Semivolatile organic compounds – from sources to the environment

Part 2: Emerging compounds, endocrine disrupting compounds

“EMERGING” COMPOUNDS -

How do we identify which compounds we should be concerned about? What are those compounds? Where do we find them? What levels are they at in the environment? What about human exposure?

Compounds we will discuss

- Chlorinated paraffins
- Current use pesticides
- Synthetic musks
- Parabens
- Phthalates
- Organophosphate flame retardants
- Bisphenol A

Endocrine disruption and endocrine disrupting compounds

(Endokrinní disruptory)

- Endocrine system – glands in the body which release hormones
  - Especially testes, ovaries, pancreas, thyroid
- Endocrine disruptor/endocrine disrupting compound – anything that interferes with the functioning of the endocrine/hormone systems in the body

Statement from Endocrine Society:

"an endocrine-disrupting substance is a compound, either natural or synthetic, which, through environmental or inappropriate developmental exposures, alters the hormonal and homeostatic systems that enable the organism to communicate with and respond to its environment"

- Especially related to learning disabilities, cognitive functioning, breast cancer, prostate cancer, thyroid cancer, and problems with reproduction and sexual development

"Human and wildlife health depends on the ability to reproduce and develop normally. This is not possible without a healthy endocrine system."

"Human and wildlife populations all over the world are exposed to EDCs."

"Endocrine-related effects have been observed in wildlife populations."

"Many endocrine-related diseases and disorders are on the rise."

"Close to 800 chemicals are known or suspected to be capable of interfering with hormone receptors, hormone synthesis or hormone conversion. However, only a small fraction of chemicals have been investigated in tests capable of identifying overt endocrine effects in intact organisms."

"Significant knowledge gaps exists as to associations between exposures to EDCs and endocrine diseases."

"Disease risk due to EDCs may be significantly underestimated."

Table 1: Potential endocrine disrupting chemicals of the highest priority (Category 1 in European Commission 2014) classified according to their physicochemical properties and/or their use

Classification	Relevant compounds
Persistent organic pollutants	1,1,1-Trichloro-2,2-bis(4-chlorophenyl)ethane (DDT) and derivates, 2,3,7,8-tetrabromodibenzo-p-dioxin, brominated diphenylether (BDE) 209, chlordane, hexachlorobenzene, hexachlorocyclohexanes, mirex, PCBs, PCDDs/PCDFs, short and intermediate chain chlorinated paraffins, toxaphene, trichlorobenzene
Pesticides	2,4-dichlorophenoxyacetic acid, 3,4-dichloroaniline, acetochlor, alachlor, amitrol, atrazine, bifenthrin, boric acid, carbaryl, chlordimeform, cyhalothrin, deltamethrin, dibromochloropropane, dibromoethane, fenarimol, fenitrothion, kepone (chlordecone), linuron (lorox), loxynil, mancozeb, maneb, metam natrium, methoxychlor, metiram (complex), metribuzin, nitrofen, omethoate, picloram, quinalphos = chinalphos, resmethrin, stannane, terbutryn, thiram, trifluralin, vinclozolin, zineb
Pharmaceuticals, growth promoters	cyclophosphamide, ketoconazol, mestranol, mestranol
Personal care product ingredients	2,6-cis diphenyl hexamethylcyclotetrasiloxane, 2-ethyl-hexyl-4-methoxycinnamate, 3-(4-methylbenzylidene)camphor, 3-benzylidene camphor, cyclotetrasiloxane, ethyl 4-hydroxybenzoate, methyl p-hydroxybenzoate
Plasticizers and other additives in materials and goods	2,2'-bis(2-(2,3 epoxypropoxy)phenyl)-propane, 4-nitrotoluene, butylbenzylphthalate (BBP), di-(2-ethylhexyl)phthalate (DEHP), dicyclohexyl phthalate, diethyl phthalate (DEP), di-n-butylphthalate (DBP), dipentylphthalate (DPP), epichlorohydrin (1-chloro-2,3-epoxypropane), methyl tertiary butyl ether, mono 2 ethyl, hexylphthalate, mono-n-butylphthalate, resorcinol, styrene, tert. butylhydroxyanisole
Polycyclic aromatic chemicals	3,9-dihydroxybenz(a)anthracene, 3-methylcholanthrene, ,6-cyclopento-1,2-benzanthracene, 7,12-dimethyl-1,2 benz(a)anthracene, benzo[a]pyrene
Halogenated phenolic chemicals	1,1-trichloro-2,2-bis(4-hydroxyphenyl)ethane, hydroxy - PCBs, pentachlorophenol
Non-halogenated phenolic chemicals	4,4'-biphenol, 4,4'-dihydroxybenzophenon, 4-cyclohexylphenol, 4-nonylphenol and nonylphenol (2 compounds), 4-isooctylphenol, 4-octyl-phenol, 4-phenylphenol 4-tert-octylphenol, benzophenone-2, bisphenol A (BPA), bisphenol B, n-butyl p-hydroxybenzoate, nonylphenolethoxylate, n-propyl p-hydroxybenzoate, octylphenol, p-benzylphenol, phenolphthaleine, resbenzophenone
Chemicals containing tin	fentin acetate, methoxyetylacrylate tinbutyltin, copolymer, phenol, 2-[[(tributylstannyl)oxy]carbony, stannanes (9 compounds), tetrabutyltin, tributyltincarboxylate, tributyltin compounds, tributyltin hydride, tributyltinnaphthalate, tributyltin oxide = bis(tributyltin) oxide, tributyltinpolyethoxylate, tri-n-propyltin, triphenyltin
Other chemicals	1,3-dichloro-2,2-bis(4-methoxy-3-methylphenyl)propane, ethylene thiourea, p-coumaric acid, o,p'-DDA-glycinat = n-(2-chlorophenyl)(4-chlorophenyl), acetylglycin

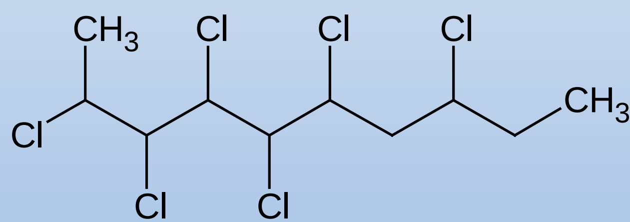
Chlorinated paraffins

- Synthetic compounds
- Classified by chain length:

C10-C13	Short chain chlorinated paraffins (SCCP)
C14-C17	Medium/intermediate chain chlorinated paraffins (MCCP)
>C17	Long chain chlorinated paraffins (LCCP)

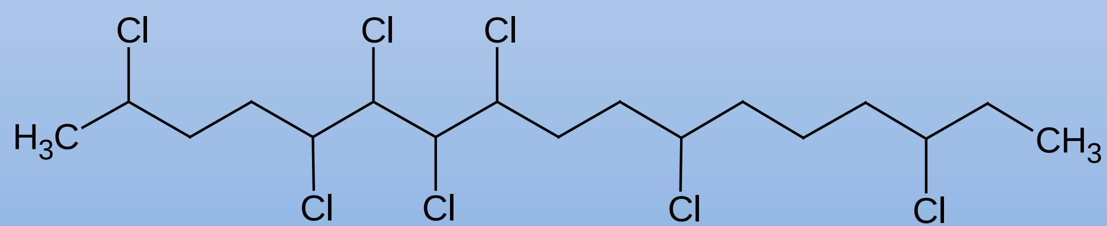
Too many individual isomers (e.g., >100000 possible MCCPs) therefore not individually identified, rather grouped by chain length and chlorine content

SCCP

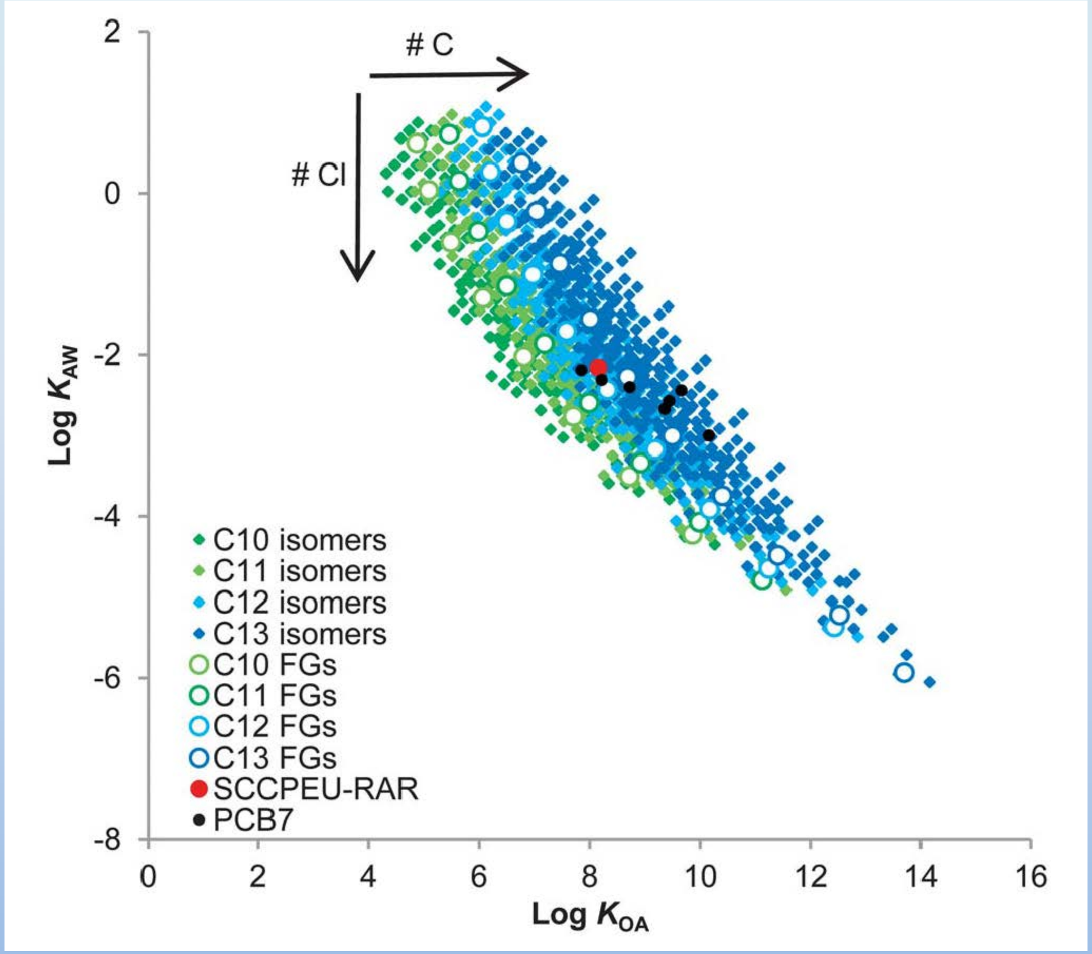


General formula:
$C_xH_{(2x+2)-y}Cl_y$

MCCP



Physicochemical properties of SCCPs



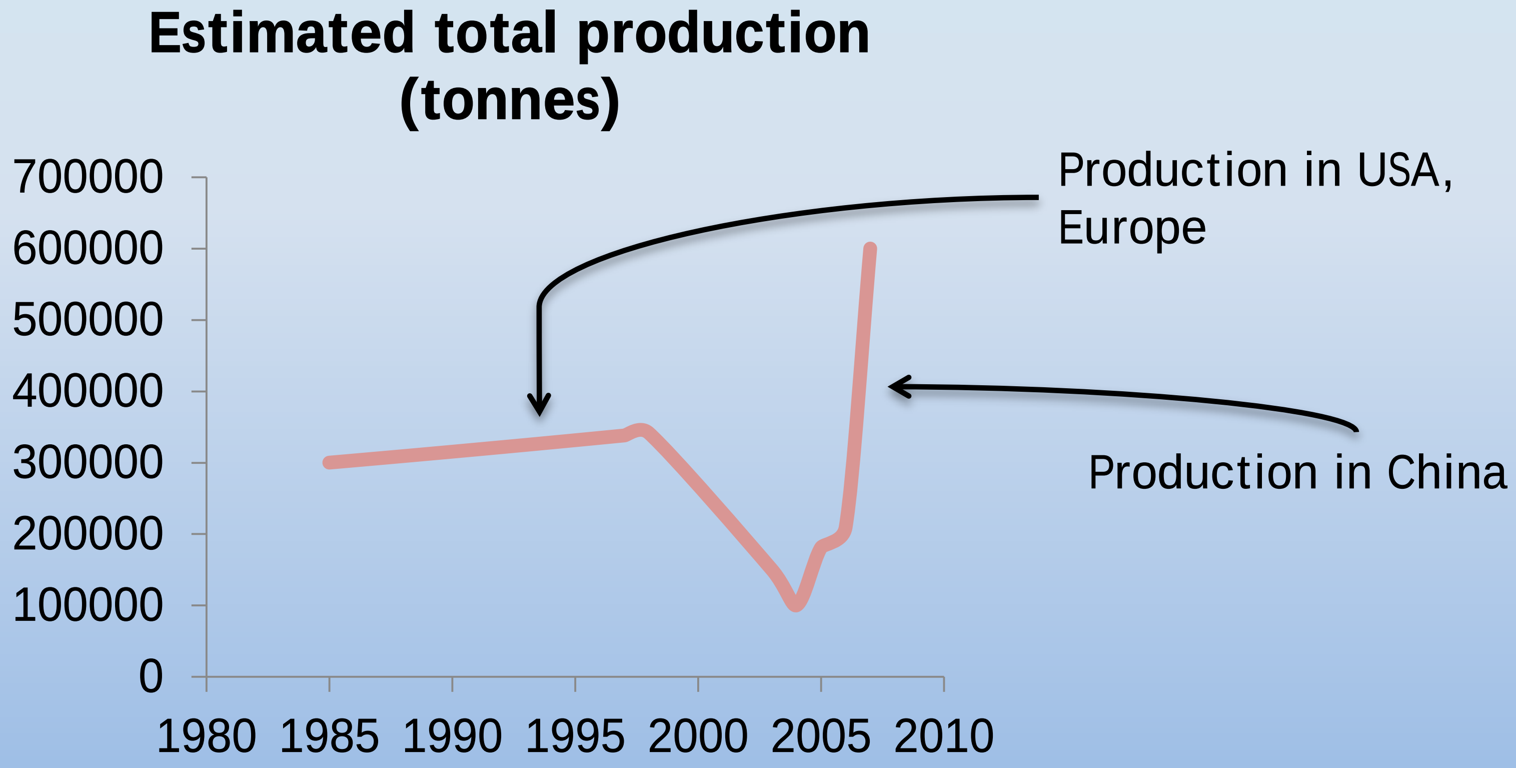
Krogseth et al. 2014

Chlorinated paraffins – uses

- Wide range of uses: sealants, paints, metal-working fluids, leather treatment chemicals, carbon-less copy paper, as flame retardants or plasticizers/softeners in rubbers, textiles, polyvinylchloride (PVC) or other polymers
- Main use in metal-working fluids (SCCPs), plasticizers in PVC (MCCPs) and flame retardants (LCCPs)
- Properties: non-flammable, very stable

