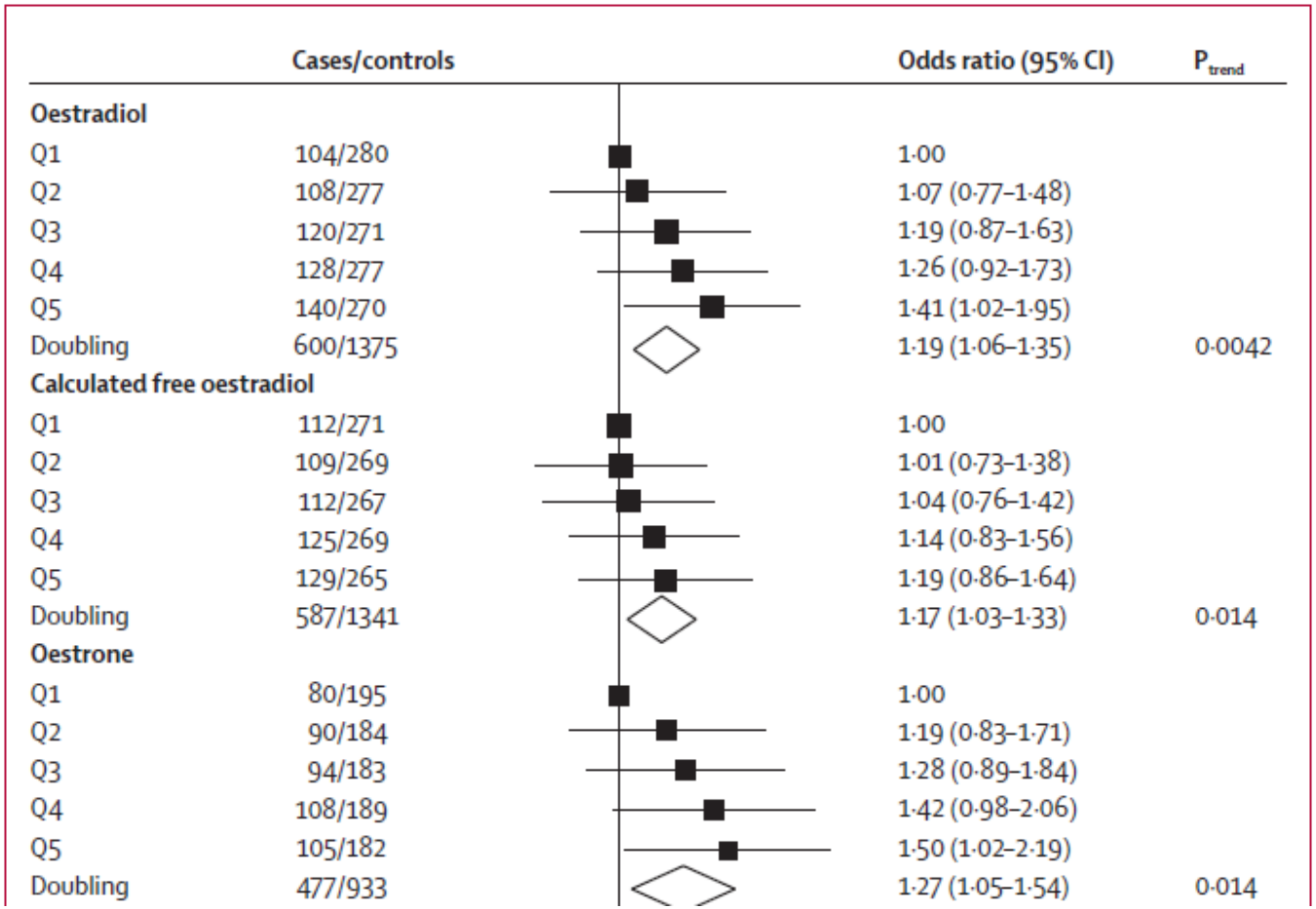


If an ED is cancerogenic, this is a thresholded mode of action . This means that a dose exists below which the probability of an effect is very low.

Dose-response for thresholded action



Endogenous Oestrogens and risk of breast cancer in premenopausal women



	Cases/controls	Odds ratio (95% CI)	P_{trend}
Oestradiol			
Q1	104/280	1·00	
Q2	108/277	1·07 (0·77–1·48)	
Q3	120/271	1·19 (0·87–1·63)	
Q4	128/277	1·26 (0·92–1·73)	
Q5	140/270	1·41 (1·02–1·95)	
Doubling	600/1375	1·19 (1·06–1·35)	0·0042
Calculated free oestradiol			
Q1	112/271	1·00	
Q2	109/269	1·01 (0·73–1·38)	
Q3	112/267	1·04 (0·76–1·42)	
Q4	125/269	1·14 (0·83–1·56)	
Q5	129/265	1·19 (0·86–1·64)	
Doubling	587/1341	1·17 (1·03–1·33)	0·014
Oestrone			
Q1	80/195	1·00	
Q2	90/184	1·19 (0·83–1·71)	
Q3	94/183	1·28 (0·89–1·84)	
Q4	108/189	1·42 (0·98–2·06)	
Q5	105/182	1·50 (1·02–2·19)	
Doubling	477/933	1·27 (1·05–1·54)	0·014

Endogenous Hormones and Breast Cancer Collaborative Group Lancet Oncol. 2013 Sep;14(10):1009-19.

