The "Cocktail-effect" – Do pesticides play a role?

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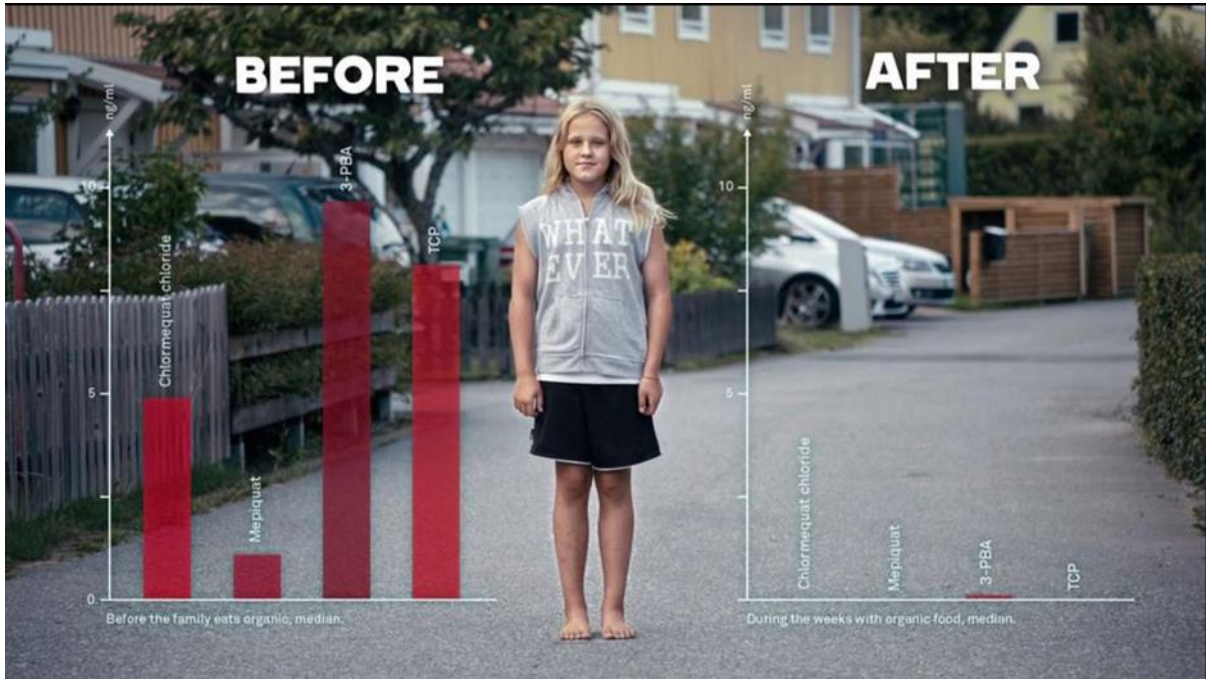
9 November 2018

Talking points

- **Why are we discussing potential health effects of pesticides?**
- **What do we know?**
  - Single compound risk
  - Combined risk (cocktail-effect)
  - Do pesticides play a role when other chemicals are considered as well?
- **Conclusion and perspective**

Why are we discussing potential health effects of pesticides?

“Ekoeffekten” – by COOP Sweden



Campaigns by COOP, the second largest supermarket chain in Sweden and Denmark.

Why are we discussing potential health effects of pesticides?

"Ekoeffekten", by COOP Sweden

"We know very little about the long term effects of consuming foods that have been sprayed (with pesticides)"

"Chemicals in combination may be far more dangerous than each single chemical on its own"

“We know very little about the long term effects of consuming foods that have been sprayed (with pesticides)

Toxicological testing package for a synthetic chemical pesticide

Study Type	Info & Result
ADME study	2.0 mg/kg or 200mg/kg bw (single low or high dose) Male & female Wistar rats
ADME study	2.0 mg/kg bw (single dose) Male & female Wistar rats
Whole-body distribution (autoradio-graphic)	5.0 mg/kg bw (single dose) Male & female Wistar rats
Whole-body distribution (autoradio-graphic)	5.0 mg/kg bw (single dose) Male & female Wistar rats
Metabolism study	5.0 mg/kg bw (single dose) Male Wistar rats
Acute oral toxicity rat	Oral LD50 > 2000 mg/kg bw
Acute dermal toxicity rat	Dermal LD50 > 2000 mg/kg bw
Acute inhalation toxicity rat	Inhalation LC50 = 2.518 mg/L
Skin irritation, rabbit	Negative
Eye irritation in vitro, isolated chicken eyes	Neither severe irritant nor non-irritant
Eye irritation, rabbit	Negative
Skin sensitization (LLNA)	Sensitizing EC3 = 29.0%
Phototoxicity Study	Negative

Study Type	Info & result
Rat 28-day toxicity study 0, 300, 1000, 3000 ppm	Diet incorporation NOAEL 300 ppm
Mouse 28-day toxicity study 0, 200, 800, 2000 ppm	Diet incorporation NOAEL = 200 ppm
Dog 28-day toxicity study 0, 300, 1000, 3000 ppm	Diet incorporation NOAEL = 1000 ppm
Rat 90-day toxicity study 0, 100, 300, 1000 ppm	Diet incorporation NOAEL 300 ppm
Mouse 90-day toxicity study 0, 100, 300, 1000 ppm	Diet incorporation NOAEL 300 ppm
Dog 90-day toxicity study 0, 170, 500, 1500 ppm	Diet incorporation NOAEL 500 ppm
Dog 1-year toxicity study 0, 150, 600, 1800 ppm	Diet incorporation NOAEL 150 ppm
2-generation reproduction toxicity study 0, 150, 450, 1200 ppm	Dietary study NOAEL 1200 ppm
Rat developmental toxicity study 0, 25, 125, 625 mg/kg bw/day	Oral gavage dosing NOAEL 125 mg/kg bw/day
Rabbit developmental toxicity study Oral gavage	NOAEL Maternal: 70 mg/kg bw/day Fetal: 500 mg/kg bw/day
Acute neurotoxicity study, Oral gavage 0, 200, 600, 2000 mg/kg bw/day	Systemic & Neurotoxic NOAEL: 2000 mg/kg bw

Study Type	Info & Result
Ames microsomally-mediated reverse mutagenesis assay	negative
Chromosomal aberrations study in human lymphocytes in vitro	clastogenic
V79 / HPRT mammalian mutagenicity study	Negative
Mouse micronucleus assay in vivo	Negative
Rat 2-year long term toxicity and carcinogenicity study	NOAEL: 450 ppm
Mouse 18-month long term toxicity and carcinogenicity study	NOAEL: 250 ppm
7 day dietary study of liver and thyroid cell proliferation in the female rat	Dietary administration
7-day dietary study of liver and thyroid cell proliferation in the female mouse	Dietary administration
28-day dietary study of hepatotoxicity and thyroid hormone concentrations in the female rat	Dietary administration
28-day dietary study of cell proliferation in the liver and thyroid of the female rat	Dietary administration
Hershberger pubertal male rat study (androgen) Oral gavage dosing 0, 400, 800 mg/kg bw/day	NOAEL 800 mg/kg bw/day Androgenicity/anti-androgenicity
Uterotrophic / vaginal opening study (estrogen) Oral gavage dosing 0, 400, 800 mg/kg bw/day	NOAEL 800 mg/kg bw/day Estrogenicity / anti-estrogenicity:

The ADI concept

Assessing the long term dietary consumer risk

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Overall (lowest) ***NOAEL*** *= No Observed Adverse Effect Level*