History of use

- In use since 1930s, increasing production since 1980s



Data from Bayen et al. 2006 and Fiedler et al. 2010

CPs - producers

- INEOS Chlor (UK, Germany, Norway, Sweden, Netherlands, France)
- Caffaro (Italy)
- Química del Cinca (Spain)
- Leuna-tenside (Germany)
- Novácke Chemické Závody (Slovakia)
- Dover Chemicals (USA)
- NCP Exports (South Africa)
- Orica (Australia)
- Tosoh(Japan)
- Others in India, China ← China now believed to be biggest global producer

Toxic?

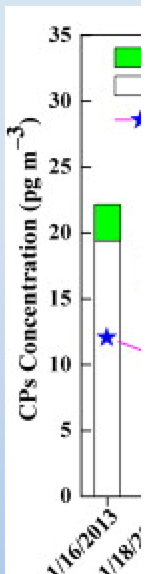
- All chlorinated paraffins bioaccumulate and biomagnify, and are considered "toxic" by a number of environment and health agencies (e.g., SCCP and MCCP "toxic" under Canadian Environmental Protection Act, EU says "need to limit risks of SCCP")
- SCCPs have higher toxicity, higher BAFs/BCFs

CPs – Regulatory status

- USA: SCCPs banned, MCCPs and LCCPs are under review, but currently in use
- Canada: SCCPs are banned, MCCPs are regulated, LCCPs are not regulated
- Europe: SCCP use is restricted to very limited mining applications, MCCPs are not considered PBT, but under evaluation, LCCPs are deemed not hazardous
- Stockholm Convention: SCCPs are under evaluation – will be discussed at next Stockholm Convention meeting

MCCP,
LCCP ?

SCCPs in air – 10-100x higher than OCPs, PCBs, PBDEs



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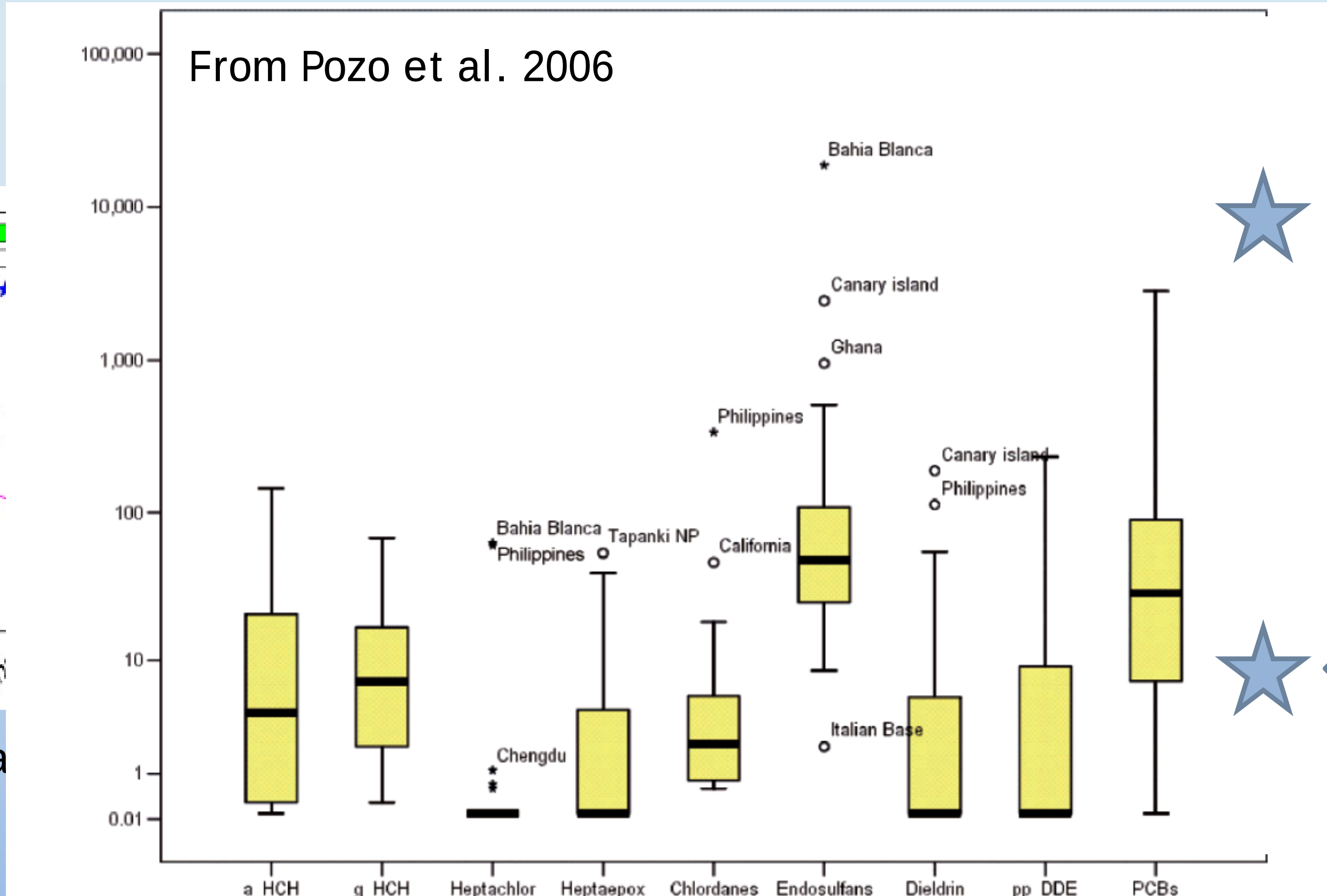
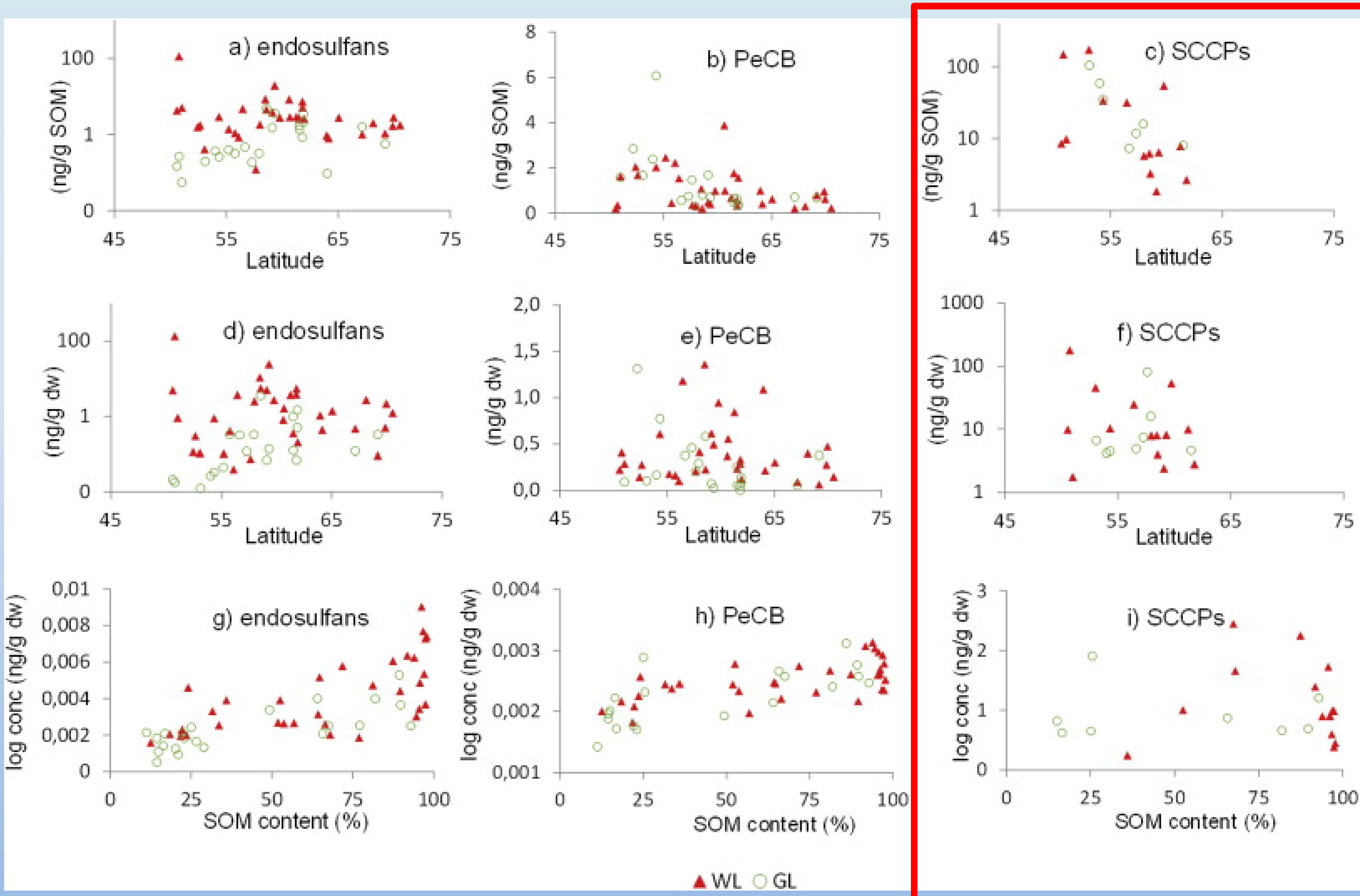


FIGURE 1. Box plot (log) concentrations (pg/m^3) of OCPs and PCBs at 38 sites. Geometric mean and range values for OCP were: 3.2 and 0.1−145 for α-HCH; 5.3 and 0.3−68 for γ-HCH; 0.2 and 0.1−63 for Heptachlor; 0.5 and 0.1−40 for Heptachlor epoxide; 2.6 and 0.7−338 for Chlordanes; 0.8 and 0.1−189 for Dieldrin; 0.8 and 0.1−192 for *p,p′*-DDE; and 17 and 0.1−2830 for PCBs (Italian Base = Antarctic site).