The Example of Isoflavone as Food Supplements

Results from the EFSA assessment 2015

Botanical sources:

Soy	Red clover	Kudzu root
Glycine max (L.) Merr	*Trifolium pratense* L.	*Pueraria montana*

EFSA Opinion, 2015

Endpoint / Intervention	Reference	Reliability	Relevance	outcome
Breast cancer in epidemiological studies			Human studies +++	↔ No difference
Use of food supplements containing isoflavones	Boucher et al. 2013	1	+++	↔
	Brasky et al. 2010	1	+++	↔
	Obi et al. 2009	1	+++	↔
	Rebbeck et al. 2007	2	+++	↔
Mammographic density				
Soy isoflavones/soy extract	3071 Colacurci et al., 2013	1	+++	↔
	16401 Del Manto et al., 2013	1	+++	↔
Soy protein	3127 Verheus et al., 2008.	1	+++	↔
Daidzein-rich isoflavones	1199 Maskarinec et al., 2009.	1	+++	↔
Genistein	3138 Marini et al., 2008.	1	+++	↔
	2282 Morabito et al., 2002.	2	+++	↔
Red clover extract (RCE)	3168 Atkinson et al., 2004	1	+++	↔
	16435 Powles et al., 2008.	2	+++	↔
Proliferation marker Ki-67 and atypical cytology				
Soy isoflavones/soy extract	16409 Khan et al., 2012.	1	+++	↔
	3158 Cheng et al., 2007.	2	+++	↔

Human studies
Mammary gland

Endpoint / intervention	Reference	Reliability	Relevance	outcome
Uterus			Human studies +++	↔ No difference
Endometrial thickness				
Soy isoflavones / soy extract	14960 Chilibeck et al., 2013.	1	+++	↔
	3071 Colacurci et al., 2013	1	+++	↔
	10231 Nahas et al., 2007.	1	+++	↔
	14945 Alekel et al., 2015	2	+++	↔
	1640 Kaari et al., 2006.	2	+++	↔
	2414 Han et al., 2002.	2	+++	↔
	3158 Cheng et al., 2007.	2	+++	↔
	16165 Upmalis et al., 2000.	2	+++	↔
Soy protein	16436 Quaas et al., 2013.	1	+++	↔
	1103 Carmignani et al., 2010	1	+++	↔
	11323 Murray et al., 2003.	3	+++	↔
Daidzein-rich isoflavones	3110 Penotti et al., 2003.	1	+++	↔
	4366 Steinberg et al., 2011.	2	+++	↔
Glycitein-rich isoflavones	1639 Nikander et al., 2005.	1	+++	

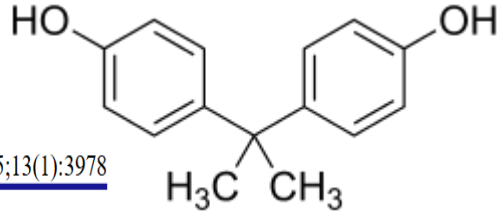
Human studies
Uterus

Why did we not see an oestrogenic effect in vivo in postmenopausal women? (III)

The relative activity of isoflavones in food supplements

	EEQ (µg E2 per capsule)[1] [1]Andres et al., 2015		Production rate expressed as External dose/day (BV =0.05) (µg/day)	Comparison endogenous vs isoflavone capsule (Endogenous/isoflavone in capsules)	
	ER alpha	ER beta		ER alpha	ER beta
1	1.4		530	380	
2		9.5	530		56
3	7.6	24.2	530	70	25
4	5.2		530	101	
5		22.4	530		24
6		36.4	530		14.5; 7% increase
7		13.8	530		38
8	11.9		530	44 ; 3% increase	
9		15.5	530		34

The Example of Bisphenol A
Results from the EFSA assessment 2015



European Food Safety Authority

EFSA Journal 2015;13(1):3978

SCIENTIFIC OPINION

Scientific Opinion on the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs: Executive summary[1]

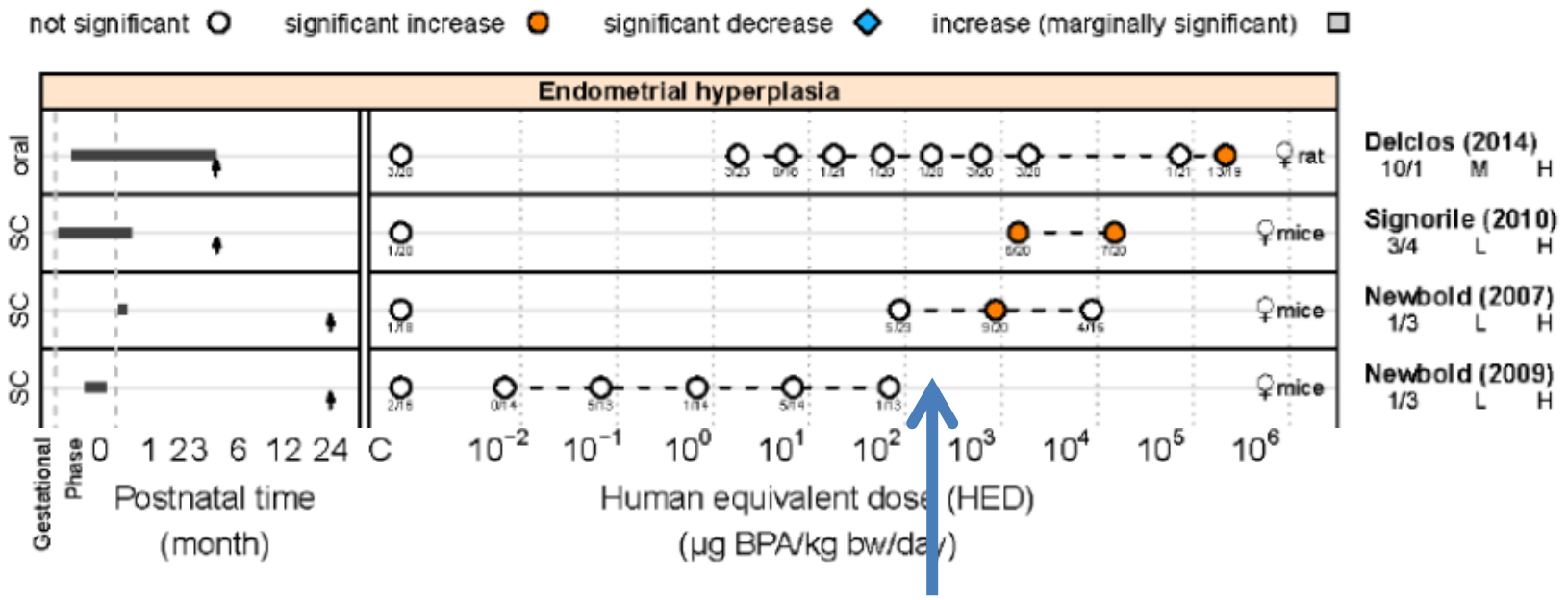
EFSA Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF)[2,3]