↓

Divided by ***safety factor*** *of minimum 100**

*minimum 100 by EU law, regulation 1107/2009

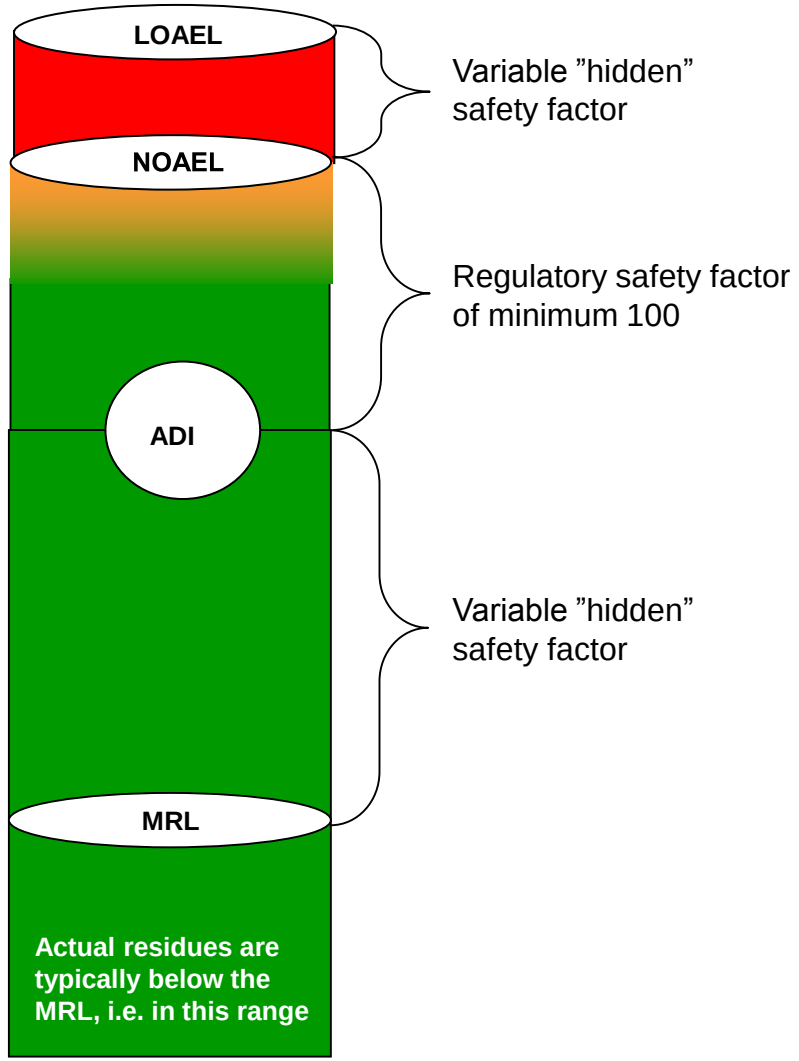
↓

ADI *= Acceptable Daily Intake = A daily intake with consumed food that is considered safe for the entire lifetime*

Assessing the long term consumer risk

Increasing exposure and risk

Very low exposure and risk



Explanations

MRL: Maximum Residue Level (maximum contents of a pesticide residue to be legally permitted in or on food commodities)

ADI: Acceptable Daily Intake (Estimate of the amount of a substance in food, which can be ingested daily over a lifetime by humans without appreciable health risk)

NOAEL: No Observable Adverse Effect Level (the greatest concentration of an agent, that causes no detectable adverse alteration of morphology, functional capacity, growth, development or lifespan of the target.

LOAEL: Lowest Observable Adverse Effect Level (similar to NOAEL, but where an effect is seen)

Assessing consumer risk for the single compound

Conclusions from the National Pesticide Residue Monitoring Programmes

Denmark

2017
2016
2015
2014
…..

"The food safety authority considers that the pesticide residues that occur in foods on the Danish market should not give cause for health concern among consumers. Intake of fruits and vegetables is healthy".

Miljø- og Fødevareministeriet
Fødevarestyrelsen

Europe

2018
…..

"Europeans continue to eat food that is largely free of pesticide residues or which contains levels of residues within legal limits, the latest monitoring figures show"

- The reporting countries analysed 84,657 samples for 791 pesticides
- 97.6% of samples for products from EU/EEA countries were within legal limits.
- 92.9% of samples for products from non-EU countries were within legal limits.
- 98.7% of samples for products from organic farming were within legal limits.

EFSA performed an acute (short-term) and chronic (long-term) dietary risk assessment, based on the results of the EUCP programme.
In both cases the health risks to consumers were considered to be low.

efsa
European Food Safety Authority

So, what is the problem??

”Chemicals in combination may be far more dangerous than each single chemical on its own”

“Chemicals in combination may be far more dangerous than each single chemical in its own”

Case [illegible] several ch[illegible] that predicted from a[illegible] (synergy)

1 [illegible]

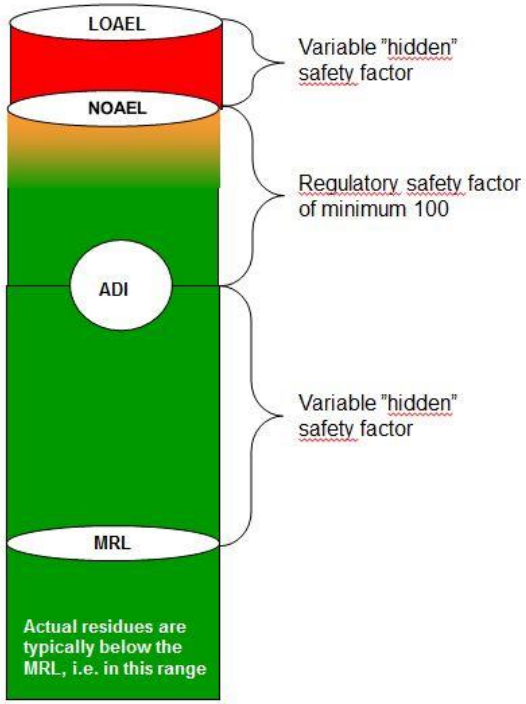
Case 2: The joint effect of several chemicals is no more than that of the single most toxic chemical. The chemicals do not share target and do not interact:

1 + 1 = 1

Case 3: The chemicals have a common target: the joint is effect <u>additive</u>

1 + 1 = 2

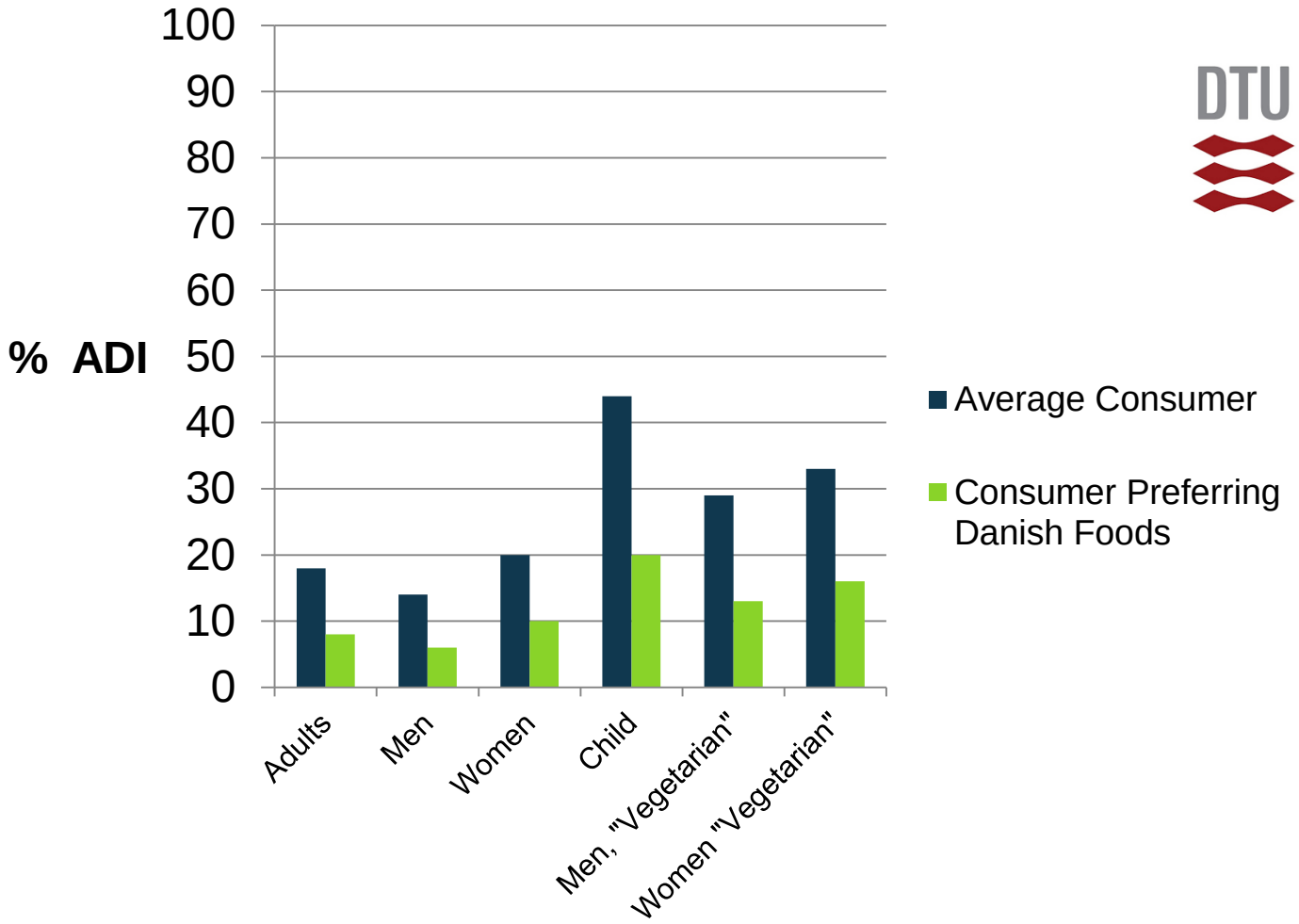
Not relevant for consumer exposure to pesticide residues.
Far below effect level, there will be no synergies either!
(Boobis et al. 2008, others)



Additive risk from combined pesticide exposure – What do we know?