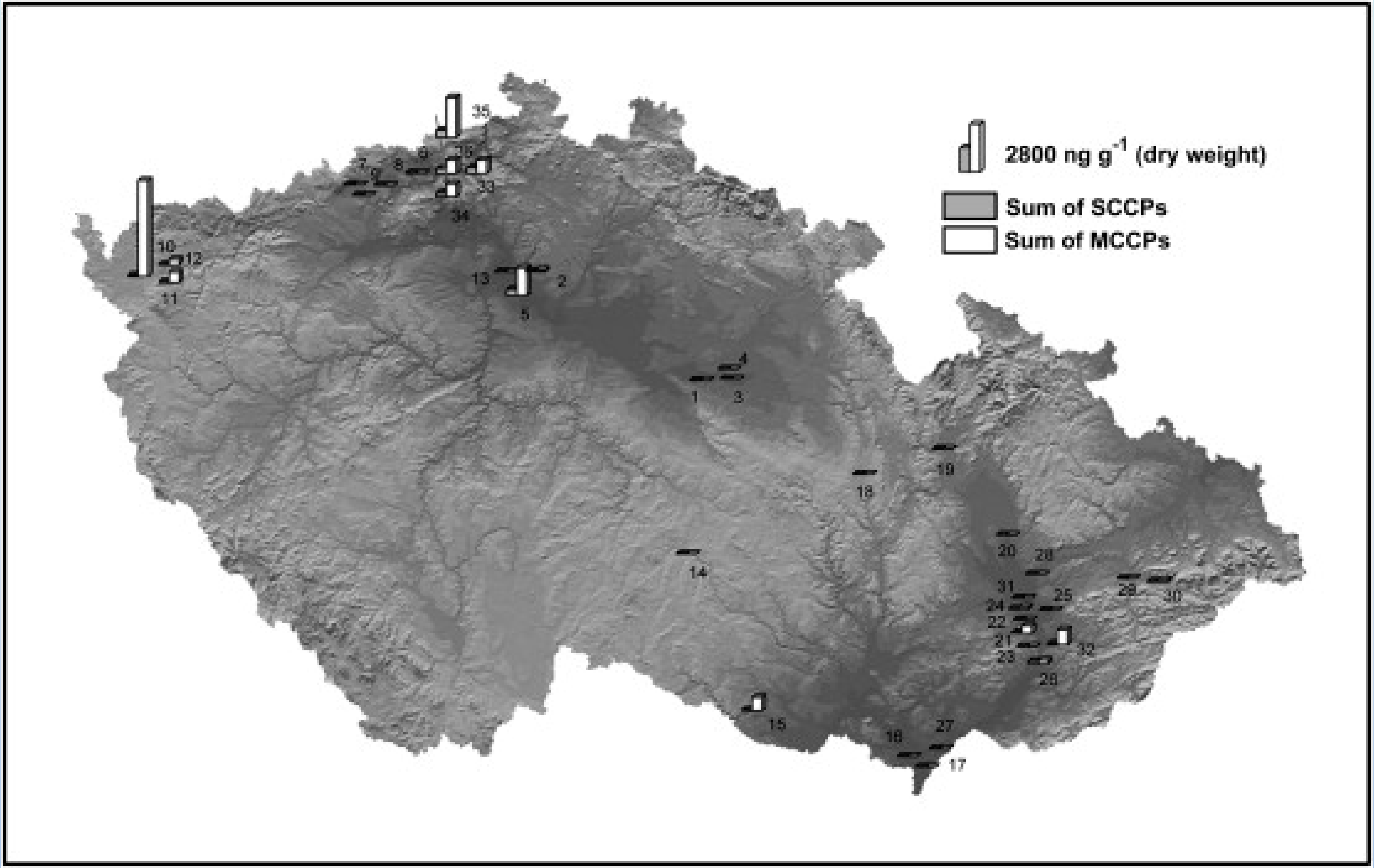
n^{-3}).

1954.

SCCPs in soil – 10-1000x higher than OCPs



Halse et al. 2015



Levels of CPs in Czech River sediments

Petra Přibylová , Jana Klánová , Ivan Holoubek

Screening of short- and medium-chain chlorinated paraffins in selected riverine sediments and sludge from the Czech Republic

Environmental Pollution, Volume 144, Issue 1, 2006, 248 - 254

Further resources on chlorinated paraffins…

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Review article

Chlorinated paraffins: A review of analysis and environmental occurrence

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Received 20 December 2005; accepted 17 May 2006
Available online 30 June 2006

Current use pesticides - CUPs

- Tricky naming – not all CUPs are in use in all areas
- Generally refers to pesticides that were replacements for the OCPs
- Should have lower environmental persistence and bioaccumulative potential than OCPs
- Often lacking in information on environmental behaviour

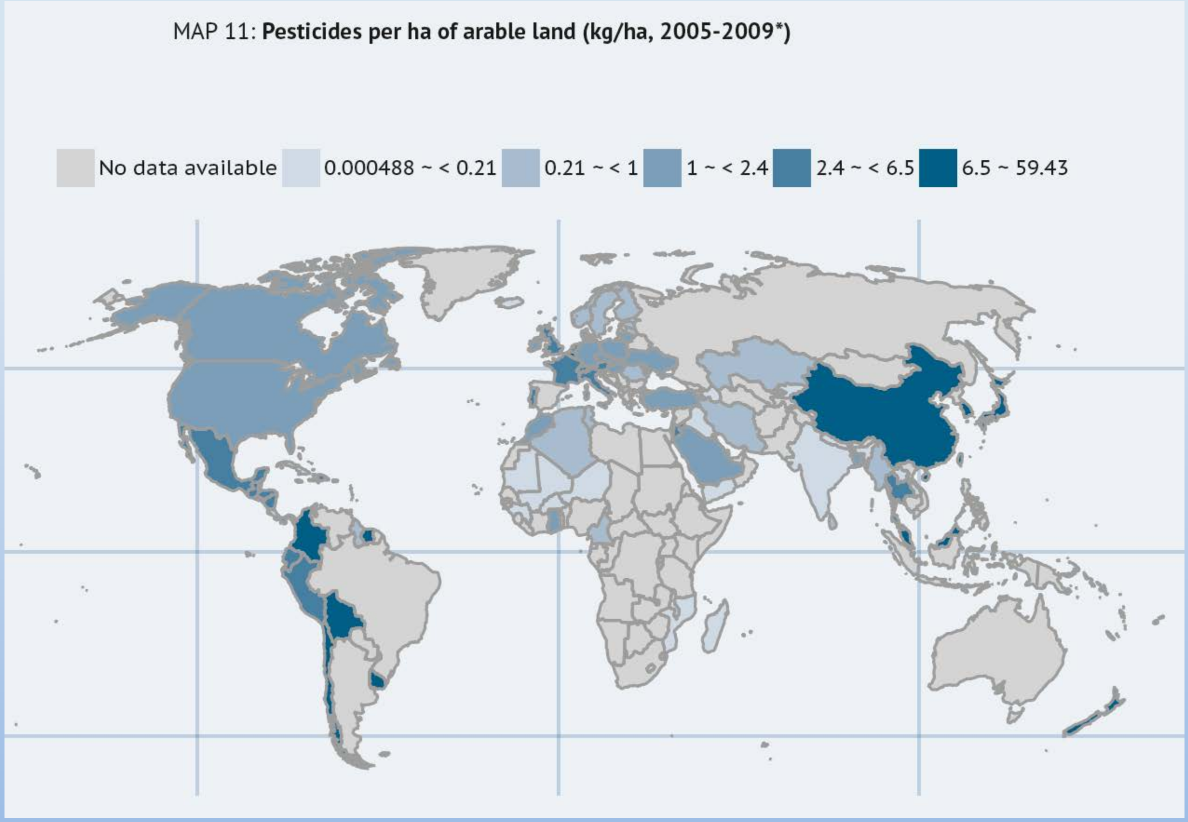
Global pesticide use

Insecticide

Herbicide

Fungicide

2.5 million tonnes per year (Alavanja, 2009)



From FAO Statistical Yearbook, UN 2013

Czech pesticide use

ÚSTŘEDNÍ KONTROLNÍ A ZKUŠEBNÍ ÚSTAV ZEMĚDĚLSKÝ
Sídlo ústavu: Hroznová 63/2, 656 06 Brno
SEKCE ZEMĚDĚLSKÉ INSPEKCE
ODDĚLENÍ KOORDINACE A KONTROLY
Korespondenční adresa: Zemědělská 1a, 613 00 BRNO

Vytvořil/telefon: Mgr. Bohumil Musil / 545 110 449
E-mail: bohumil.musil@ukzuz.cz
Datum: 30.09.2014
č.j. : UKZUZ 075107/2014

Ústřední kontrolní a zkušební ústav zemědělský **Česká republika - Spotřeba účinný…**
Central Institute for Supervising and Testing in Agriculture **Czech Republic - Usage of active s…**

LÁTKA ACTIVE	CELKEM TOTAL	OBILOVINY CEREALS	KUKUŘICE MAIZE	LUS… LEG…	OSTATNÍ OTHERS
ABAMECTIN	6,093	0	0		0,132
ACEQUINOCYL	48,995	0	0		0
ACETAMIPRID	6 436,17[illegible]	0,666	2,349		1,752
ACETOCHLOR	101 052,805	256,100	91 001,503		0
ACLONIFEN	4 448,849	0	295,114		582,329
ALKYLAMINE ETHOXYLATE PROPOXYLATE	3 091,983	1 674,169	53,958		0,653
ALKYLPHENOL ALKOXYLATE	3 542,119	2 143,842	912,767		0
ALLYLOXYPOLYETHYLENEGLYCOL	4 847,171	2 798,987	160,589		4,609
ALPHA-CYPERMETHRIN	2 600,742	1 700,667	37,587		0
ALUMINIUM SULFATE	97,717	0	0		0
AMIDOSULFURON	1 206,646	1 201,831	0		0
AMINOPYRALID	5 695,904	4 818,723	1,698		0

Round-up

>200 active substances in use

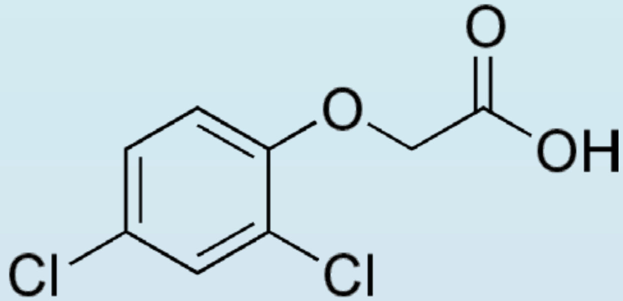
10 most used pesticides in CZ

	Compound	**2013 use (kg)**
	Total	5510952
1	GLYPHOSATE	935469
2	TEBUCONAZOLE	179055
3	CHLORPYRIFOS	178362
4	PROCHLORAZ	176504
5	METAZACHLOR	169985
6	PENDIMETHALIN	124274
7	PETHOXAMIDE	115125
8	SULPHUR	113832
9	TERBUTHYLAZINE	113124
10	CHLOROTOLURON	107418

Potential EDC pesticides in use in CZ

2,4-dichlorophenoxyacetic acid, 3,4-dichloroaniline, acetochlor, alachlor, amitrol, atrazine, bifenthrin, boric acid, carbaryl, chlordimeform, cyhalothrin, deltamethrin, dibromochloropropane, dibromoethane, fenarimol, fenitrothion, kepone (chlordecone), linuron (lorox), loxynil, mancozeb, maneb, metam natrium, methoxychlor, metiram (complex), metribuzin, nitrofen, omethoate, picloram, quinalphos = chinalphos, resmethrin, stannane, terbutryn, thiram, trifluralin, vinclozolin, zineb

2,4-D



- Most widely used herbicide
- 2,4-dichlorophenoxyacetic acid
- Kills broad-leaf plants
- Used on cereal crops and corn, home use on lawns
- 65 tonnes used in Czech Rep. in 2013
- 21000 tonnes used globally
- Developed in US during WWII – intended to be a chemical weapon – herbicidal properties discovered in 1944
- One of the ingredients in Agent Orange
- Soil half-life ~10 days

2,4-D -- Exposure

- Exposure to agricultural workers
- Drift from pesticide application – higher levels in homes in agricultural areas or where 2,4-D is used in gardens

2,4-D -- Toxicity

- IARC – possible carcinogen
- Potential endocrine disrupter

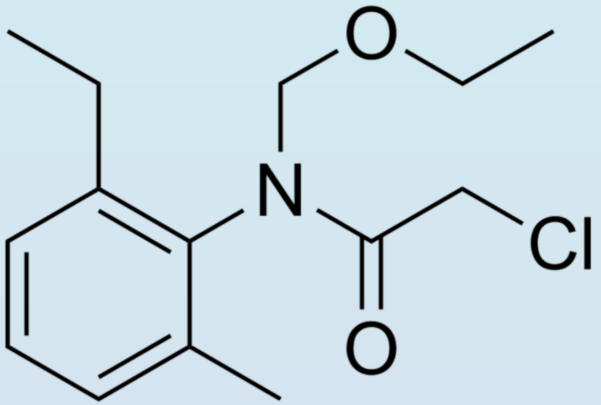
Endocrine Disruption:

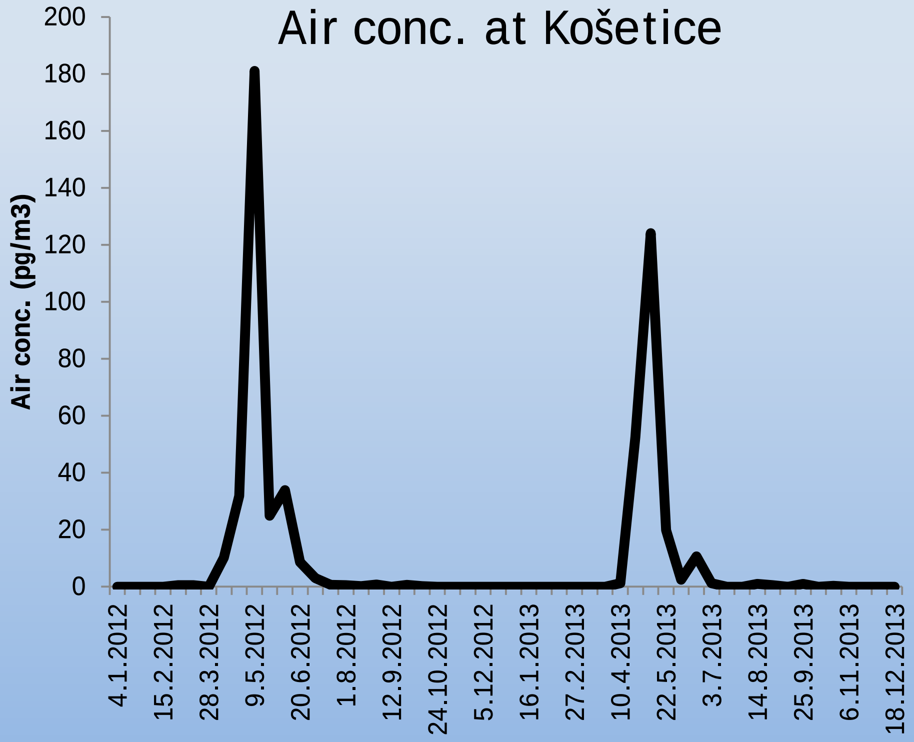
- Because 2,4-D has demonstrated toxic effects on the thyroid and gonads following exposure, there is concern over potential endocrine-disrupting effects.[3] 2,4-D is included in the U.S. EPA June 2007 Draft List of Chemicals for Tier 1 Screening.[24]