European Food Safety Authority (EFSA), Parma, Italy

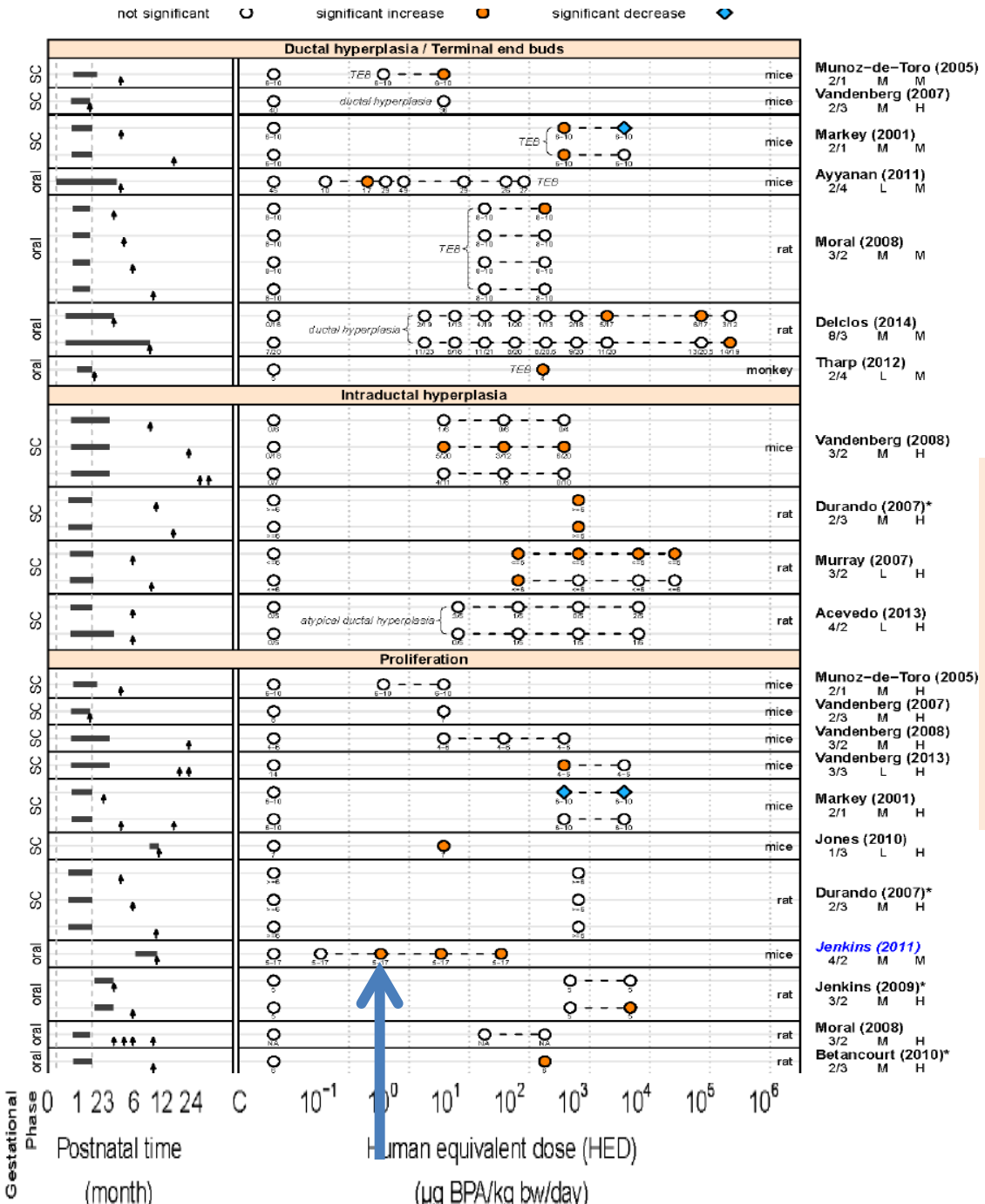
*nmary of the Scientific Opinion, published on 25 March 2015, replaces the earlier version nuary 2015.**

Bisphenol A

Endpoint Uterus hyperplasia
Rat data



The effective oral dose in humans is > 100 mg/kg bw/day
The cumulative **human exposure** (dermal plus oral) is 4 µg/kg bw/day, **10,000 fold lower** than the effective dose.