Chronic risk in consumer from intake of dietary pesticide residues – full diet study – deterministic*

Study Facts
Population: Danish
Age: 4-75
Subpopulations: Male, Female, Child (4-6), Vegetarian, Domestic Foods Consumer
Diet Data: Full diet, National Dietary Habits Survey, DTU 2010 (n=2700)
Residue Data: Danish National Pesticide Residue Monitoring Programme
Data Period: 2004-2011
Toxicity data: ADI, (chronic long term)
Model: Hazard Index, deterministic model. No CAG:s
CAG = Cumulative Assessment Group



Jensen et al, 2015 *"Food and Chemical Toxicology" vol.* 83 (2015) p. 300-307

***Deterministic**
lower tier (first stage) worst case, simpler input and output

.

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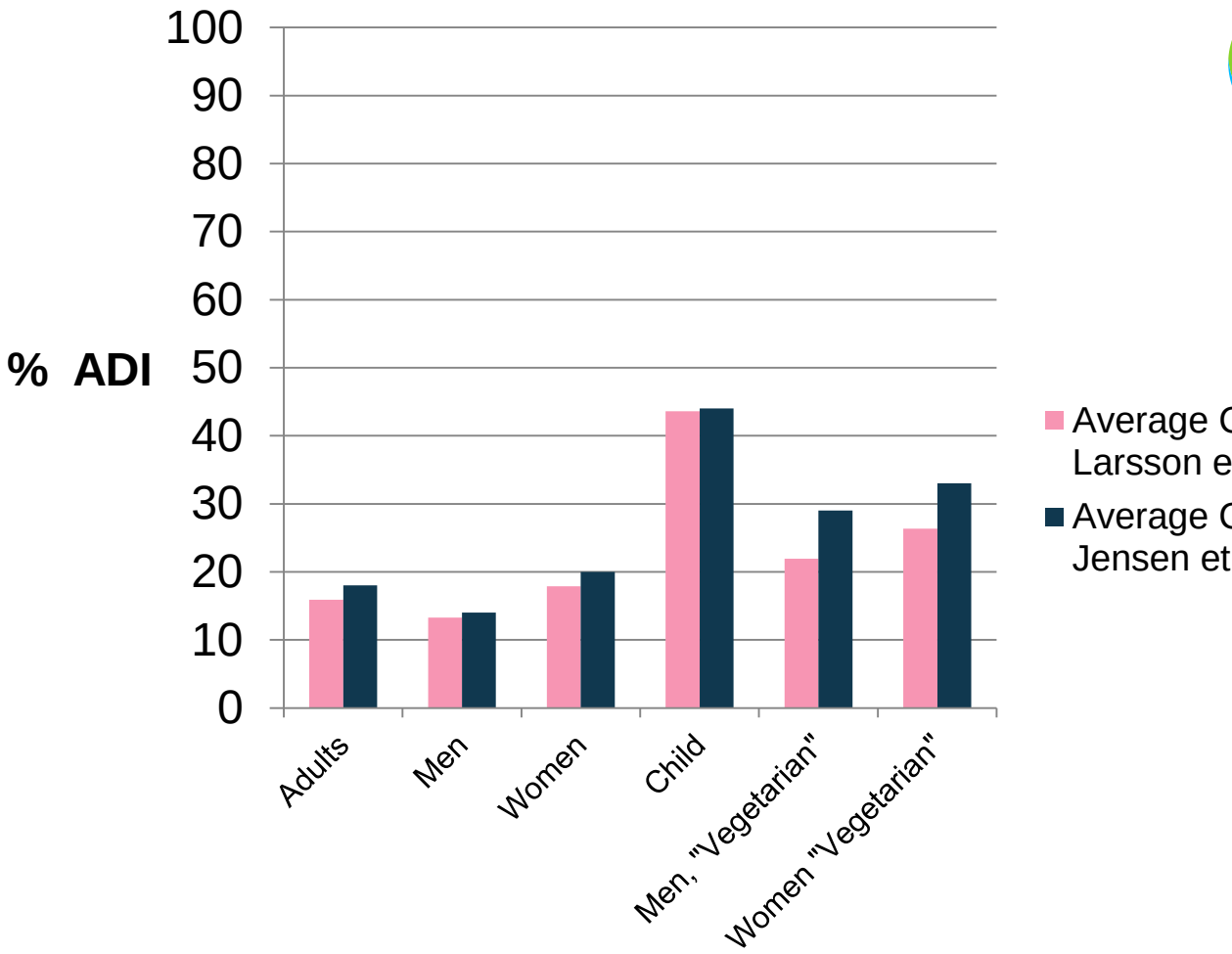

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Larsson et al., 2018 ”Food and Chemical Toxicology” vol. 111 (2018) p. 207-267

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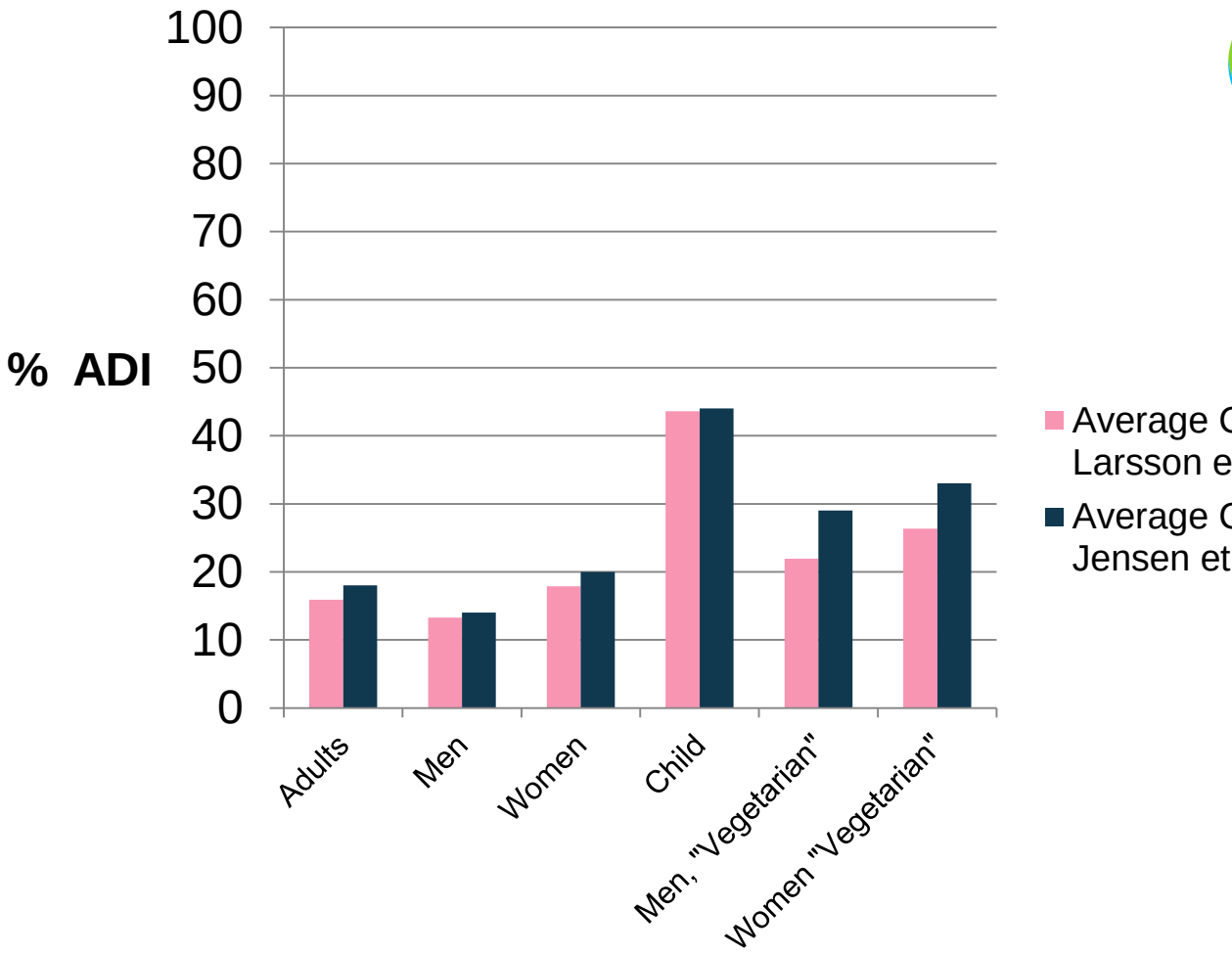