From US National Pesticide Information Centre

Acetochlor

- Used on cereal, corn, oil plants
- 101 tonnes used in Czech Rep. in 2013
- No longer authorized in EU as of 2012, with 12 months for phase-out
- Soil half-life ~9 days





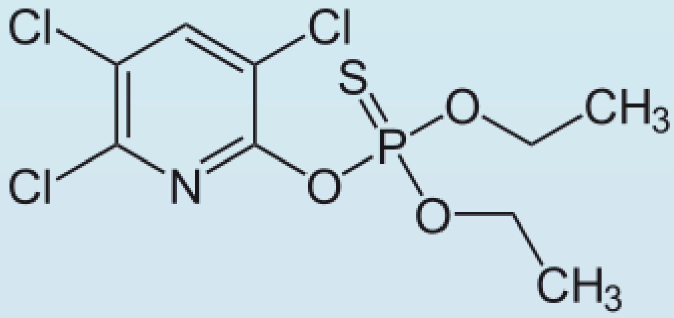
Acetochlor -- Exposure

- Exposure to agricultural workers
- Drift from pesticide application, e.g, to indoor environments in agricultural areas

Acetochlor -- Toxicity

- IARC – probably carcinogen
- Mutagenic, carcinogenic effects, reduced fertility in lab studies
- Moderately toxic to honeybees
- Potential endocrine disrupter

Chlorpyrifos



- 3rd most used pesticide in CZ
- Broad-spectrum insecticide – disrupts nervous system function
- Used on cereals and oil plants, also golf courses, industrial uses, wood treatment
- Used in more than 100 countries
- 178 tonnes used in Czech Rep. in 2013

- Under review in Europe. In North America, regulations mostly limit use in buffer zones around areas where children might be exposed and where it could enter water systems

Chlorpyrifos – Toxicity and risks

Human risks:

- US EPA identified risks to workers, risks to drinking water in agricultural areas, risks from indoor use

- Developmental effects
- Autoimmune effects
- Reduced IQ due to prenatal exposure

Common Insecticide May Harm Boys' Brains More Than Girls'

Results from a new study suggest that a pesticide banned from homes but still used on farms impairs boys' memories

August 21, 2012 | By Brett Israel and Environmental Health News

A widely used pesticide – banned in homes but still commonly used on farms – appears to harm boys' developing brains more than girls', according to a new study of children in New York City.

In boys, exposure to chlorpyrifos in the womb was associated with lower scores on short-term memory tests compared with girls exposed to similar amounts.

The study is the first to find gender differences in how the insecticide harms

Wildlife risks

- Toxicity to bees, high toxicity to crustaceans if enters water system

Personal care products (PCPs)

- Soap, shampoo, conditioner, deodorant, make-up, perfume, lotions and creams, nail polish, hair dye, etc.
- What are the potential concerns in PCPs?
  - Parabens
  - Synthetic musks
  - Phthalate esters
  - UV filters
  - Antimicrobial compounds
- High potential for human exposure
- Entry to environment through wastewater treatment

Review of personal care products in surface water

Table 1
Summary of measured concentration of personal care products in surface water (ng L^{-1}).

Compound	Class	n[a]	Range (ng L^{-1})	Median (ng L^{-1})
Triclosan	Disinfectant	710	<0.1–2300	48
Methyltriclosan	Disinfectant	4	0.5–74	–
Triclocarban	Disinfectant	29	19–1425	95
Musk ketone	Fragrance	178	4.8–390	11
Musk xylene	Fragrance	93	1.1–180	9.8
Celestolide	Fragrance	73	3.1–520	3.2
Galaxolide	Fragrance	282	64–12 470	160
Tonalide	Fragrance	245	52–6780	88
DEET	Insect repellant	188	13–660	55
Paraben[b]	Preservative	6	15–400	–
4MBC	UV filter	19	2.3–545	10.2
BP3	UV filter	18	2.5–175	20.5
EHMC	UV filter	21	2.7–224	6.1
OC	UV filter	22	1.1–4450	1.9

[a] n = Number of samples.
[b] Includes all parabens.

Brausch and Rand, 2011

Fragrance compounds

Historically, many fragrance compounds were extracted from musk glands of male musk deer.

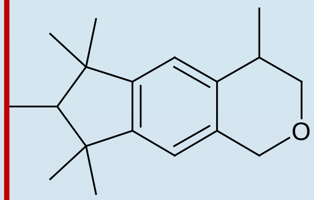
"In order to get access to the natural musk, the animal must be killed to remove the gland, also called musk pod. The fully developed pods (50–70 g) contain about 40% musk. Upon drying, the reddish-brown paste turns into a black, granular material (musk grain) which is used for alcoholic solutions. The aroma of the tincture, which is described for example as animal-like, earthy, and woody, becomes more intensive during storage."

- Natural musk first used in ancient China
- Brought to Europe by Crusaders
- Musk deer species now endangered
- Trade of musk from many Asian countries banned since 1979 by Convention on International Trade in Endangered Species of Wild Fauna and Flora
- EU banned musk trade with Russia and China in 1998
- Natural musk very expensive – in 1998, 1 g of musk cost 30-50 US$ (more than gold)

Synthetic musks

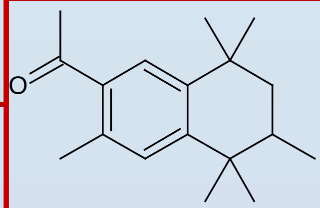
- Attempts to synthesize musks since 1759
- 1906 – nitro musks (Musk ketone, musk xylene)
- 1950s – polycyclic musks – low cost and good smell
- 1980s, 1990s – concerns about bioaccumulation and carcinogenic potential of nitro musks – shift towards polycyclic musks
- 2000s – 70% of use was polycyclic musks, 12% nitro musks

Polycyclic musks



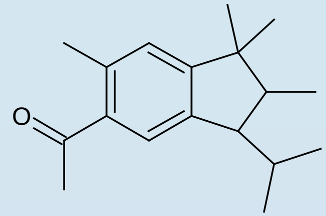
Galaxolide

HHCB



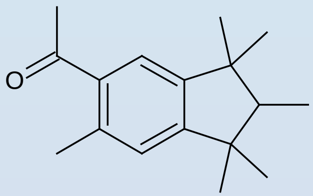
Tonalide

AHTN



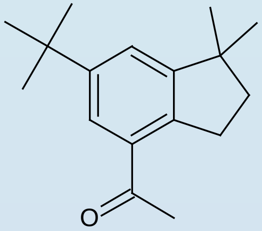
Traseolide

ATII



Phantolide

AHDI



Celestolide

ADBI

Table 4 Industrial use of polycyclic musks in Europe (in tonnes) [50]

Year	HHCB	AHTN	ADBI	AHDI	ATII
1992	2400	885			
1995	1482	585	34	50	40
1998	1473	385	18	19	2

Musks in consumer products linked to musk exposure

Table 3
Estimated human exposure to Musk T and HHCB by using cosmetics and household commodoties in Japan.

	N	Conentration in product (μg/g)	Application quantity[a] (g/time)	Application frequency[a] (time/day)	Absorption rate[b] (%)	Retention factor[b]	**EHE (μg/kg/day)**	**Composition (%)**
Musk T								
Perfume	13	2800	0.75	1	10	1	*4.2*	*54*
Shampoo	11	170	8	1	10	0.01	*0.03*	*0.35*
Body lotion	9	300	8	0.71	10	1	*3.4*	*44*
Body soap	5	170	5	1.07	10	0.01	*0.02*	*0.23*
Antiperspirant	5	140	0.5	1	10	1	*0.14*	*1.8*
Total							**7.8**	100
HHCB								
Perfume	13	4000	0.75	1	10	1	*6.0*	*76*
Shampoo	11	130	8	1	10	0.01	*0.021*	*0.26*
Body lotion	9	140	8	0.71	10	1	*1.6*	*20*
Body soap	5	190	5	1.07	10	0.01	*0.020*	*0.26*
Antiperspirant	5	250	0.5	1	10	1	*0.25*	*3.2*
Total							**7.9**	100

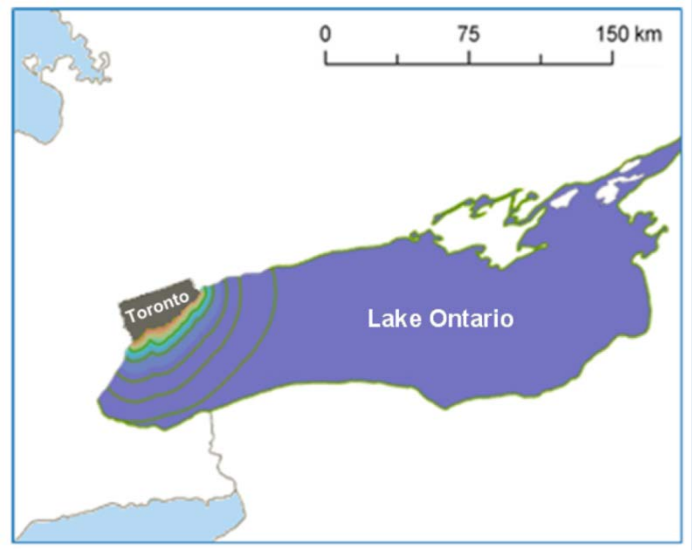
[a] Cited from McGinty et al. (2011) .
[b] Cited from Sommer and Juhl (2004).

(n = 13) (n = 11) (n = 11) (n = 9) (n = 5) (n = 5) (n = 4)

Fig. 3. Concentrations of synthetic musk fragrances in commercial household commodities purchased in Japan. MMs: Macrocyclic musks, PMs: Polycyclic musks, NMs: Nitro musks.

Nakata et al. 2015

Releases of musks from cities to North American lakes



- Major musk pathway is from WWTP
- Loadings >10x higher than for PCBs or PBDEs

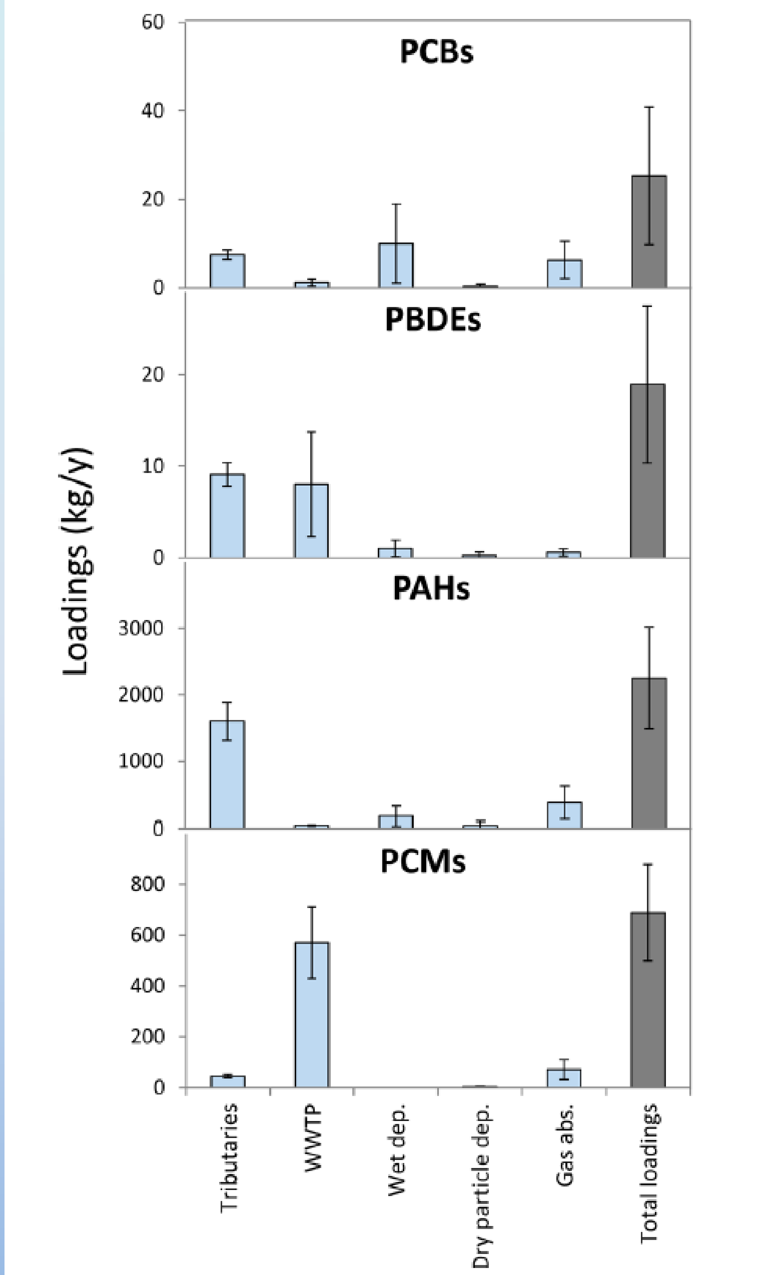
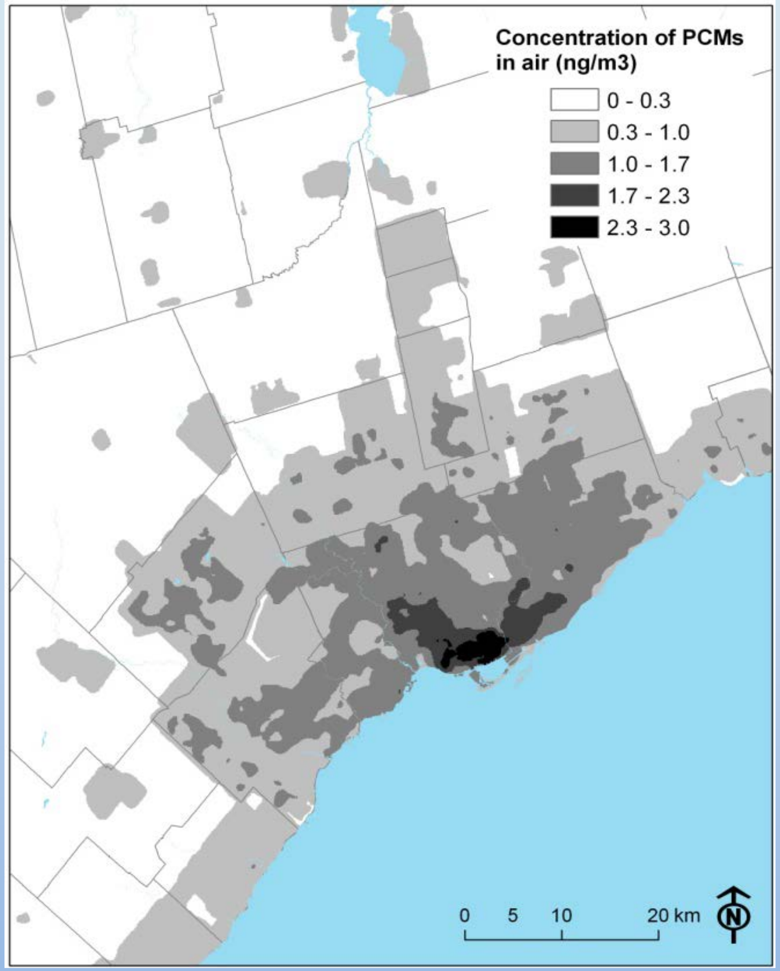