Endpoints in the breast in rats

The effective oral dose in humans is 1-10 mg/kg/day

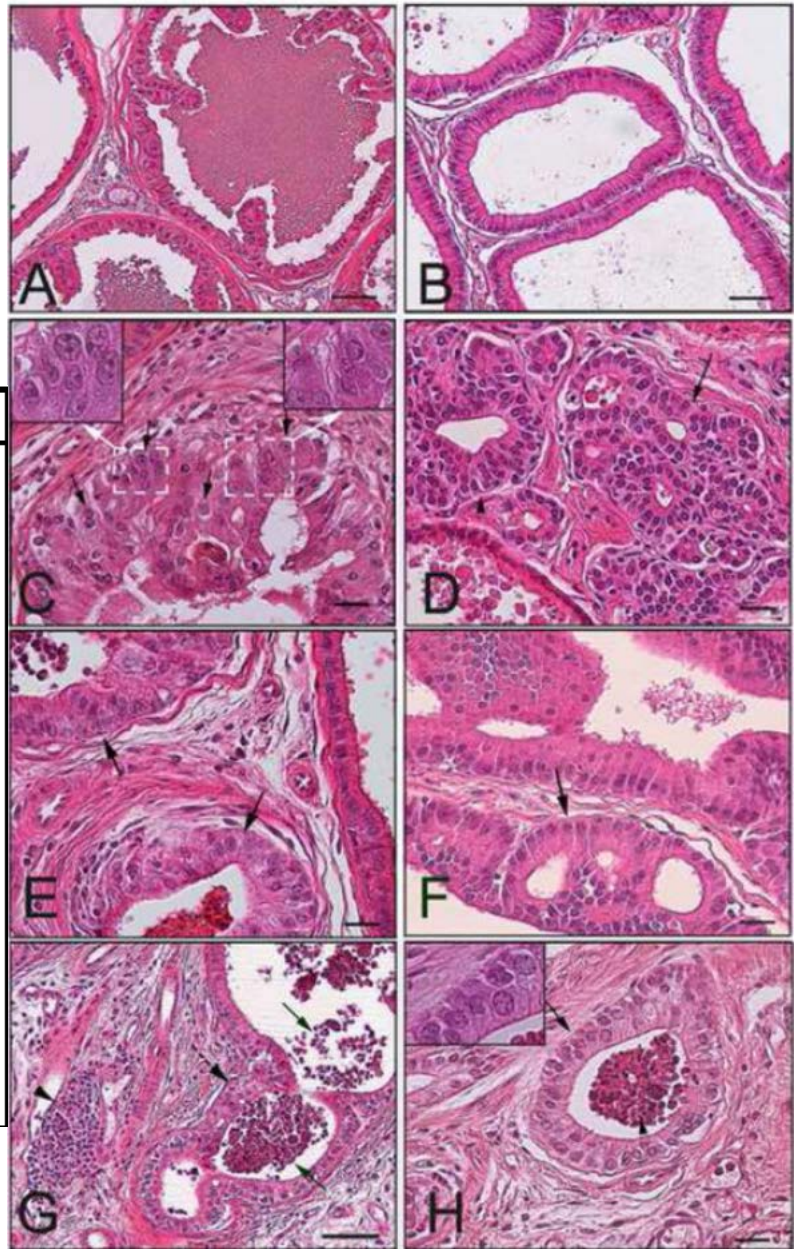
The cumulative **human exposure** (dermal plus oral) is 4 µg/kg bw/d,

1000 – 10,000 fold **lower** than the effective dose.

Bisphenol A and Prostate pre-cancererous lesions

Incidence of prostatic leasion at 7 months in SD rats treated neonatally with oil or BPA via s.c. or oral route of exposure and with T+E as adults

	PIN	Atypical Hyperplasia	Epithelial Hyperplasia	Inflammatory Cells
Ventral				
Oil	18%	12%	35%	18%
BPA: s.c.	40%	45%	90%†	20%
BPA: oral	40%	50%	70%†	0%
Lateral				
Oil	64%	59%	70%	47%
BPA: s.c.	100%*	42%	58%	89%**
BPA: oral	90%*	50%	50%	90%**
Dorsal				
Oil	33%	7%	33%	33%
BPA: s.c.	47%	35%	59%	29%
BPA: oral	66%	22%	22%	33%



Prins et al. Reprod Toxicol. 2011 31(1):1-9.
Serum bisphenol A pharmacokinetics and prostate neoplastic responses following oral and subcutaneous exposures in neonatal Sprague-Dawley rats.

Relevance of Prins et al. for humans – considerations on the internal exposure

	Rat data		Human data		Ratio concentration experimental exposure rat p.o./ human mean exposure
	s.c. injection	oral	oral		
Dose BPA (µg/kg bw)	400 (Prins et al., 2011)	400 (Prins et al., 2011)	100 (Thayer et al., 2015)		
Exposure (µg/kg bw)				4 (EFSA,2015)	
Cmax BPA (nM)	7.73 (measured)	1.13 (measured)	6.5 (measured)	0.26 (calculated)	4.3

The internal exposure was 4 fold higher in rats as is the current combined exposure in humans calculated as oral exposure

Prins et al. Reprod Toxicol. 2011 31(1):1-9.

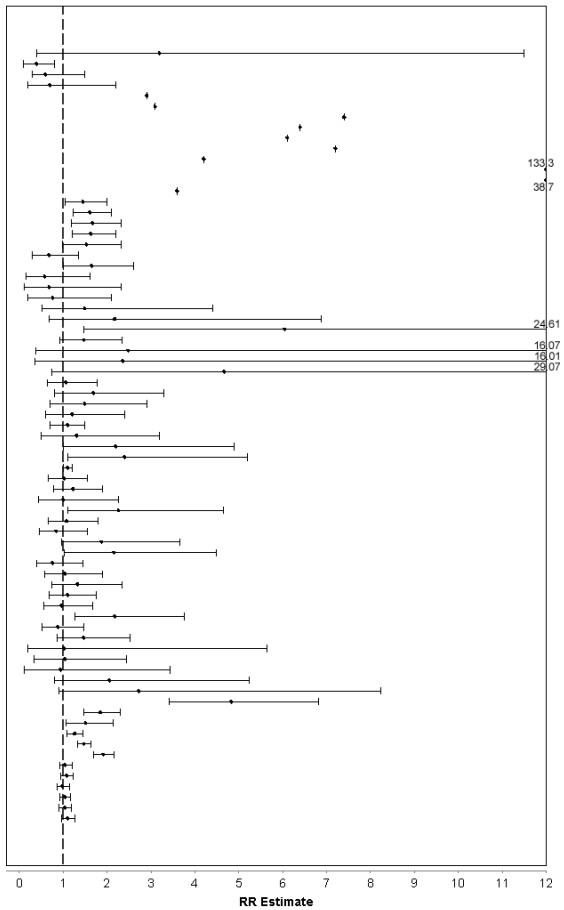
Other substances – in occupational scenarios