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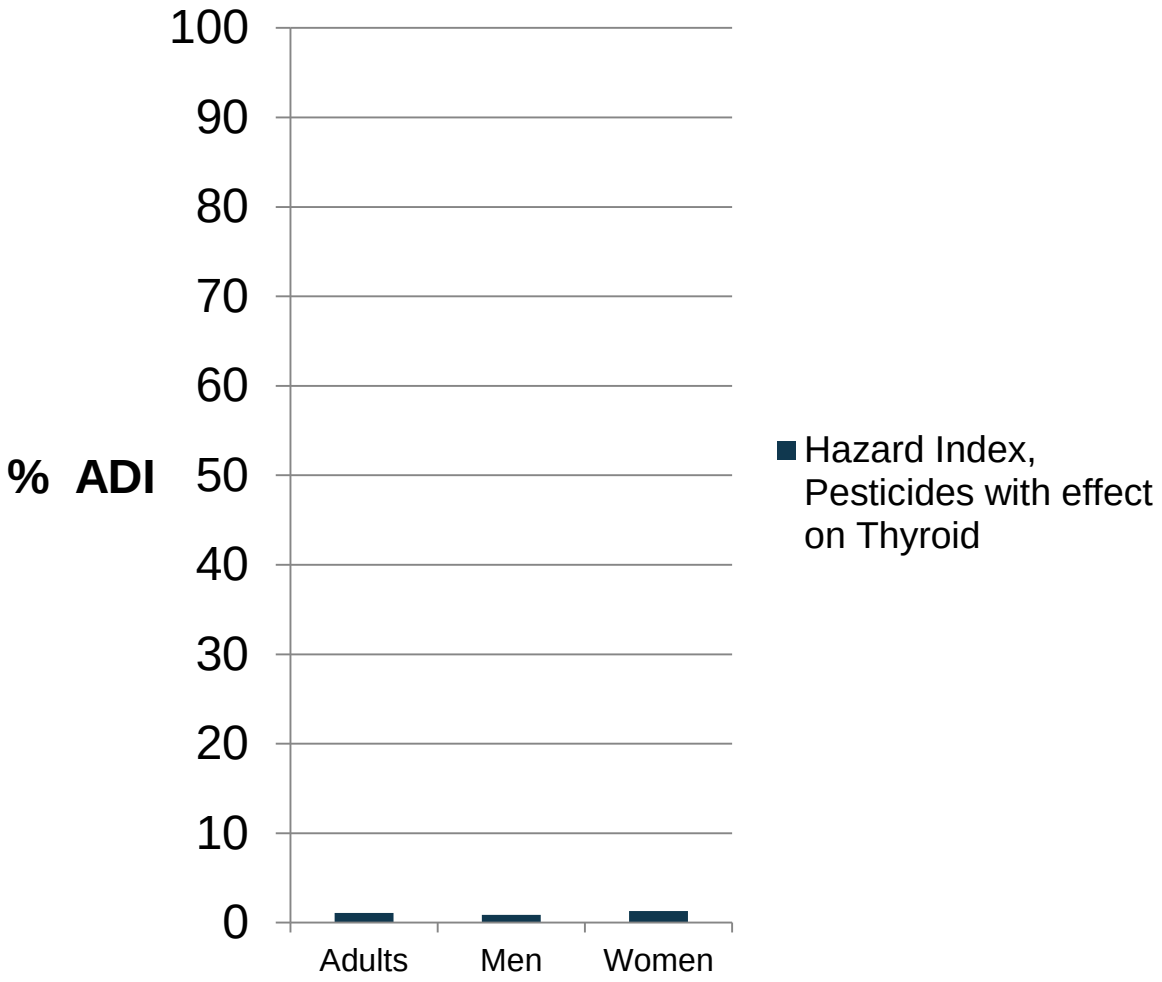
***Deterministic**
lower tier (first stage) worst case, simpler input and output

.

Additive risk from combined pesticide exposure – What do we know?

Chronic risk in consumer intake of dietary pesticide residues – fruit and vegetables – deterministic*

Study Facts:
Population: Swedish
Subpopulations: Adults, Men, Women
Diet Data: Riksmaten 2010-2011, Livsmedelsverket
Residue Data: Swedish national monitoring programme.
Data Period: 2013-2015
Toxicity data: ADI, based on NOAEL for thyroid effect
Model: Hazard Index, deterministic model.



EFSA CAG for pesticides with effect on the thyroid.

***Deterministic**
lower tier (first stage) worst case, simpler input and output

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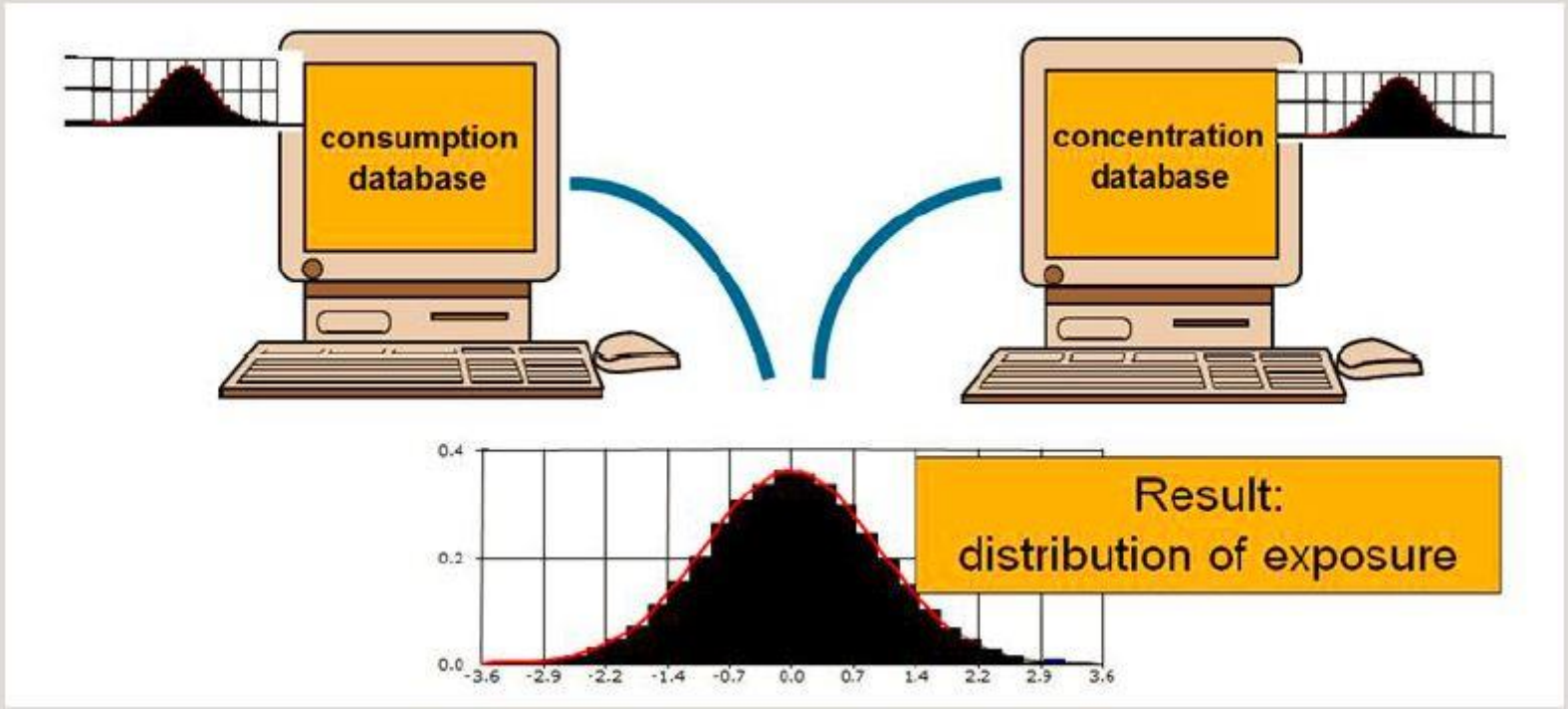
Probabilistic modelling

Box 5: *Probabilistic modelling of dietary exposure*



Additive risk from combined pesticide exposure – What do we know?

Chronic risk in consumer intake of dietary pesticide residues – 30 widely consumed commodities + drinking water – probabilistic*

Study Facts:
Population: Dutch
Subpopulations: Child (2-6), Young (7-17) Adult (18-69) Elderly (70+)
Diet Data: Dutch National Food Consumption Survey
Residue Data: Dutch national monitoring programme + EUCP data
Data Period: 2014-2016 (dutch data), 2011-2013 (EUCP data)
Toxicity data: MOE (margin of exposure), acute & chronic
Model: RPF (relative potency factor, MCRA probabilistic model.

CAGs covering **acute** effects on the nervous system

Table 1. Margins of exposure per exposure percentile for the CAG covering neurochemical effects

Age (years)	Margins of exposure per exposure percentile		
	P99	P99.9	P99.99
2-6	396 (280 – 567)	116 (54 – 181)	31 (21 -82)
7-17	881 (707 – 1245)	254 (167 – 379)	109 (52 – 214)
18-69	1192 (998 – 1601)	331 (166 – 571)	114 (74 – 285)
70+	1355 (1058 – 1727)	240 (89 - 536)	62 (39 – 225)

CAG: cumulative assessment group

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

EFSA CAG's thyroid and nervous system

RIVM Letter report 2018-0018
P.E. Boon et al.

***Probabilistic**
higher tier, realistic, complex requiring computer simulation. Greater ability to characterize uncertainty and variability
.

Additive risk from combined pesticide exposure – What do we know?