Figure 2. Loadings of PCBs, PBDEs, PCMs, and PAHs from Toronto to nearshore Lake Ontario via five loadings pathways.

Melymuk et al. 2014

Musks in the urban area

- Distributions correspond with population density



Musks are not very persistent
~6 h atmospheric half-life

Pseudo-persistence?

Synthetic musks – risk evaluation

- UK, EU, USA → risk assessments for HHCB found no further regulation needed
- Concerns regarding human exposure via PCP use
- Environmental exposure via wastewater releases and application of sewage sludge to agricultural fields

Persistence vs. pseudo-persistence

588

Integrated Environmental Assessment and Management — Volume 10, Number 4—pp. 588–594

The Role of Persistence in Chemical Evaluations

Donald Mackay,† Dianne M Hughes,‡ M Luisa Romano,‡ and Mark Bonnell§*

†Canadian Centre for Environmental Modelling and Chemistry, Trent University, Peterborough, Ontario, Canada

‡New Substances Assessment and Control Bureau, Health Canada, Ottawa, Ontario, Canada

§Ecological Assessment Division,

(Submitted 6 September 2013; Re

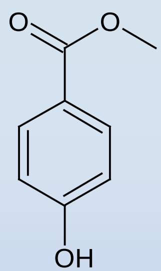
ABSTRACT

The initial stage in the asses
environment is usually a hazar
hazard assessment is followed
and processes influencing pers
include 1) an initial focus on
universally applicable as distin
treatments of near-field and f
substances for which "time to
show that "continuously prese

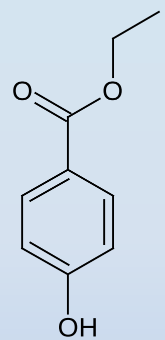
raised in connection with the continuous discharge of low concentrations of chemicals used indoors under conditions of restricted ventilation or from pharmaceuticals that survive removal in WWTPs. Daughton (2002) noted that "Many drugs from a wide array of therapeutic classes have been established as ever-present trace environmental pollutants in surface and ground waters." He coined the adjective "pseudo-persistent" to describe these substances, and that term has been widely used in the pharmaceutical literature since. "Pseudo-persistence" is not an intensive property of a substance; rather, it is a function of its use patterns or mode of entry and the characteristics of the aquatic receiving environment as well as the chemical's half-life. In our view the term *continuously present* is less likely to be misinterpreted as an intensive chemical-specific property.

Parabens

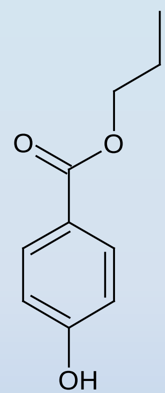
- Used as preservatives in personal care products
- Synthetically produced
- Most common are:



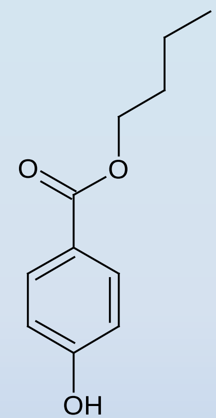
Methylparaben



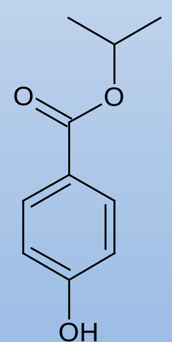
Ethylparaben



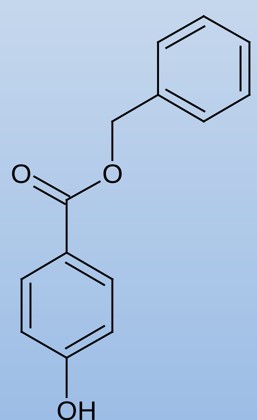
Propylparaben



Butylparaben



Isopropylparaben



Benzylparaben

Paraben use

- Found in over 22000 personal care products
- Also used as food preservatives (jams, baked goods, syrups)
- Added at concentrations up to 0.8% as a mixture
- Legal limit for products in EU is 0.4% of an individual paraben
- Typical daily use of parabens is 17.76 g/day for adults, 0.378 g/day for babies
- Dominant exposure through skin and diet
- Skin penetration is inversely proportional to molecule size (e.g., penetration of methylparaben > butylparaben)

Parabens – evidence of effect?

Let's look at what the European Commission evaluated…

Conclusion:

Reference	Test species	Dosage level	Effect(s) noted
Butyl Paraben			
Fisher et al. 1999	Male neonatal Wistar rat of 2 days old	2 mg/kg/day for 16 days sc injected	No detectable effect on any reproductive parameter
Oishi 2001	Male post-weaning Crj:Wistar rat	10 mg/kg/day for 8 weeks oral administration	↓ cauda epididymal sperm reserve ↓ sperm count ↓ daily sperm production ↓ serum testosterone
Kang et al. 2002	Female pregnant Sprague Dawley rat	100 to 200mg/kg/day for 14 days sc injected	Offspring: ↓ sperm count ↓ sperm motile activity in epididymus
Oishi 2002a	Male Crj:CD-1 ICR mouse	14.4, 146 and 1504 mg/kg/day for 10 weeks oral administration	↑ epididymal weights ↓ testis spermatid count ↓ serum testosterone (NOAEL = 14.4 mg/kg/day)
Daston [illegible]	Female pregnant [illegible]	0, 10, 100 and 1000 [illegible]	Foetuses examination on gestational day 20 : only developmental parameters measured, no changes [illegible]
[illegible]	[illegible]	[illegible]	[illegible]
[illegible] 2002b	[illegible] rat	[illegible] weeks oral administration	[illegible] reserve [illegible] Only minor effects at 10 mg/kg/day
Ethyl and Methyl Paraben			
Oishi 2004	Male Crj:Wistar rat	103 and 1030 mg/kg/day for 8 weeks oral administration	No adverse effects noted

As explained in detail under section 3 of the present opinion, the tests provided in Submission I of February 2006 contain too many shortcomings in order to be considered as scientifically valid.

Therefore, the conclusion of opinion SCCP/0873/05 remains unchanged.

Precautionary principle??

From European Commission Health and Consumer Protection Directorate, "Opinion on Parabens", 2006

Precautionary principle

The precautionary principle states that if an action or policy has a suspected risk of causing harm to the public or to the environment, in the absence of scientific consensus that the action or policy is not harmful, the burden of proof that it is *not* harmful falls on those taking an action.

Paraben exposure

House dust (Ma et al. 2014)

- Mean: 1.52±0.52 µg/g
- Range: 0.03-125 µg/g

In food (USA study): (Liao et al. 2013)

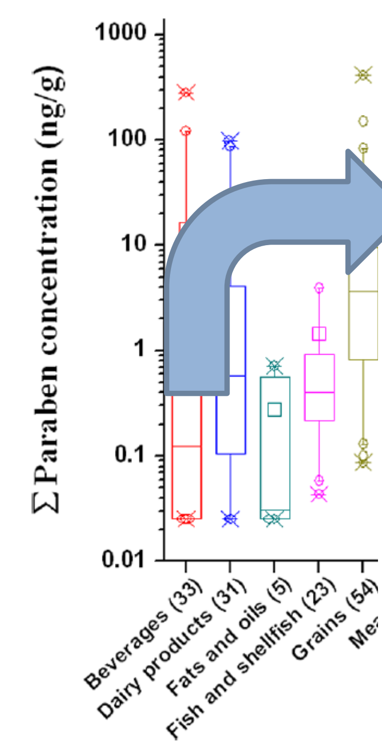
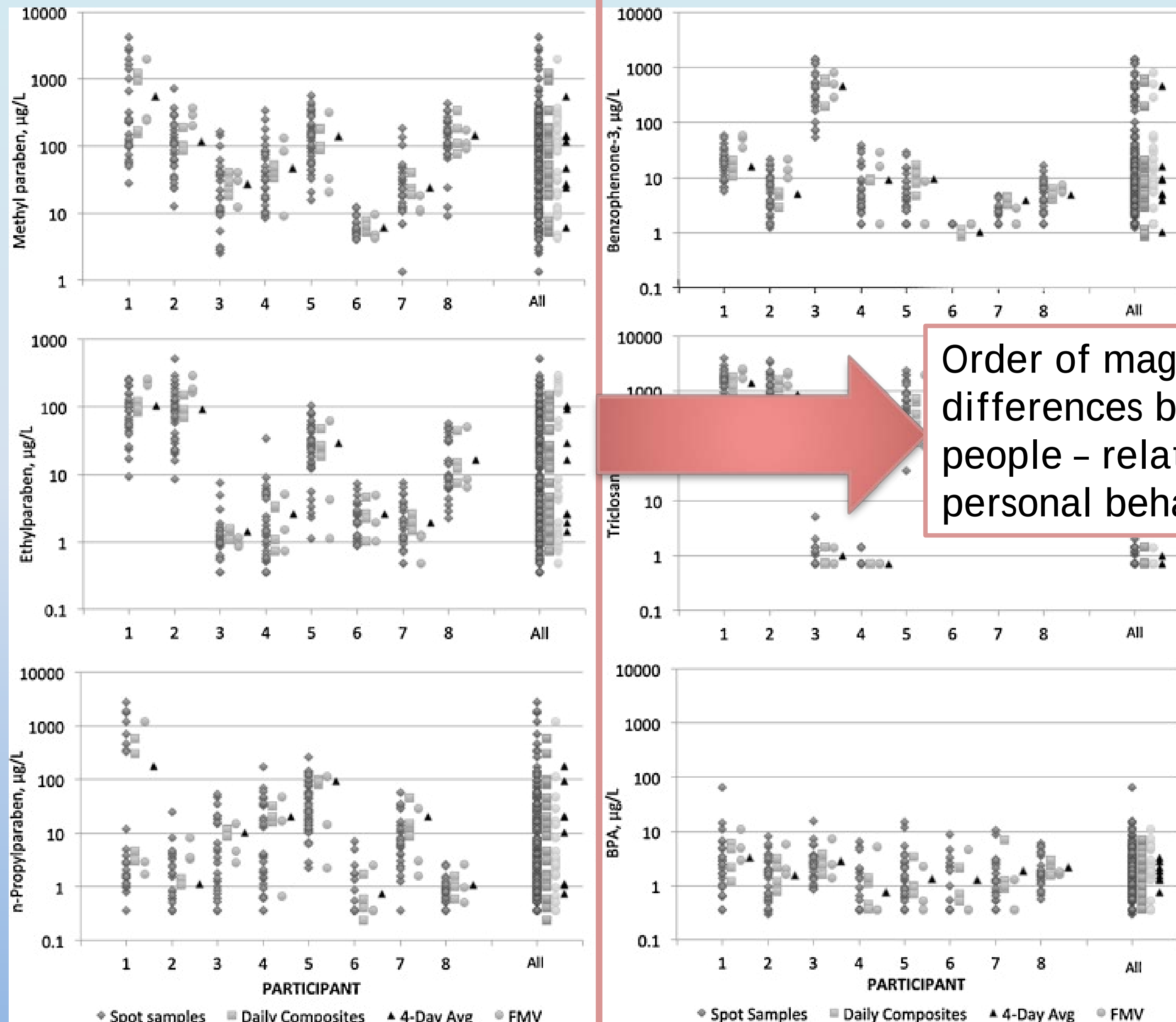