- TCCD
- Pesticides
- Phthalates
- Organic solvents
- Alkylphenols
- Chlorpyriphos (animal study)

Studies of veterans with estimated Agent Orange/TCCD exposure N= 4533

Figure 1

Reference	Exposure Groups	RR Type
Ketchum 1996	Ranch Hands vs. comparisons	SMR
Ketchum 1999	Ranch Hands background TCDD vs. comparisons	OR
Ketchum 1999	Ranch Hands low TCDD vs. comparisons	OR
Ketchum 1999	Ranch Hands high TCDD vs. comparisons	OR
Kayajanian 2001	0 ppt TCDD vs. general US, whites	SIR*
Kayajanian 2001	1.25–2.50 ppt TCDD vs. general US, whites	SIR*
Kayajanian 2001	2.51–4.00 ppt TCDD vs. general US, whites	SIR*
Kayajanian 2001	4.01–8.00 ppt TCDD vs. general US, whites	SIR*
Kayajanian 2001	8.01–10.00 ppt TCDD vs. general US, whites	SIR*
Kayajanian 2001	27.18–127.45 ppt TCDD vs. general US, whites	SIR*
Kayajanian 2001	128.13–3290.18 ppt TCDD vs. general US, whites	SIR*
Kayajanian 2001	0 ppt TCDD vs. general US, blacks	SIR*
Kayajanian 2001	1.25–4.00 ppt TCDD vs. general US, blacks	SIR*
Kayajanian 2001	≥4.01 ppt TCDD vs. general US, blacks	SIR*
Akhtar 2004	Ranch Hands vs. general US, whites	SIR
Akhtar 2004	Comparisons vs. general US, whites	SIR
Akhtar 2004	Ranch Hands ending 1966–1970 vs. general US, whites	SIR
Akhtar 2004	Comparisons ending 1966–1970 vs. general US, whites	SIR
Akhtar 2004	Ranch Hands ≤2 yrs in SEA vs. general US, whites	SIR
Akhtar 2004	Comparisons ≤2 yrs in SEA vs. general US, whites	SIR
Akhtar 2004	Ranch Hands 100% VN vs. general US, whites	SIR
Akhtar 2004	Comaparisons 0% VN vs. general US, whites	SIR
Akhtar 2004	Ranch Hands vs. general US, whites	SMR
Akhtar 2004	Comparisons vs. general US, whites	SMR
Akhtar 2004	Ranch Hands vs. comparisons ≤2 yrs in SEA, background TCDD	RR
Akhtar 2004	Ranch Hands vs. comparisons ≤2 yrs in SEA, low TCDD	RR
Akhtar 2004	Ranch Hands vs. comparisons ≤2 yrs in SEA, high TCDD	RR
Akhtar 2004	Per 1 unit log-TCDD, Ranch Hands + comparisons ≤2 yrs in SEA	RR
Akhtar 2004	Ranch Hands 100% VN background TCDD vs. comparisons 0% VN	RR
Akhtar 2004	Ranch Hands 100% VN low TCDD vs. comparisons 0% VN	RR
Akhtar 2004	Ranch Hands 100% VN high TCDD vs. comparisons 0% VN	RR
Akhtar 2004	Per 1 unit log-TCDD, Ranch Hands 100% VN + comparisons 0% VN	RR
Pavuk 2005	2.6–3.8 vs. 0.4–2.6 pg/g lipid TCDD, comparisons	RR
Pavuk 2005	3.8–5.2 vs. 0.4–2.6 pg/g lipid TCDD, comparisons	RR
Pavuk 2005	5.2–54.8 vs. 0.4–2.6 pg/g lipid TCDD, comparisons	RR
Pavuk 2005	Per 1 pg/g lipid TCDD, comparisons	RR
Pavuk 2005	1.3–2.1 vs. 0.1–1.3 yrs in SEA, comparisons	RR
Pavuk 2005	2.1–3.7 vs. 0.1–1.3 yrs in SEA, comparisons	RR
Pavuk 2005	3.7–16.4 vs. 0.1–1.3 yrs in SEA, comparisons	RR
Pavuk 2005	Per 1 yr in SEA, comparisons	RR
Pavuk 2006	Ranch Hands lower TCDD vs. comparisons	RR
Pavuk 2006	Ranch Hands higher TCDD vs. comparisons	RR
Pavuk 2006	Ranch Hands lower TCDD vs. comparisons, in SEA <1969	RR
Pavuk 2006	Ranch Hands higher TCDD vs. comparisons, in SEA <1969	RR
Pavuk 2006	Ranch Hands lower TCDD vs. comparisons, in SEA ≥1969	RR
Pavuk 2006	Ranch Hands higher TCDD vs. comparisons, in SEA ≥1969	RR
Pavuk 2006	Ranch Hands lower TCDD vs. comparisons, in SEA <2 yrs	RR
Pavuk 2006	Ranch Hands higher TCDD vs. comparisons, in SEA <2 yrs	RR
Pavuk 2006	Ranch Hands lower TCDD vs. comparisons, in SEA ≥2 yrs	RR
Pavuk 2006	Ranch Hands higher TCDD vs. comparisons, in SEA ≥2 yrs	RR
Pavuk 2006	>434 vs. ≤434 ppt-yrs TCDD, Ranch Hands	RR
Pavuk 2006	>77.2 vs. ≤77.2 ppt-yrs TCDD, comparisons	RR
Pavuk 2006	>426 vs. ≤426 days in SEA, Ranch Hands	RR
Pavuk 2006	>789 vs. ≤789 days in SEA, comparisons	RR
Pavuk 2006	SEA ≥1969 vs. <1969, Ranch Hands	RR
Pavuk 2006	SEA ≥1969 vs. <1969, comparisons	RR
Cypel 2010	Vietnam vs. non-Vietnam Army Chemical Corps	MRR
Cypel 2010	Vietnam Army Chemical Corps vs. general US	SMR
Cypel 2010	Non-SEA Army Chemical Corps vs. general US	SMR
Giri 2004	Agent Orange exposed vs. nonexposed	OR
Giri 2004	Agent Orange exposed vs. nonexposed, whites	OR
Chamie 2008	Agent Orange exposed vs. nonexposed	OR
Chamie 2008	Agent Orange exposed vs. nonexposed, excl. post-diagnosis reports	OR
Ansbaugh 2013	Agent Orange exposed vs. nonexposed	OR
Yi 2013a	Self-reported low Agent Orange exposure vs. none	OR
Yi 2013a	Self-reported moderate Agent Orange exposure vs. none	OR
Yi 2013a	Self-reported high Agent Orange exposure vs. none	OR
Yi 2013a	Division/brigade low Agent Orange exposure vs. none	OR
Yi 2013a	Division/brigade moderate Agent Orange exposure vs. none	OR
Yi 2013a	Division/brigade high Agent Orange exposure vs. none	OR
Yi 2013a	Battalion/company low Agent Orange exposure vs. none	OR
Yi 2013a	Battalion/company moderate Agent Orange exposure vs. none	OR
Yi 2013a	Battalion/company high Agent Orange exposure vs. none	OR