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

RIVM Letter report 2018-0018,
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Two CAGs, **acute** effects on nervous system

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70+	1355 (1058 – 1727)	240 (89 - 536)	62 (39 – 225)

CAG: cumulative assessment group

Table 2. Margins of exposure per exposure percentiles for the CAG covering effects on motor division

Age (years)	Margins of exposure per exposure percentile		
	P99	P99.9	P99.99
2-6	1192 (935 – 1431)	415 (327 – 567)	209 (144 – 343)
7-17	1932 (1374 – 2464)	716 (546 – 932)	326 213 – 577)
18-69	2903 (2196 – 3550)	1065 (813 – 1486)	512 (352 – 962)
70+	2706 (2006 – 3317)	868 (610 – 1255)	443 (353 – 895)

CAG: cumulative assessment group

Two CAGs, **chronic** effects on thyroid

Table 3. Margins of exposure per exposure percentile for the CAGs covering effects on parafollicular (C-)cells or the calcitonin system on follicular cells and/or the thyroid hormone (T3/T4) system

Age (years)	Margins of exposure per exposure percentile		
	P99	P99.9	P99.99
CAG-calcitonin			
2-6	1729 (1445 – 1981)	1049 (922 – 1358)	903 (726 – 1143)
7-17	3156 (2778 - 3484)	2286 (2139 – 2720)	2092 (1989 – 2597)
18-69	2716 (2404 – 3045)	2112 (2004 – 2226)	1929 (1821 – 2196)
70+	3625 (3421 – 3916)	2949 (2806 – 3411)	2791 (2743 – 3264)
CAG-thyroid hormone			
2-6	6824 (4475 – 10270)	3126 (2151 – 5849)	3054 (2047 – 4625)
7-17	12820 (9208 – 16840)	7202 (4695 – 11470)	6043 (4343 – 9369)
18-69	17620 (11960 – 21590)	10710 (5410 – 15640)	6118 (3939 – 13240)
70+	17330 (11700 – 24090)	13110 (8047 – 18170)	10580 (7278 – 17180)

CAG: cumulative assessment group

Additive risk from combined pesticide exposure – What do we know?

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

RIVM Letter report 2018-0018,
P.E. Boon et al.

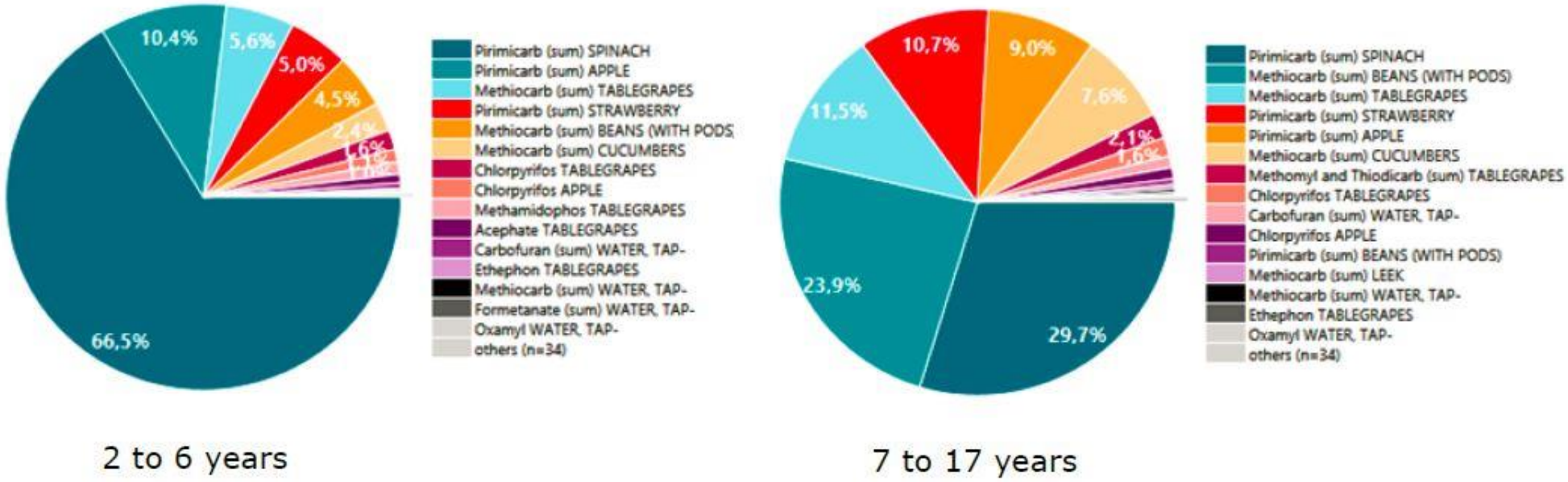


Figure 1. Contribution of substance/commodity combinations to the upper 0.1% of the acute cumulative exposure distribution of CAG-neurochemical for children aged 2 to 6 and 7 to 17. For the two other age groups, see Appendix S.

MRL for pirimicarb was reduced in 2016.

Multiple factors contribute to overestimation of risk

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

RIVM Letter report 2018-0018,
P.E. Boon et al.

Erring on the safe side in risk assessment leads to overestimation of risk.

Table 4. Sources, direction and magnitude of uncertainty in the cumulative exposure assessment to the four cumulative assessment groups via food

Source of uncertainty[1]	Direction & Magnitude[2]	Section[3]
Food consumption data		5.1
Food consumption data of 2005-2012	-/•	
Overreporting of fruits and vegetables	+	
Underreporting of body weights for ages 7 to 69	+	
Coding according to FoodEx1	+	
Concentrations		5.2
Representativity samples for consumed foods	+	
Imputation of samples with concentration < LOQ	--/++	
Imputation of samples with missing values[4]	--/++	
Assumed levels in drinking water	+	
30 RACs included	•	
Least potent substance in complex residue definitions (except for CAG-neurochemical and CAG-calcitonin)	--	
Processing factors		5.3
Lack of processing factors	++	
Food mapping		5.4
Via RAC	•	
Exposure model		5.5
Use of OIM for calculating chronic exposure	+	
Cumulative assessment groups (CAGs)		5.6
CAGs defined at level 2 (except for CAG-neurochemical)	++	
Overall assessment: Based on this qualitative evaluation of different uncertainty sources, it was concluded that the cumulative exposure to all CAGs is likely to be conservative due to the assumption of pesticide residues in drinking water, the use of monitoring data and lack of processing factors. In addition, the use of CAGs defined at level 2 may have resulted in an overestimation of the exposure for the two CAGs covering effects on the thyroid and the CAG for acute effects on motor division. The cumulative exposure to the two CAGs covering effects on the thyroid was furthermore most likely overestimated at the right tail of the exposure distribution by the use of OIM.	++	5.7

Additive risk from combined pesticide exposure – What do we know?

Chronic risk in consumer intake of dietary pesticide residues – 4 endocrine disrupting pesticides – probabilistic

Food and Chemical Toxicology
Volume 55, May 2013, Pages 113-120

Probabilistic assessment of the cumulative dietary exposure of the population of Denmark to endocrine disrupting pesticides

Bodil Hamborg Jensen, Annette Petersen, Sofie Christiansen, Julie Boberg, Marta Axelstad, Susan S. Herrmann, Mette Erecius Poulsen, Ulla Hass

Study Facts:
Population: Danish
Subpopulations: Women of childbearing potential
Diet Data: Danish National Food Consumption Survey
Residue Data: Danish and Swedish monitoring
Data Period: 2006-2009
Toxicity data: MOE (margin of exposure), acute & chronic
Model: RPF (relative potency factor,) probabilistic model.

- Four fungicides: epoxiconazole, prochloraz, procymidone and tebuconazole, all suspected of acting as endocrine disrupters.
- For women of childbearing age, the high-end cumulative exposure (99.9th percentile) was 9% of the Adjusted Reference Value (ARV) for nipple retention and 1% of the ARV for the effect on increased gestation period.
- In other words, the safety margin to bench mark dose (NOAEL) was 10.000 for nipple retention and 100.000 for increased gestation period.
- **Conclusion: no reason for concern in relation to cumulative acute risk for Danish consumers to the four endocrine disrupting pesticides.**