Table 3. Estimated Daily Dietary Intakes (EDI, ng/kg bw/day) of Parabens for Various Age Groups in the United States

	BzP	BuP	EtP	MeP	PrP	Σparabens
			mean			
infants (<1 year)	1.88	1.25	467	372	97	940
toddlers (1 to <6 years)	1.97	2.29	240	437	198	879
children (6 to <11 years)	1.06	1.08	155	230	83	470
teenagers (11 to <21 years)	0.60	0.57	100	129	42	273
adults (≥21 years)	0.66	0.50	137	133	35	307
			95th percentile			
infants (<1 year)	6.66	4.58	1735	1382	387	3510
toddlers (1 to <6 years)	4.94	5.12	681	1027	449	2170
children (6 to <11 years)	2.94	2.66	455	579	208	1250
teenagers (11 to <21 years)	1.74	1.51	324	364	122	813
adults (≥21 years)	1.85	1.30	398	358	98	856

For comparison, BDE-47 dietary exposure estimated 1-3 ng/kg bw/day (Fromme et al. 2009)

Parabens in urine (Koch et al. 2014)

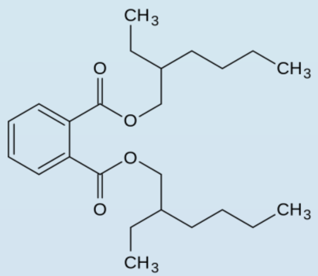


Order of magnitude differences between people – related to personal behaviours

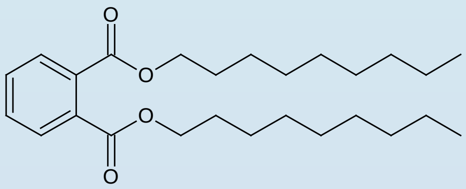
Phthalate esters

- One of the most broadly uses classes of synthetic compounds
- 1-2 million tonnes per year
- Plasticizers – increase material flexibility and transparency
- Up to 60% by weight of material
- Wide range of uses: vinyl building and construction materials (e.g: flooring, wall coverings, piping), adhesives, sealants, printing inks, paints, personal care products, and medical applications (eg: blood storage bags)

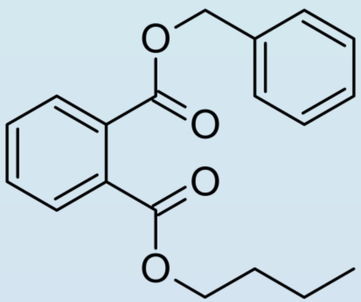
- More than 25 commercial phthalates in use
- Most common phthalates are DEHP, DNIP, and BBP



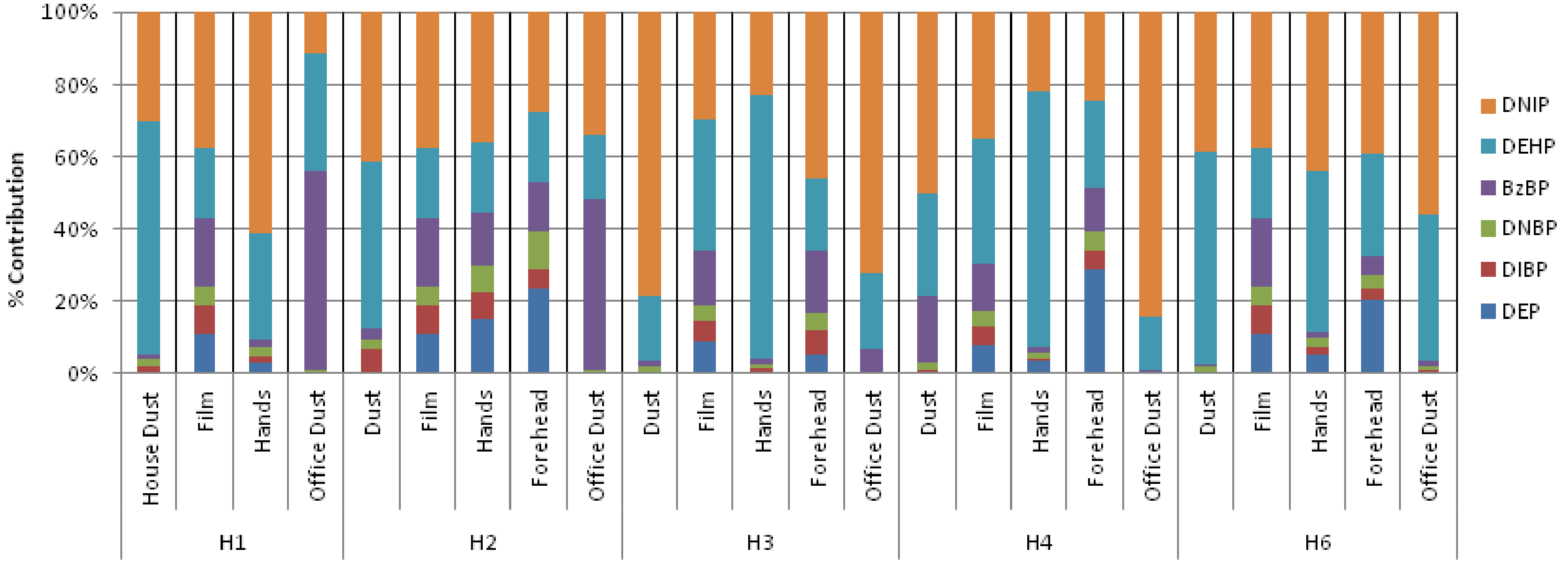
Diethylhexyl phthalate - DEHP
54% of phthalate market in 2010



Diisononyl phthalate - DINP



Benzylbutylphthalate – BBP



Chaudhuri et al. in prep

Phthalates in house dust

93 house dust samples from 2010/2011

Concentrations in µg/g

Compound	Average	Min	Max
DEP	0.4	0.02	6.8
DIBP	2.5	0.2	41.9
DNBP	6.8	0.5	104.0
BzBP	47.0	0.2	1957.2
DEHP	138.9	3.1	1515.2
DNIP	197.7	7.1	1521.2
SUM(phthalate)	**393.4**	**14.5**	**3574.1**

Chaudhuri et al. in prep

Phthalates
14-3574 µg/g

PBDEs
0.01-520 µg/g

236 *S. Harrad et al. / Environment International 34 (2008) 232–238*

Table 3
Summary of concentrations (ng g^{-1}) of selected PBDE congeners in dust samples from different cities in this and selected other studies

Location (reference)	Statistical parameter/ congener #	28	47	99	100	153	154	183	209	Σtri–hexa–BDE[a]	ΣBDE[b]
Toronto, Canada, this study[c]	Average	6.6	300	510	120	71	69	13	670	1100	1400
	σ_{n-1}	6.0	270	530	130	84	86	8.1	320	1100	1000
	Median	4.1	140	330	65	43	39	9.0	560	620	950
	Geometric mean	4.6	200	340	74	43	38	11	590	740	1200
	Minimum	1.4	47	80	14	9.4	6.2	7.0	290	160	750
	Maximum	20.0	720	1800	420	260	280	30	1100	3600	3500
Wellington, New Zealand, this study[d]	Average	0.86	36	87	16	9.8	8.7	–	–	160	–
	σ_{n-1}	0.57	39	100	19	11	10	–	–	180	–
	Median	0.65	24	51	8.9	5.4	5.1	–	–	96	–
	Geometric mean	0.66	22	47	8.8	5.5	4.4	–	–	92	–
	Minimum	0.11	3.3	6.4	1.2	0.66	0.56	–	–	13	–
	Maximum	2.1	150	380	70	35	35	–	–	680	–
Birmingham, UK, this study[e]	Average	0.75	20	47	7.0	14	5.4	64	45,000	98	45,000
	σ_{n-1}	0.65	32	74	9.8	26	7.2	140	130,000	140	130,000
	Median	0.53	13	23	4.2	5.2	3.3	13	2800	59	2900
	Geometric mean	0.49	10	23	3.9	5.9	2.9	14	3800	52	4500
	Minimum	<dl	1.2	2.8	0.53	0.63	0.31	2.0	120	5.7	360
	Maximum	2.3	160	320	50	110	31	550	520,000	610	520,000

Phthalates exposure

Indoor Air 2013; 23: 32–39
wileyonlinelibrary.com/journ
Printed in Singapore. All ri

PVC floori

Abstract Polyviny
has been shown t
indoor dust. Phth
Consecutive infan
A questionnaire a
used. Urinary me
phthalate (DBP),
(DEHP) were mea
(52%) participate
of the BBzP meta

Journal of Exposure Science and Environmental Epidemiology **22**, 468-475 (September/October 2012)
|doi:10.1038/jes.2012.33

Consumer product exposures associated with urinary phthalate levels in pregnant women

Jessie P Buckley, Rachel T Palmieri, Jeanine M Matuszewski, Amy H Herring, Donna D Baird, Katherine E Hartmann and Jane A Hoppin

Abstract

Human phthalate exposure is ubiquitous, but little is known regarding predictors of urinary phthalate levels. To explore this, 50 pregnant women aged 18–38 years completed two questionnaires on potential phthalate exposures and provided a first morning void. Urine samples were analyzed for 12 phthalate metabolites. Associations with questionnaire items were evaluated via Wilcoxon tests and t-tests, and r-squared values were calculated in multiple linear regression models. Few measured factors were statistically significantly associated with phthalate levels. Individuals who used nail polish had higher levels of mono-butyl phthalate (P=0.048) than non-users. Mono-benzyl phthalate levels were higher among women who used eye makeup (P=0.034) or used makeup on a regular basis (P=0.004). Women who used cologne or perfume had higher levels of di-(2-ethylhexyl) phthalate metabolites. Household products, home flooring or paneling, and other personal care products were also associated with urinary phthalates. The proportion of variance in metabolite concentrations explained by questionnaire items ranged between 0.31 for mono-ethyl phthalate and 0.42 for mono-n-methyl phthalate. Although personal care product use may be an important predictor of urinary phthalate levels, most of the variability in phthalate exposure was not captured by our relatively comprehensive set of questionnaire items.

n's Health | Article

in Children and

jörn Lundgren,[1]
Lyngby, Denmark; [3]Public Health
obert Wood Johnson Medical

ort interval over which it has occurred
that the increase is caused by changes
onmental exposures rather than genetic
(Etzel 2003; Strachan 2000). Changes
or environments warrant special atten-
cause indoor air constitutes a domi-
posure route. Increased exposures to
s and/or adjuvants (enhancing factors)
ch be partially responsible for the

Health effects of phthalates

- Reproductive effects, especially in men
- Associated with diabetes in women (James-Todd et al., *Environmental health perspectives*, 2012)
- Occurrence of asthma and allergies in children (Jaakkola and Knight, *Environmental health perspectives*, 2010)
- Autism spectrum disorders (Kalkbrenner et al. *Current Problems in Pediatric and Adolescent Health Care*, 2014)

Current regulatory status

IP/11/196

Brussels, 17 February 2011

Chemicals/REACH: six dangerous substances to be phased out by the EU

Six substances of very high concern will be banned within the next three to five years unless an authorisation has been granted to individual companies for their use. These substances are carcinogenic, toxic for reproduction or persist in the environment and accumulate in living organisms. Operators wishing to sell or use these substances will need to demonstrate that the required safety measures have been taken to adequately control the risks, or that the benefits for the economy and society outweigh the risks. Where feasible alternative substances or techniques exist, a timetable for substitution will also have to be submitted. Today's Commission decision follows the successful first phase of registration and notification of chemicals (see IP/10/1632, IP/11/2). It is part of REACH, Europe's initiative to make the use of chemicals safer.

<u>EU REACH Legislation</u>

DHP – reproductive toxin

DEHP – serious effects on environment

DEHP, DBP, BBP, DIBP – serious effects on human health

DEHP, DBP, BBP – should be banned in EU as of 1 month ago (February 2015)…

But…

"This ban will only cover these substances when they are:

- Supplied on their own;
- Supplied in a mixture;
- Incorporated into an article with the European Union.

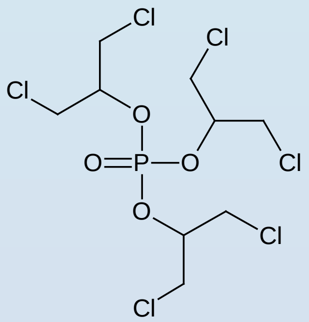
Imported articles containing any of these substances that were incorporated outside the EU are not covered by the Authorisation process."