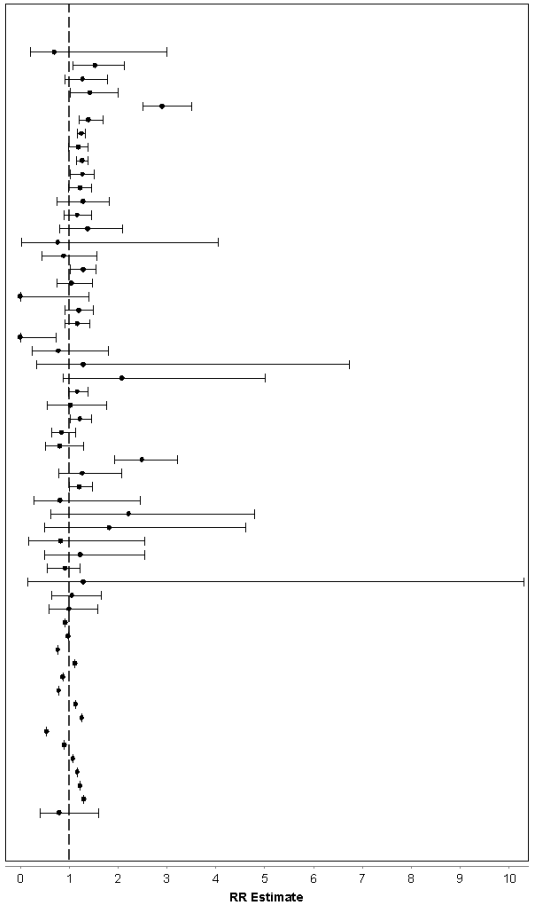


Chang ET, Boffetta P, Adami HO, Cole P, Mandel JS
A critical review of the epidemiology of Agent Orange/TCDD and prostate cancer.
Eur J Epidemiol. 2014 Oct;29(10):667-723.

Studies of Vietnam veterans without estimated Agent Orange/TCCD exposure N = 19 000