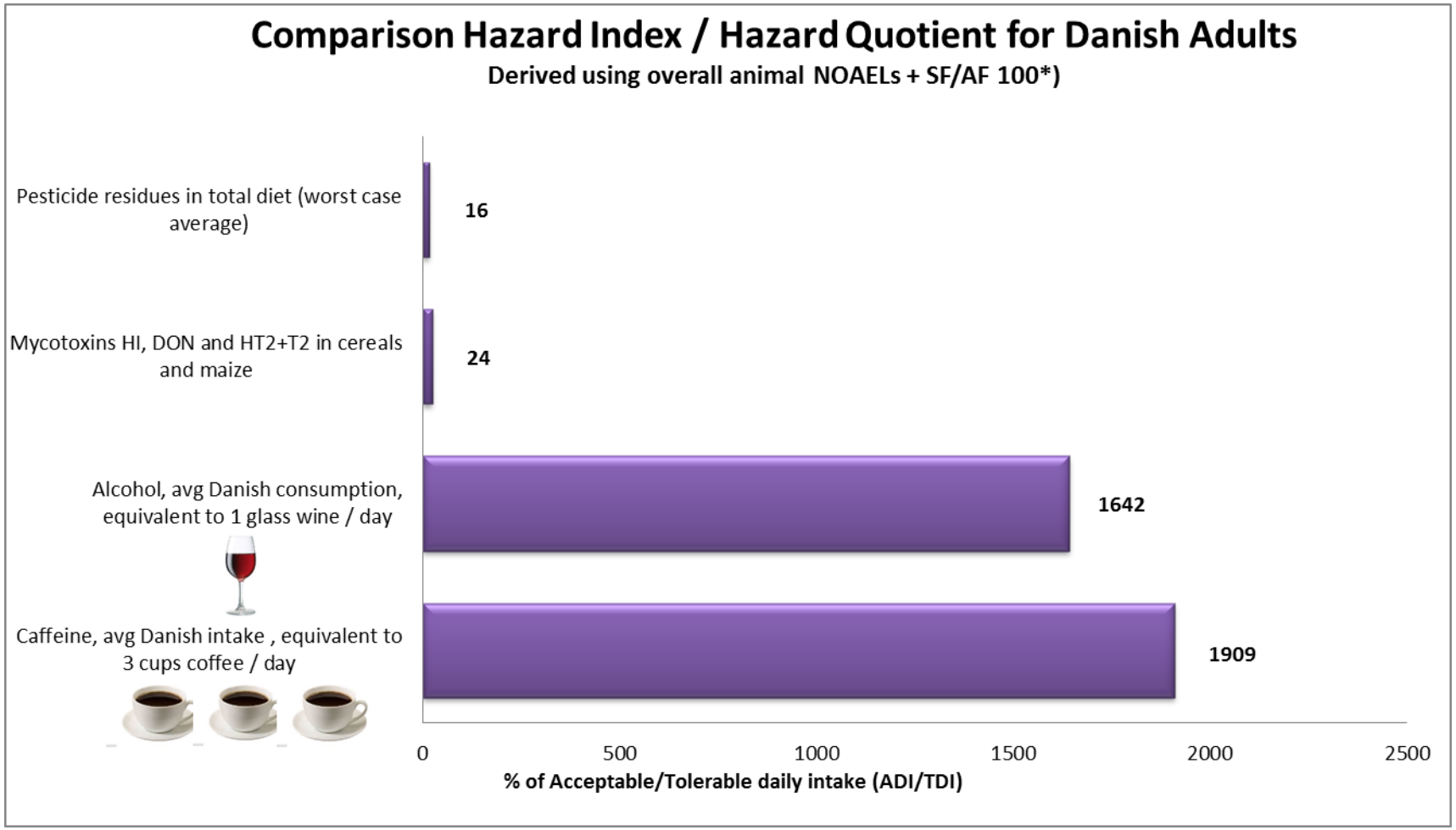
…But EU will ban these substances as EDs anyway…?!?

So, what is the Problem??

”Pesticides in combination with other chemicals may pose a risk for health ”

“Pesticides in combination with other chemicals may pose a risk for health”

Larsson et al. “Food and Chemical Toxicology” 2018 Mar. 113:345-346



"Pesticides in combination with other chemicals may pose a risk for health"

Dietary pesticides (99.99% all natural)*

(carcinogens/mutagens/clastogens/coffee)

BRUCE N. AMES†‡, MARGIE PROFET†, AND LOIS SWIRSKY GOLD†§

Division of Biochemistry and Molecular Biology, Barker Hall, University of California, Berkeley, CA 94720; and §Cell and Molecular Biology Division, Lawrence Berkely Laboratory, Berkeley, CA 94720

Contributed by Bruce N. Ames, July 19, 1990

ABSTRACT **The toxicological significance of exposures to synthetic chemicals is examined in the context of exposures to naturally occurring chemicals. We calculate that 99.99% (by weight) of the pesticides in the American diet are chemicals that plants produce to defend themselves. Only 52 natural pesticides have been tested in high-dose animal cancer tests, and about half (27) are rodent carcinogens; these 27 are shown to be present in many common foods. We conclude that natural and synthetic chemicals are equally likely to be positive in animal cancer tests. We also conclude that at the low doses of most human exposures the comparative hazards of synthetic pesticide residues are insignificant.**

Table 2. Some natural pesticide carcinogens in food

Rodent carcinogen	Conc., ppm	Plant food
5-/8-Methoxypsoralen	14	Parsley
	32	Parsnip, cooked
	0.8	Celery
	6.2	Celery, new cultivar
	25	Celery, stressed
p-Hydrazinobenzoate	11	Mushrooms
Glutamyl *p*-hydrazinobenzoate	42	Mushrooms
Sinigrin* (allyl isothiocyanate)	35–590	Cabbage
	250–788	Collard greens
	12–66	Cauliflower
	110–1,560	Brussels sprouts
	16,000–72,000	Mustard (brown)
	4,500	Horseradish
D-Limonene	31	Orange juice
	40	Mango
	8,000	Pepper, black
Estragole	3,800	Basil
	3,000	Fennel
Safrole	3,000	Nutmeg
	10,000	Mace
	100	Pepper, black
Ethyl acrylate	0.07	Pineapple
Sesamol	75	Sesame seeds (heated oil)
α-Methylbenzyl alcohol	1.3	Cocoa
Benzyl acetate	82	Basil
	230	Jasmine tea
	15	Honey
Catechol	100	Coffee (roasted beans)
Caffeic acid	50–200	Apple, carrot, celery, cherry, eggplant, endive, grapes, lettuce, pear, plum, potato
	>1,000	Absinthe, anise, basil, caraway, dill,

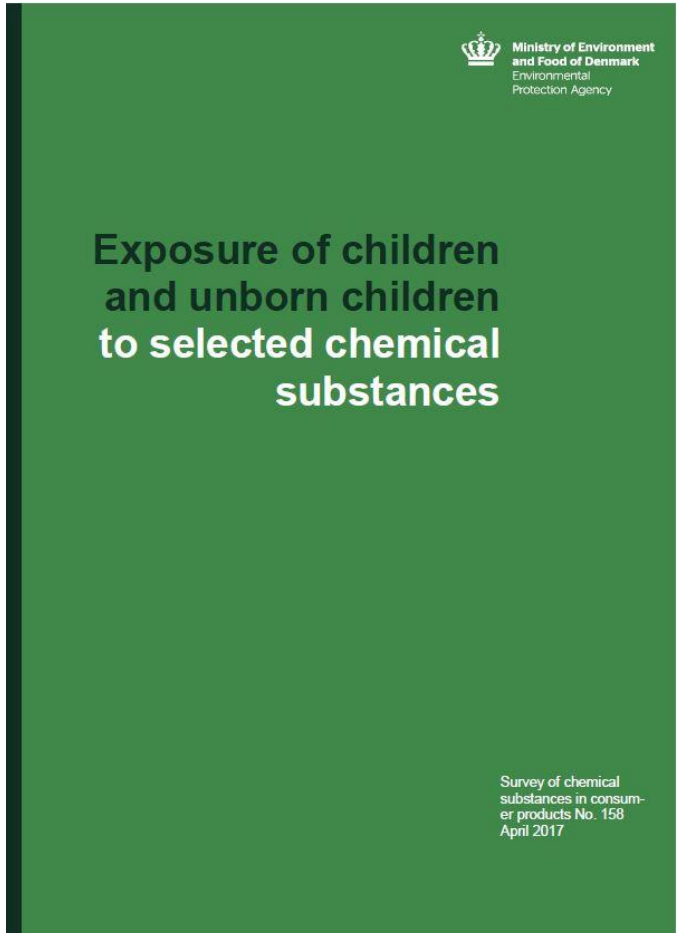
“Pesticides in combination with other chemicals may pose a risk for health”

Comprehensive 433 pages report issued in 2017

Objective: assess the risk of overall exposure of children under 3 years and pregnant women/ unborn children to endocrine disrupting (ED)- and chronic neurotoxic substances.