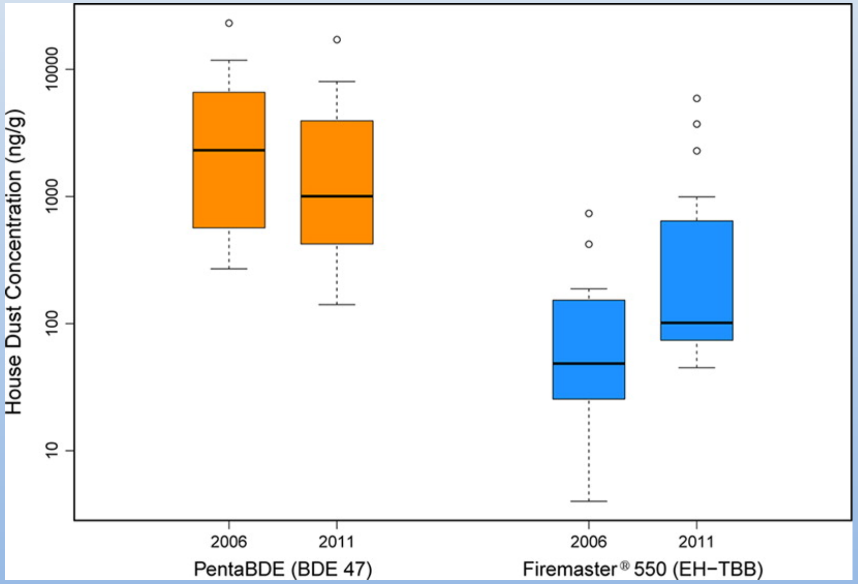
Plastic additives

- Flame retardants
  - PBDEs
  - Novel brominated and chlorinated FRs
  - Organophosphate FRs
- Plasticizers
  - Phthalates
  - other
- Phenols

Organophosphate flame retardants

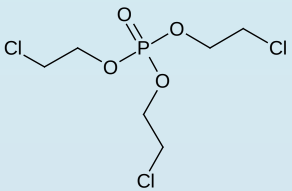
- 1950s-1970s – "chlorinated tris" – TDCIPP – used as flame retardant in children's pyjamas – banned after metabolites found to be mutagenic and metabolites identified in children's urine



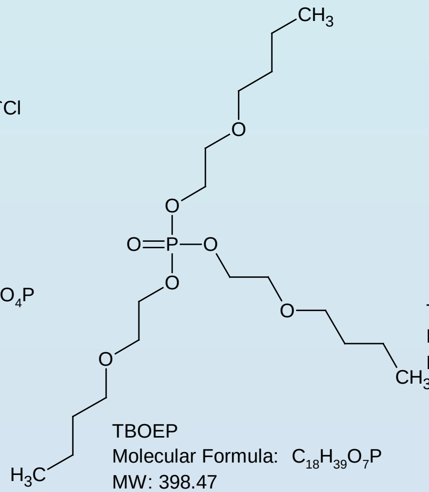


Dodson et al. 2012

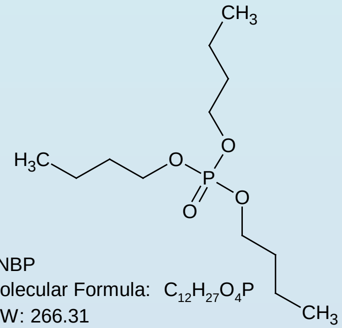
Increasing use as market moves away from PBDEs and other BFRs in response to regulatory action and public concern.



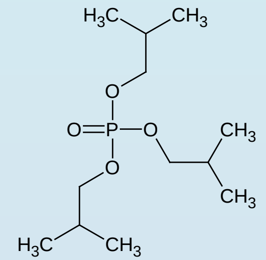
TCEP
Molecular Formula: $C_6H_{12}Cl_3O_4P$
MW: 285.49



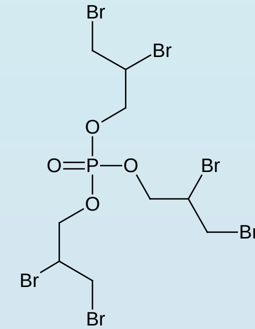
TBOEP
Molecular Formula: $C_{18}H_{39}O_7P$
MW: 398.47



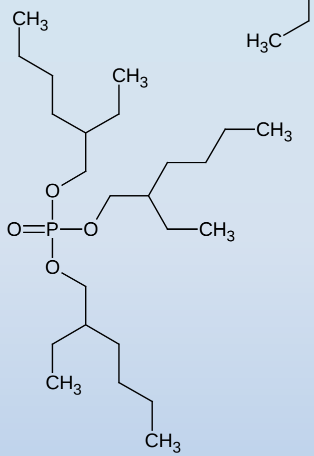
TNBP
Molecular Formula: $C_{12}H_{27}O_4P$
MW: 266.31



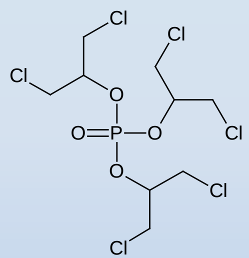
TIBP
Molecular Formula: $C_{12}H_{27}O_4P$
MW: 266.31



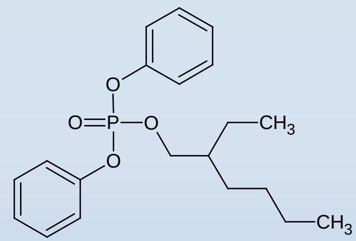
TDBPP
Molecular Formula: $C_9H_{15}Br_6O_4P$
MW: 697.61



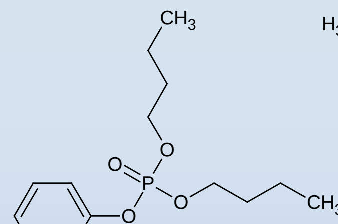
TEHP
Molecular Formula: $C_{24}H_{51}O_4P$
MW: 434.63



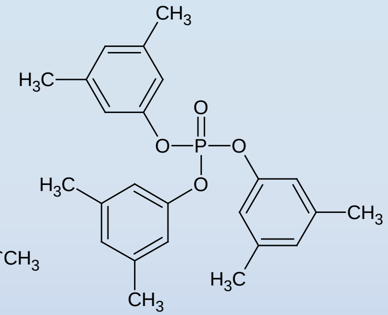
TDCIPP
Molecular Formula: $C_9H_{15}Cl_6O_4P$
MW: 430.90



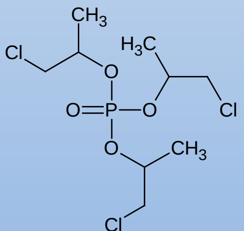
EHDPP
Molecular Formula: $C_{20}H_{27}O_4P$
MW: 362.40



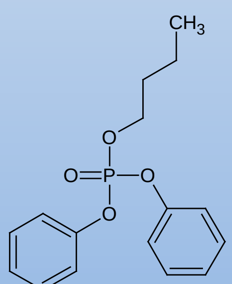
DBPP
Molecular Formula: $C_{14}H_{23}O_4P$
MW: 286.30



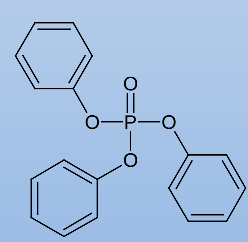
TDMPP
Molecular Formula: $C_{24}H_{27}O_4P$
MW: 410.44



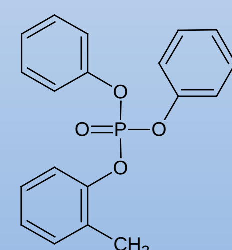
TCIPP
Molecular Formula: $C_9H_{18}Cl_3O_4P$
MW: 327.57



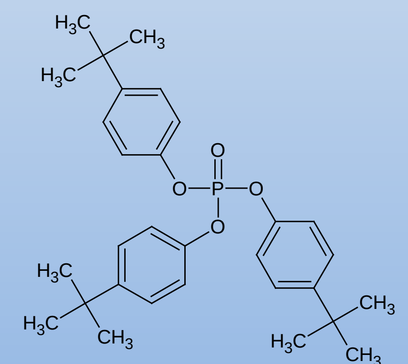
BDPP
Molecular Formula: $C_{16}H_{19}O_4P$
MW: 306.29



TPHP
Molecular Formula: $C_{18}H_{15}O_4P$
MW: 326.28



CDP
Molecular Formula: $C_{19}H_{17}O_4P$
MW: 340.31



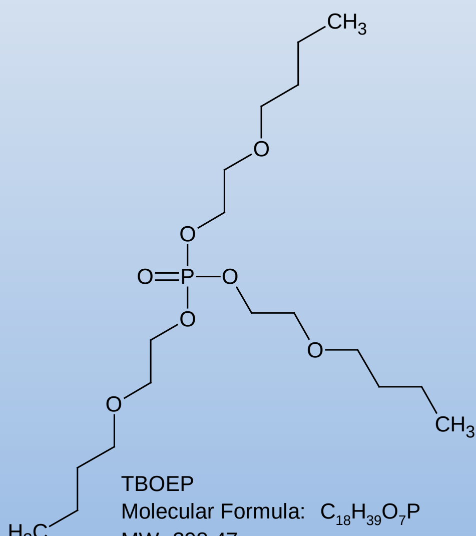
TBPP
Molecular Formula: $C_{30}H_{39}O_4P$
MW: 494.60

Current OPFRs

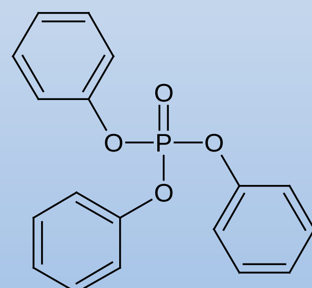
- 4 classes:

(1) alkyl phosphate esters – e.g. TBOEP
(2) aromatic phosphate esters – e.g. TPHP
} Plasticizers

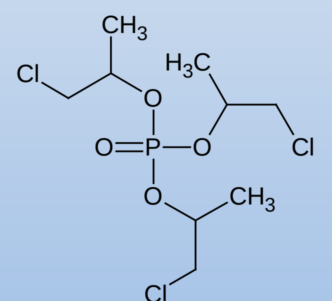
(3) chloroalkyl phosphate esters – e.g. TCIPP
(4) bromoalkyl phosphate esters – e.g. TDBPP
} Flame retardants



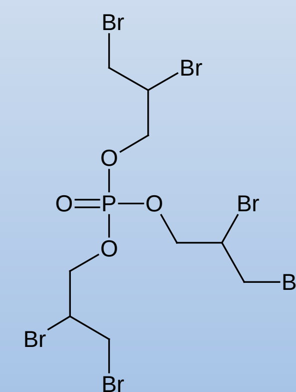
TBOEP
Molecular Formula: $C_{18}H_{39}O_7P$
MW: 398.47



TPHP
Molecular Formula: $C_{18}H_{15}O_4P$
MW: 326.28



TCIPP
Molecular Formula: $C_9H_{18}Cl_3O_4P$
MW: 327.57



TDBPP
Molecular Formula: $C_9H_{15}Br_6O_4P$
MW: 697.61

OPFRs in consumer products

TABLE 1. Characteristics of the Polyurethane Foam Samples Analyzed in This Study[a]

sample ID	source	year purchased	flame retardant detected	% by weight of flame retardant
1	chair	2004	unidentified	
2	mattress pad	2009	N/D	
3	leather couch	2005	unidentified	
4	sofa bed	2008	TDCPP	1.3
5	chair	2008	N/D	
6	foam from footstool	2006	TCPP	2.2
7	headrest of chair	2008	TCPP	0.5
8	chair	2006	TDCPP	3.2
9	chair	2004	TDCPP	3.0
10	chair	2007	TCPP	1.5
11	futon	N/A	pentaBDE	0.5
12	ottoman	2007	TCPP	0.7
13	chair	2003	TDCPP	1.0
14	chair	2006	TDCPP	2.9
15	pillow	2006	TDCPP	2.8
16	chair	2007	TDCPP	3.8
17	chair	2005	TDCPP	3.2
18	mattress pad	2006	TDCPP	1.2
19	couch	2007	TDCPP	5.0
20	chair	2005	TDCPP	2.5
21	office chair	2005	N/D	
22	futon	2008	TDCPP	2.8
23	nursery glider/rocker	2009	TDCPP	2.9
24	foam insulation from sieve/shaker	2008	TDCPP	2.2
25	baby stroller	2009	TDCPP	NM
26	couch	2007	TBB, TBPH	4.2

[a] N/A - Not available. N/D - Not detected. NM - not measured due to low mass of foam available. TDCPP - Tris-(1,3-dichloro-2-propyl)phosphate. TCPP - Tris(1-chloro-2-propyl)phosphate. PentaBDE - Pentabromodiphenyl ether commercial mixture. TBB - ethylhexyl 2,3,4,5-tetrabromobenzoate. TBPH - bis(2-ethylhexyl) tetrabromophthalate.