Figure 2

Reference	Exposure Groups	RR Type
Fett 1987	Vietnam vs. non-Vietnam veterans	MRR
Crane 1997	Vietnam veterans vs. general Australia	SMR
Crane 1997	Vietnam veterans vs. general Australia, prostate cancer vs. other cancer deaths	SMRR
Crane 1997	Vietnam veterans vs. general Australia, prostate cancer vs. other deaths	SMRR
ADVA 1998	Vietnam veterans self-reported prostate cancer vs. general Australia	PR
AIHW 1999	Vietnam veterans estimated validated prostate cancer vs. general Australia	PR
Wilson 2005a	Vietnam veterans vs. general Australia	SIR
Wilson 2005a	Vietnam Navy veterans vs. general Australia	SIR
Wilson 2005a	Vietnam Army veterans vs. general Australia	SIR
Wilson 2005a	Vietnam Air Force veterans vs. general Australia	SIR
Wilson 2005b	Vietnam veterans vs. general Australia	SMR
Wilson 2005b	Vietnam Navy veterans vs. general Australia	SMR
Wilson 2005b	Vietnam Army veterans vs. general Australia	SMR
Wilson 2005b	Vietnam Air Force veterans vs. general Australia	SMR
Wilson 2005b	Vietnam veterans vs. general Australia, 1963–1979 deaths	SMR
Wilson 2005b	Vietnam veterans vs. general Australia, 1980–1990 deaths	SMR
Wilson 2005b	Vietnam veterans vs. general Australia, 1991–2001 deaths	SMR
Wilson 2005c	Vietnam vs. non-Vietnam National Service conscripts	RR
Wilson 2005c	Vietnam vs. non-Vietnam National Service conscripts	MRR
Wilson 2005c	Vietnam National Service conscripts vs. general Australia	SIR
Wilson 2005c	Non-Vietnam National Service conscripts vs. general Australia	SIR
Wilson 2005c	Vietnam National Service conscripts vs. general Australia	SMR
Wilson 2005c	Non-Vietnam National Service conscripts vs. general Australia	SMR
O'Toole 2009	Vietnam veterans vs. general Australia	PR
Leavy 2006	Vietnam military service vs. none	OR
McBride 2013	Vietnam veterans vs. general New Zealand	SIR
McBride 2013	Vietnam veterans vs. general New Zealand	SMR
Yi 2013c	Vietnam veterans vs. general Republic of Korea	SIR
Yi 2013c	Vietnam enlisted veterans vs. general Republic of Korea	SIR
Yi 2013c	Vietnam noncommissioned officer veterans vs. general Republic of Korea	SIR
Yi 2013c	Vietnam officer veterans vs. general Republic of Korea	SIR
Yi 2013c	Vietnam veterans vs. general Republic of Korea, 1992–1997	SIR
Yi 2013c	Vietnam veterans vs. general Republic of Korea, 1998–2003	SIR
Lawrence 1985	Vietnam vs. non-Vietnam veterans	MOR
Holmes 1986	Vietnam vs. non-Vietnam veterans	PMR
Holmes 1986	Vietnam veterans vs. non-veterans	PMR
Holmes 1986	Non-Vietnam veterans vs. non-veterans	PMR
Holmes 1986	All veterans vs. non-veterans	PMR
Breslin 1988	Vietnam vs. non-Vietnam Army veterans	PMR
Breslin 1988	Vietnam vs. non-Vietnam Marine Corps veterans	PMR
Visintainer 1995	Vietnam vs. non-Vietnam veterans	PMR
Visintainer 1995	Vietnam vs. non-Vietnam veterans, non-blacks	PMR
Watanabe 1996	Vietnam vs. non-Vietnam Army veterans	PMR*
Watanabe 1996	Vietnam vs. non-Vietnam Army, ≤10 yrs since Vietnam	PMR*
Watanabe 1996	Vietnam vs. non-Vietnam Army, 11–15 yrs since Vietnam	PMR*
Watanabe 1996	Vietnam vs. non-Vietnam Army, ≥16 yrs since Vietnam	PMR*
Watanabe 1996	Army Vietnam vs. Army + Marine Corps non-Vietnam veterans	PMR*
Watanabe 1996	Vietnam vs. non-Vietnam Marine Corps veterans	PMR*
Watanabe 1996	Vietnam vs. non-Vietnam Marine Corps veterans, ≤10 yrs since Vietnam	PMR*
Watanabe 1996	Vietnam vs. non-Vietnam Marine Corps veterans, 11–15 yrs since Vietnam	PMR*
Watanabe 1996	Vietnam vs. non-Vietnam Marine Corps veterans, ≥16 yrs since Vietnam	PMR*
Watanabe 1996	Marine Corps Vietnam vs. Army + Marine Corps non-Vietnam veterans	PMR*
Watanabe 1996	Army Vietnam veterans vs. general US	PMR*
Watanabe 1996	Marine Corps Vietnam veterans vs. general US	PMR*
Watanabe 1996	Army non-Vietnam veterans vs. general US	PMR*
Watanabe 1996	Marine Corps non-Vietnam veterans vs. general US	PMR*
Clapp 1997	Vietnam vs. non-Vietnam veterans	SMOR



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Eur J Epidemiol. 2014 Oct;29(10):667-723.