Summary

- ED: **paracetamol** highest risk compound, but EMA says Not sufficient evidence for link with antiandrogenic effect
- Neurotox: **Lead** by far highest risk compound
- “A number of pesticides suspected as ED are omitted because of low exposure”



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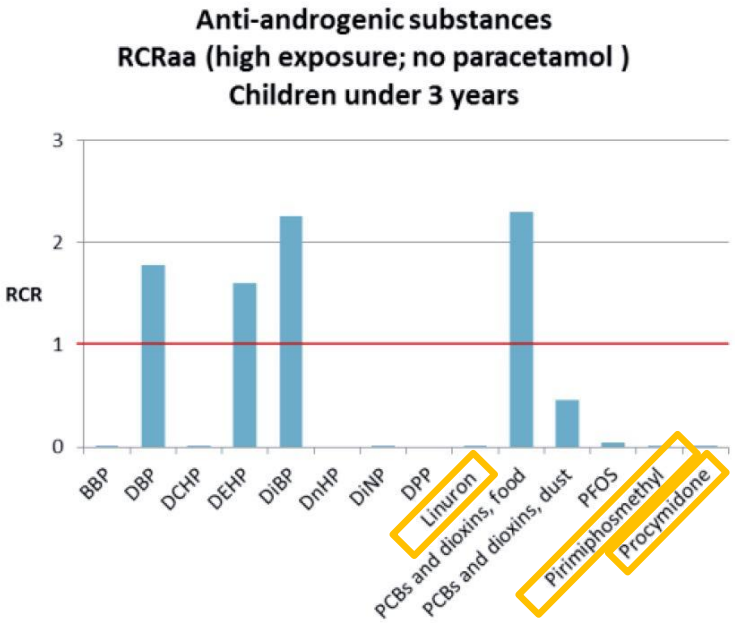
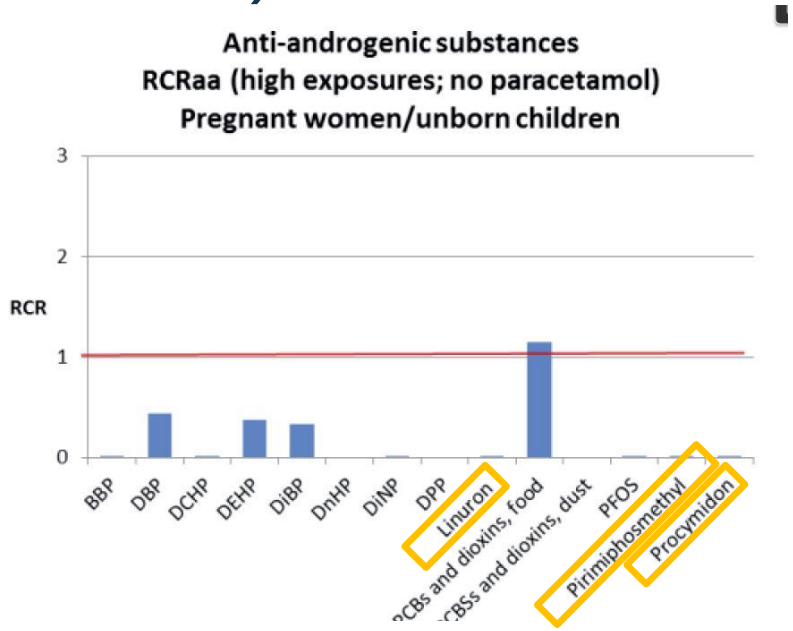
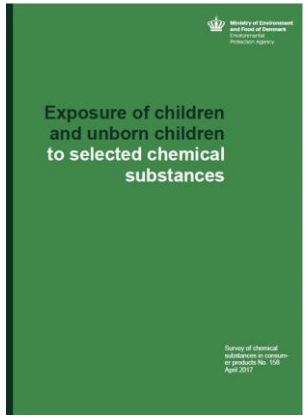
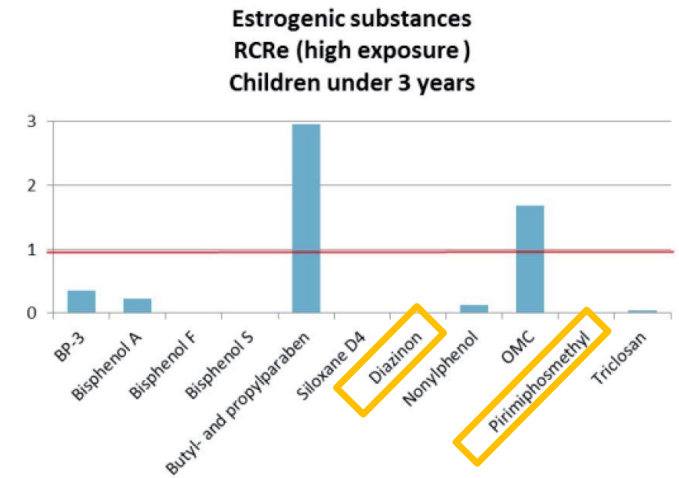
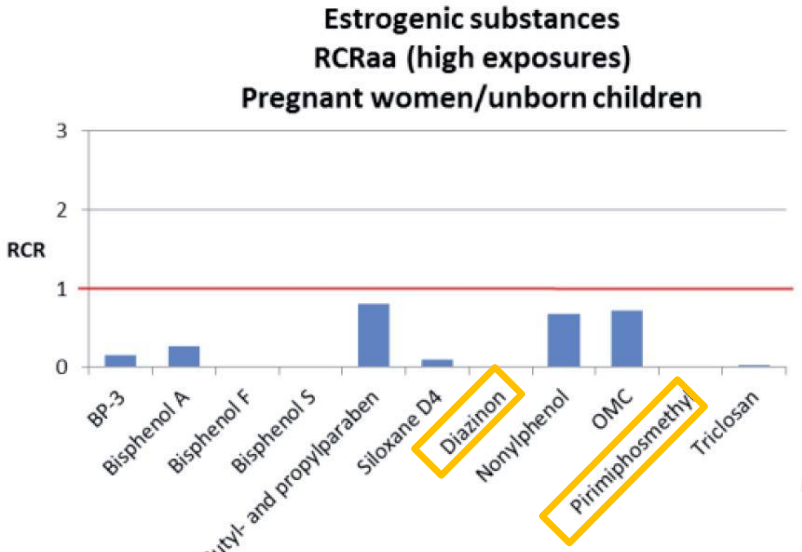
Results: ED (high exposure scenario)





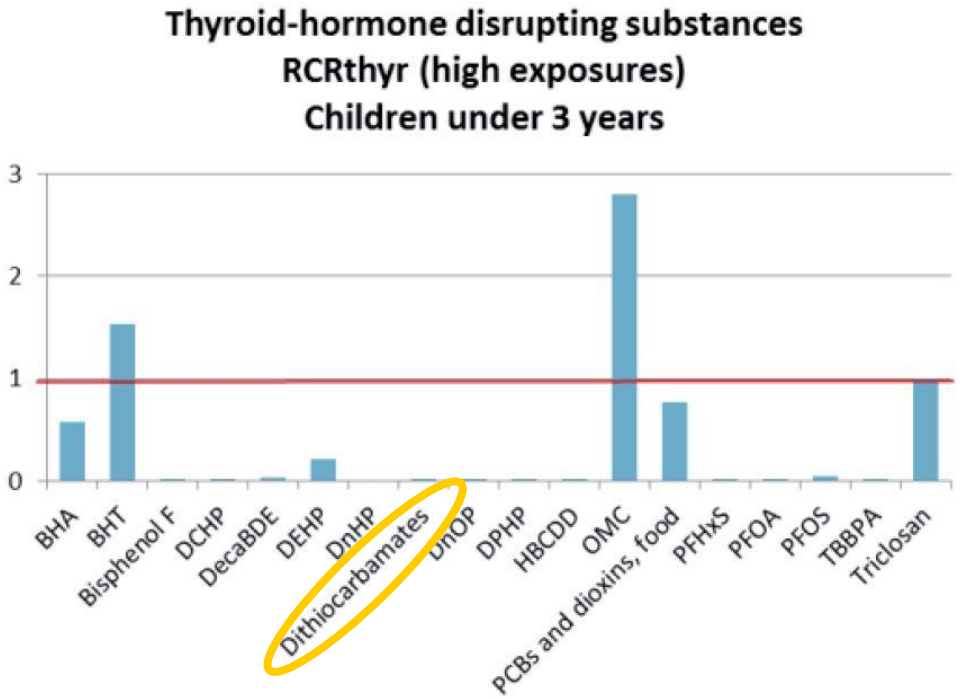


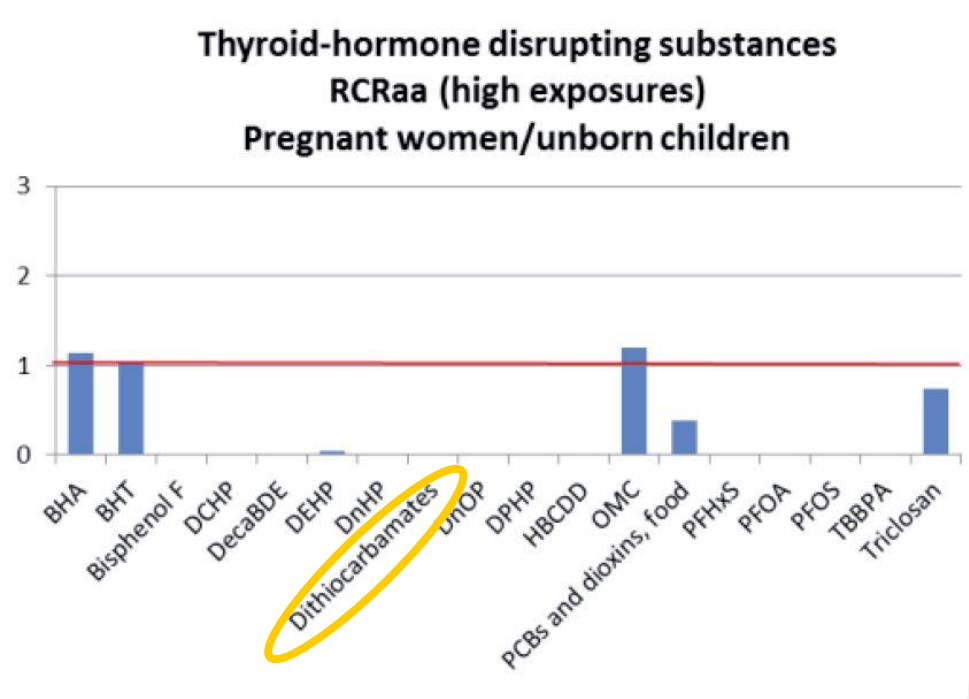


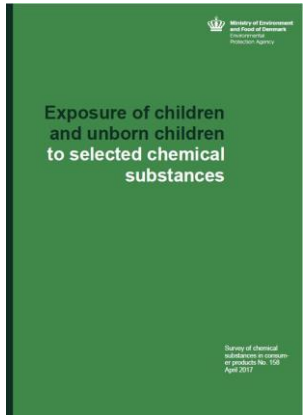


RCR = exposure (µg/kg/d) / DNEL (µg/kg/d).
Safety Factor for DNEL pesticide: 100
RCR = exposure at ADI level