Stapleton et al. Environmental Science and Technology, 2009

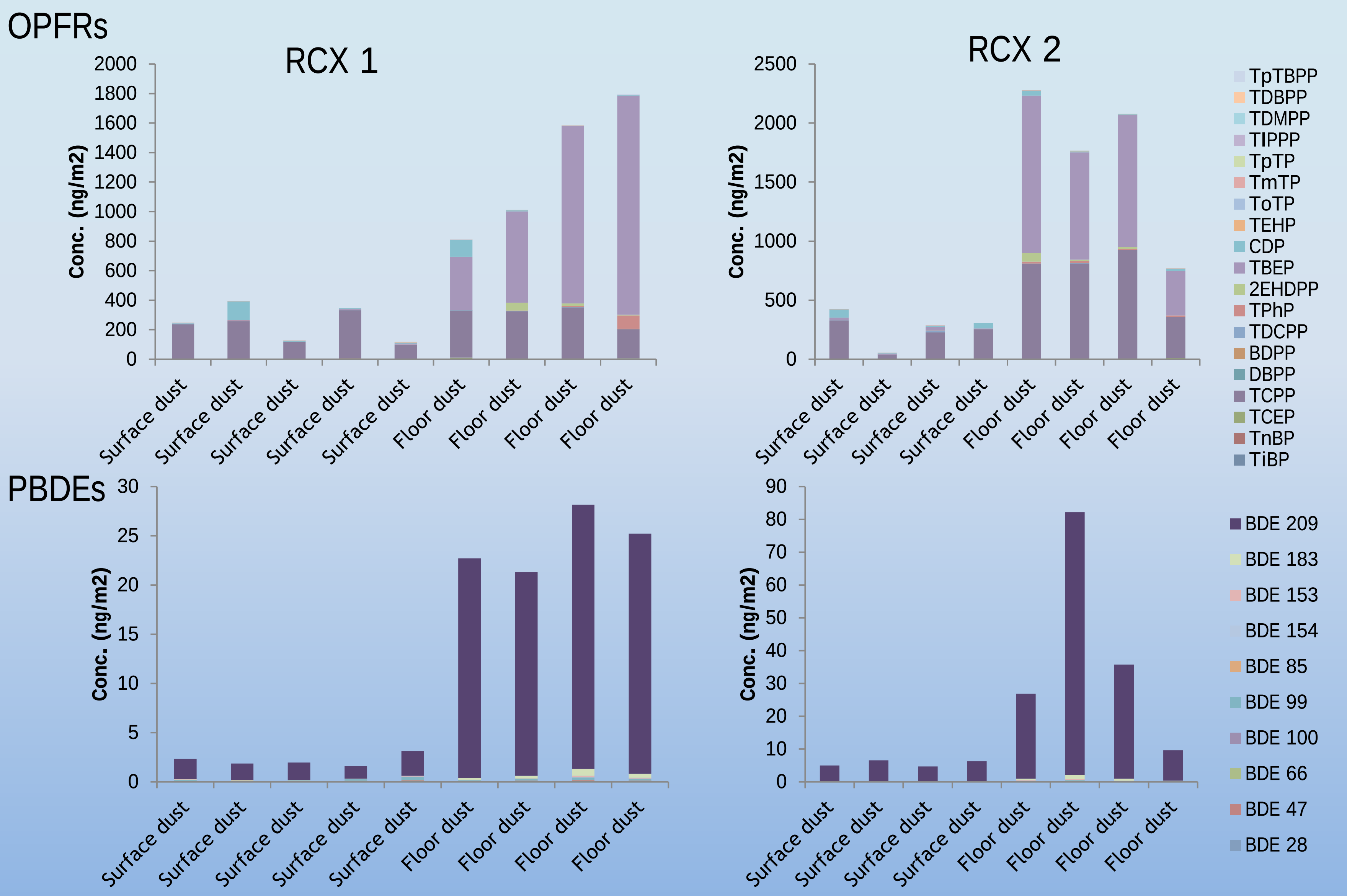
OPFRs – evidence of health concerns

- Carcinogenic or potentially carcinogenic: TDCIPP, TCEP, TCIPP
- Reproductive toxin: DCP, TCP, TCEP
- Neurotoxic effects: TPP
- Aquatic toxicity: DCP

** most compounds/scenarios have insufficient evidence to evaluate **

(van den Veen and de Boer, 2012)

Case Study: OPFRs at RECETOX



More info on OPFRs

Chemosphere 88 (2012) 1119–1153

Contents lists available at SciVerse ScienceDirect

Chemosphere

journal homepage: www.elsevier.com/locate/chemosphere

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Review

Phosphorus flame retardants: Properties, production, environmental occurrence, toxicity and analysis

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ARTICLE INFO

Article history:
Received 23 December 2011
Received in revised form 22 March 2012
Accepted 26 March 2012

ABSTRACT

Since the ban on some brominated flame retardants (BFRs), phosphorus flame retardants (PFRs), which were responsible for 20% of the flame retardant (FR) consumption in 2006 in Europe, are often proposed as alternatives for BFRs. PFRs can be divided in three main groups, inorganic, organic and halogen containing PFRs. Most of the PFRs have a mechanism of action in the solid phase of burning materials

Bisphenol A

- Used in polycarbonate plastic: transparent, durable, shatter-proof, light-weight
- Coating on tinned food cans
- Thermal paper (e.g., store receipts)

Bisphenol A in the news

BPA use

- Most recent global production estimate is from 2003: 2 million tonnes/year
- As of 2013, US and European regulators state that BPA is safe at the low levels that occur in foods
- Europe and Canada – banned in baby products, but regulators explicitly say this was based on precaution, not scientific evidence
- Widespread use and widespread exposure – detectable levels of BPA in 93% of Americans older than 6 years old

vom Saal and Hughes, 2012; NHANES, US Center for Diseaes Control; Royal Society of Chemistry, UK

BPA – the concerns

All *EHP* content is accessible to individuals with disabilities. A fully accessible (Section 508–compliant) HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1307728.

Review

Bisphenol A and Reproductive Health: Update of Experimental and Human Evidence, 2007–2013

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Evidence of BPA as:

- Estrogen mimicking compound
-Ovarian toxicant
- Associated with adverse birth outcomes, sexual dysfunction, poor development of uterus
- May be testicular toxicant
- CONCLUSION: “we conclude that BPA is a reproductive toxicant”

The Washington Post

To Your Health

How to avoid products with toxic bisphenol-s

By Amy Ellis Nutt January 13

Studies of bisphenol-S, the chemical compound sometimes used to replace bisphenol-A in "BPA-free" plastic products, found it is disruptive not only to the body's hormone system, but to brain circuitry in developing animal embryos.

Known to mimic estrogen, BPA and BPS are not the only synthetic chemicals found in hard plastic and certain resins that do so. (Close relatives include Bisphenol B, C, E, F, G, M. P, PH, TMC and Z.) In laboratory tests, 95 percent of hundreds of ordinary plastic products put through "real world" conditions, such as through a microwave or dishwasher, tested positive for leaching estrogenic chemicals. Since companies are under no obligation to tell consumers what chemicals are used in the manufacture of their product, many health experts say the best thing to do is avoid contact with household plastics altogether.

The Centre for Food Safety, which conducted a literature review on the EDCs in food, has chosen OCPs, PCDDs, PCBs, BPA, styrene, phthalates, organotins, and nonylphenol as the chemicals with the highest relevance to the human health compared to other potential EDCs because they are either persistent in the environment or high in production volume globally (Centre for Food Safety 2012).

Dioxins and dioxin-like PCBs (from food and dust), propyl and butyl-parabens (from cream/sunscreen), UV-filters (from sunscreen), triclosan (from deodorant and toothpaste), nonylphenol (clothes) and phthalates (consumer products and dust) were identified as the main contributors to the potential endocrine effects of Danish pregnant women (Danish EPA 2012).

Indoor Air 2010; 20: 458–472
www.blackwellpublishing.com/ina
Printed in Singapore.

INDOOR AIR
doi:10.1111/j.1600-0668.2010.00667.x

Health ranking of ingested semi-volatile organic compounds in house dust: an application to France

Abstract People spend most of their time indoors. Dust settled in the home may be contaminated by semi-volatile organic compounds (SVOCs). Exposure to these compounds is of great concern, in particular for infants. Their number is large so arose the question of which ones should be selected for dust ingestion exposure assessment. This work proposes a health ranking of SVOCs ingested through settled dust. This ranking is based on the toxicity and contamination of SVOCs in dust. Data on compounds and contamination was retrieved from a bibliographic review. Where possible, toxicity data was retrieved from databases, otherwise it was calculated from raw data. One hundred and fifty-six SVOCs were selected, 66 of which were prioritized. Forty-two could not be prioritized because contamination data was below the limit of detection, and 48 could not be prioritized because there was no contamination or toxicity data. The top-ranked compounds were phthalates, pesticides, short-chain chlorinated paraffins, PBDEs, PFCs, organotins, PCBs, and PAHs. As most of these have reprotoxic and neurotoxic properties, an integrated multi-pollutants approach to exposure is required and simultaneous measurement methods should be developed.

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Key words: Ranking; SVOCs; Dust; Indoor; Health; Exposure; Infant.

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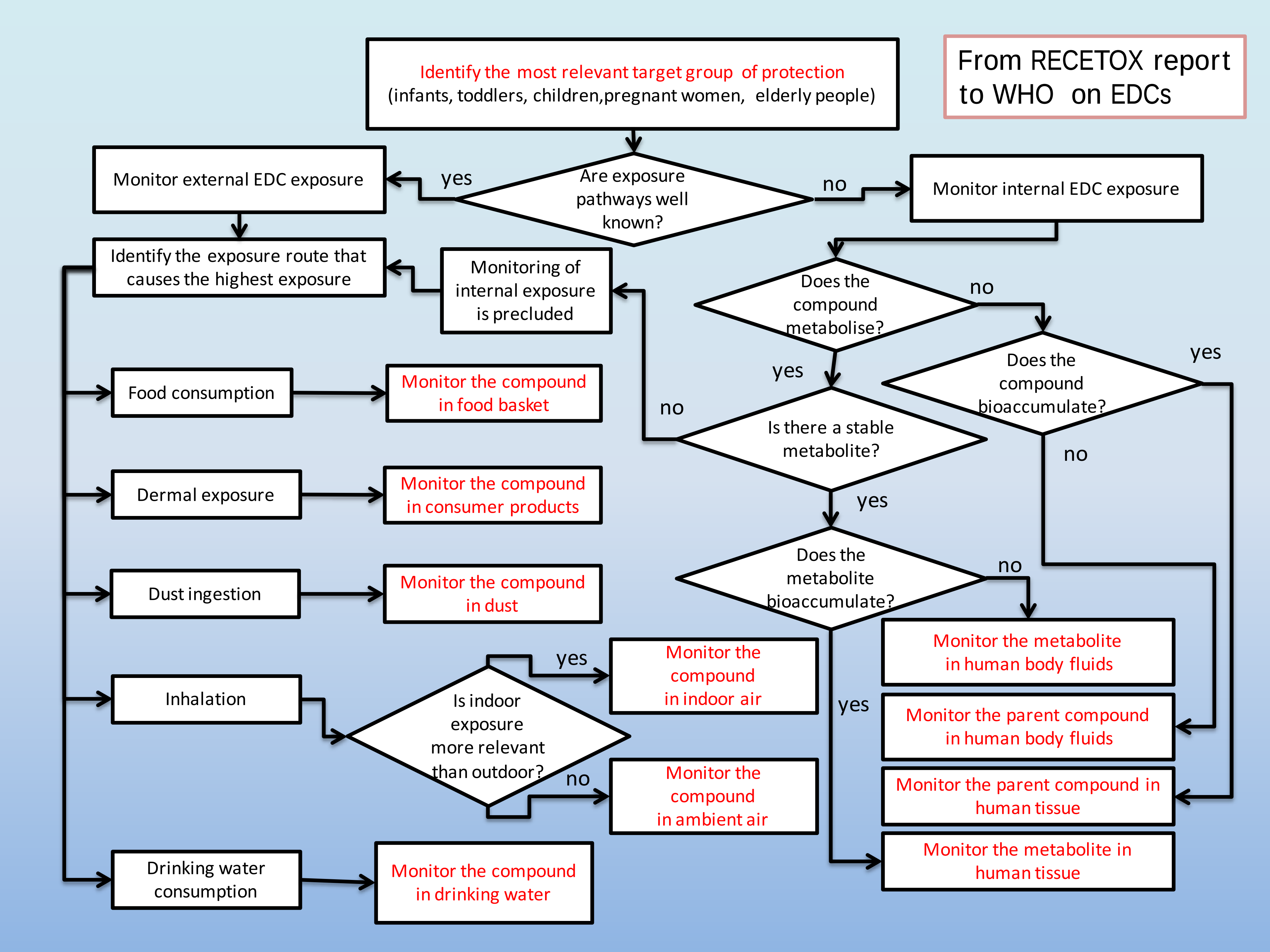

From RECETOX report to WHO on EDCs
Identify the most relevant target group of protection
(infants, toddlers, children, pregnant women, elderly people)
Are exposure pathways well known?
yes
no
Monitor external EDC exposure
Monitor internal EDC exposure
Identify the exposure route that causes the highest exposure
Monitoring of internal exposure is precluded
Does the compound metabolise?
no
yes
Does the compound bioaccumulate?
yes
no
Is there a stable metabolite?
no
yes
Does the metabolite bioaccumulate?
no
yes
Food consumption
Monitor the compound in food basket
Dermal exposure
Monitor the compound in consumer products
Dust ingestion
Monitor the compound in dust
Inhalation
Is indoor exposure more relevant than outdoor?
yes
Monitor the compound in indoor air
no
Monitor the compound in ambient air
Drinking water consumption
Monitor the compound in drinking water
Monitor the metabolite in human body fluids
Monitor the parent compound in human body fluids
Monitor the parent compound in human tissue
Monitor the metabolite in human tissue

Take-home messages

- Lots of complexity in new compounds
- Prioritization is challenging
- Persistence vs. pseudo-persistence
- Exposure routes are different from legacy compounds – more exposure from “daily life” rather than industrial sources
- Understanding the phys-chem properties can help estimate exposure and environmental distributions
- More measurement data for these compounds is needed

Little things matter

https://youtu.be/E6KoMAbz1Bw