Studies of manufactureres and sprayers of herbicides N = 13 381

Figure 2

Reference	Exposure Groups	RR Type
Fett 1987	Vietnam vs. non-Vietnam veterans	MRR
Crane 1997	Vietnam veterans vs. general Australia	SMR
Crane 1997	Vietnam veterans vs. general Australia, prostate cancer vs. other cancer deaths	SMRR
Crane 1997	Vietnam veterans vs. general Australia, prostate cancer vs. other deaths	SMRR
ADVA 1998	Vietnam veterans self-reported prostate cancer vs. general Australia	PR
AIHW 1999	Vietnam veterans estimated validated prostate cancer vs. general Australia	PR
Wilson 2005a	Vietnam veterans vs. general Australia	SIR
Wilson 2005a	Vietnam Navy veterans vs. general Australia	SIR
Wilson 2005a	Vietnam Army veterans vs. general Australia	SIR
Wilson 2005a	Vietnam Air Force veterans vs. general Australia	SIR
Wilson 2005b	Vietnam veterans vs. general Australia	SMR
Wilson 2005b	Vietnam Navy veterans vs. general Australia	SMR
Wilson 2005b	Vietnam Army veterans vs. general Australia	SMR
Wilson 2005b	Vietnam Air Force veterans vs. general Australia	SMR
Wilson 2005b	Vietnam veterans vs. general Australia, 1963–1979 deaths	SMR
Wilson 2005b	Vietnam veterans vs. general Australia, 1980–1990 deaths	SMR
Wilson 2005b	Vietnam veterans vs. general Australia, 1991–2001 deaths	SMR
Wilson 2005c	Vietnam vs. non-Vietnam National Service conscripts	RR
Wilson 2005c	Vietnam vs. non-Vietnam National Service conscripts	MRR
Wilson 2005c	Vietnam National Service conscripts vs. general Australia	SIR
Wilson 2005c	Non-Vietnam National Service conscripts vs. general Australia	SIR
Wilson 2005c	Vietnam National Service conscripts vs. general Australia	SMR
Wilson 2005c	Non-Vietnam National Service conscripts vs. general Australia	SMR
O'Toole 2009	Vietnam veterans vs. general Australia	PR
Leavy 2006	Vietnam military service vs. none	OR
McBride 2013	Vietnam veterans vs. general New Zealand	SIR
McBride 2013	Vietnam veterans vs. general New Zealand	SMR
Yi 2013c	Vietnam veterans vs. general Republic of Korea	SIR
Yi 2013c	Vietnam enlisted veterans vs. general Republic of Korea	SIR
Yi 2013c	Vietnam noncommissioned officer veterans vs. general Republic of Korea	SIR
Yi 2013c	Vietnam officer veterans vs. general Republic of Korea	SIR
Yi 2013c	Vietnam veterans vs. general Republic of Korea, 1992–1997	SIR
Yi 2013c	Vietnam veterans vs. general Republic of Korea, 1998–2003	SIR
Lawrence 1985	Vietnam vs. non-Vietnam veterans	MOR
Holmes 1986	Vietnam vs. non-Vietnam veterans	PMR
Holmes 1986	Vietnam veterans vs. non-veterans	PMR
Holmes 1986	Non-Vietnam veterans vs. non-veterans	PMR
Holmes 1986	All veterans vs. non-veterans	PMR
Breslin 1988	Vietnam vs. non-Vietnam Army veterans	PMR
Breslin 1988	Vietnam vs. non-Vietnam Marine Corps veterans	PMR
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Watanabe 1996	Vietnam vs. non-Vietnam Army, ≥16 yrs since Vietnam	PMR*
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Watanabe 1996	Vietnam vs. non-Vietnam Marine Corps veterans, 11–15 yrs since Vietnam	PMR*
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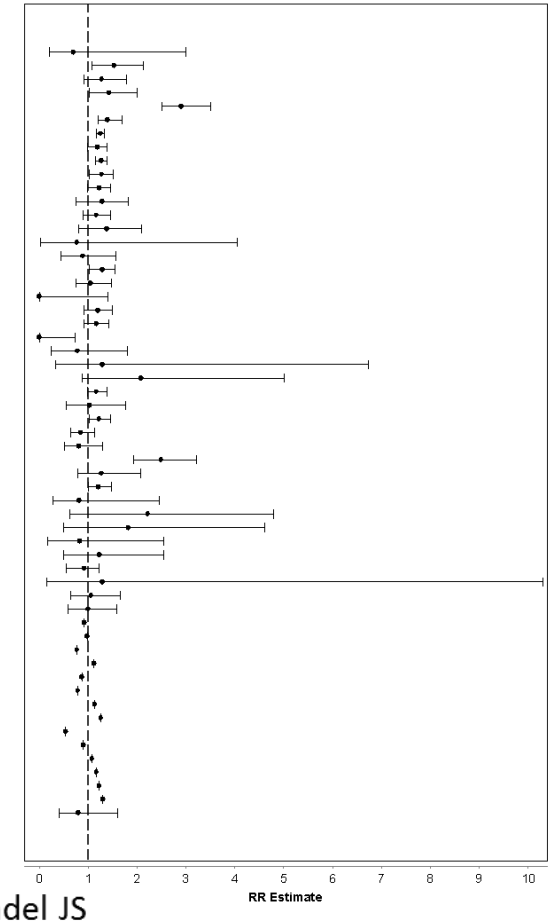
Watanabe 1996	Army Vietnam veterans vs. general US	PMR*
Watanabe 1996	Marine Corps Vietnam veterans vs. general US	PMR*
Watanabe 1996	Army non-Vietnam veterans vs. general US	PMR*
Watanabe 1996	Marine Corps non-Vietnam veterans vs. general US	PMR*
Clapp 1997	Vietnam vs. non-Vietnam veterans	SMOR



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A critical review of the epidemiology of Agent Orange/TCDD and prostate cancer.

Chang ET, Boffetta P, Adami HO, Cole P, Mandel JS Eur J Epidemiol. 2014; 29(10):667-723.

- Overall, epidemiologic research offers no consistent or convincing evidence of a causal relationship between exposure to Agent Orange or TCDD and prostate cancer

Phthalates AND cancer

Table 1 Carcinogenicity assessments by national and international organizations.

Substance	U.S. EPA	National Toxicology Program	International Agency for Research on Cancer (IARC)	American Conference of Governmental Industrial Hygienists	Japan Society for Occupational Health
DIDP	D (Not classifiable as a human carcinogen)	Insufficient to establish the carcinogenic potential	—	—	—
DEHP	B2 (Probable human carcinogen)	R (Reasonably anticipated to be human carcinogen)	Group 3 (Unclassifiable as to carcinogenicity to humans)	A3 (Animal carcinogen)	Group 2B (carcinogenicity in human but the evidence is insufficient)
BBP	C (Possible human carcinogen)	—	Group 3	—	—
DBP	D	—	—	—	—
Di-ethyl phthalate	D	—	—	A4 (Not classifiable as a human carcinogen)	—
Di-octyl phthalate	—	—	—	—	—
Di-isononyl phthalate	—	—	—	—	—
Di-methyl phthalate	—	—	—	—	—

Testicular germ cell tumours and parental occupational exposure to pesticides: a register-based case–control study in the Nordic countries (NORDTEST study)

Le Cornet C, *et al. Occup Environ Med* 2015;**72**:805–811.

Initial number of cases and controls extracted from registries	DENMARK	FINLAND	SWEDEN	NORWAY
	1498 Cases 5924 Controls	1807 Cases 7198 Controls	4114 Cases 14027 Controls	3692 Cases 11404 Controls

Conclusions This is the largest study on prenatal exposure to pesticides and TGCT risk, overall providing no evidence of an association. Limitations to assess individual exposure in registry-based studies might have contributed to the null result.

Burden of disease and costs of exposure to endocrine disrupting chemicals in the European Union: an updated analysis

Trasande L, Zoeller RT, Hass U, Kortenkamp A, Grandjean P, Myers JP, DiGangi J, Hunt PM, Rudel R, Sathyanarayana S, Bellanger M, Hauser R, Legler J, Skakkebaek NE, Heindel JJ.

Andrology. 2016 Mar 22

Expert panels consensus was achieved for probable (>20%) endocrine disrupting chemical causation for IQ loss and associated intellectual disability; autism; attention deficit hyperactivity disorder; endometriosis; fibroids; childhood obesity; adult obesity; adult diabetes; cryptorchidism; male infertility, and mortality associated with reduced testosterone.

BUT NOT CANCER!

It is the dose which makes the poison

Sola dosis facit venenum

Paracelsus (1493 - 1541)

Thank you for your attention

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