Results: ED (high exposure scenario)



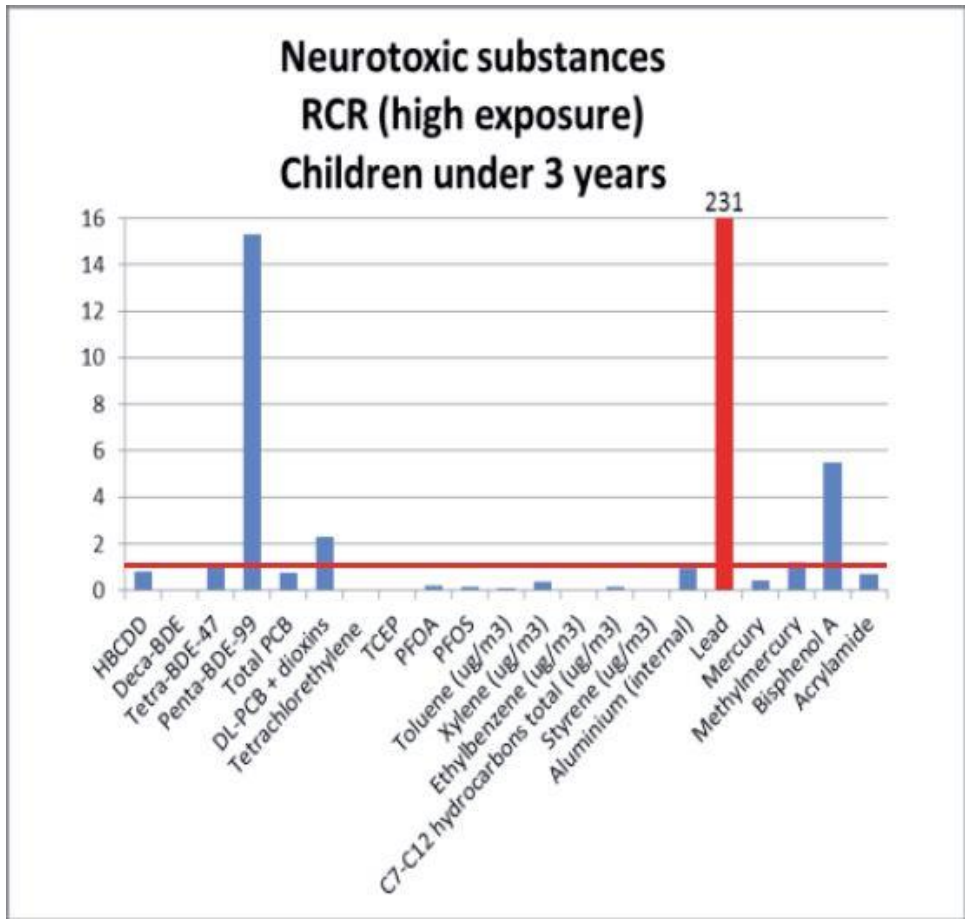


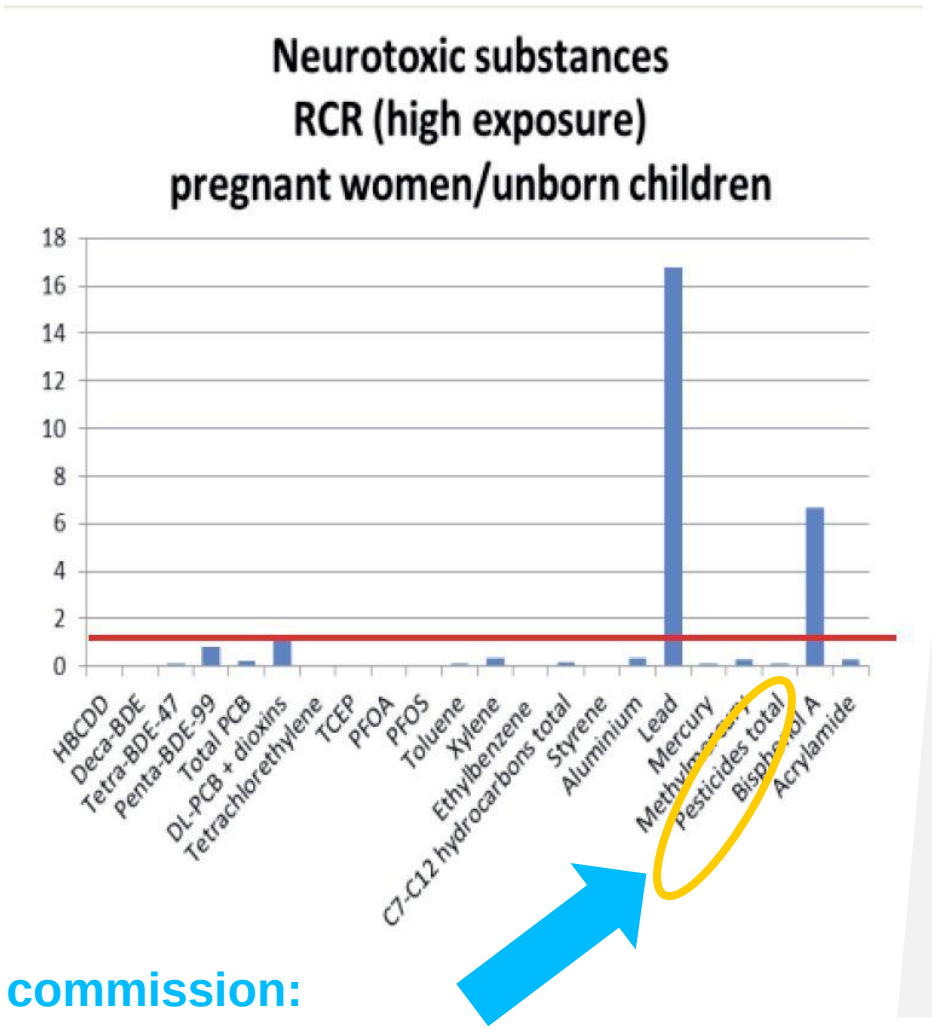


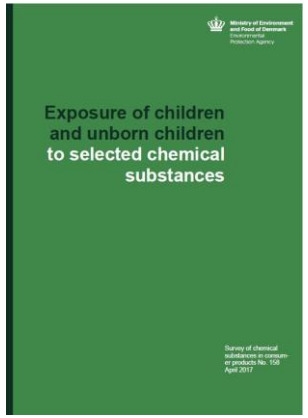
Will health improve if EU bans all the ”ED”-pesticides??

RCR = exposure (µg/kg/d) / DNEL (µg/kg/d).
Safety Factor for DNEL pesticide: 100
RCR = exposure at ADI level

Results: Neurotoxic substances (high exposure scenario)







RCR = exposure (µg/kg/d) / DNEL (µg/kg/d).
Safety Factor for DNEL pesticide: 100
RCR = exposure at ADI level

Northern zone countries' letter to EU commission:
Amend regulation 1107 to ban these pesticides

Conclusion and perspective

- Concern over health effect of pesticide residues mainly driven by campaigns by commercial and political interests
- From a scientific point of view, adverse health effects resulting of pesticide residues in foods is very unlikely.
- Pesticide residues in foods are unlikely to contribute significantly to any ”cocktail” of chemicals (natural or man-made) implied in any disease etiology
- Science and regulation has made significant progress and soon EFSA is expected to publish comprehensive probabilistic risk assessments for EU populations.

Thank you for your attention!

ADI: how do we know the consumer intake does not exceed ADI level?

1 Set an **MRL**

1. Define how to use the pesticide to control the weed/disease/pest: example: use 1 x 1 L/ha in growthstage BBCH 20
2. Measure the (eventual) pesticide residue that occurs in the crop with this pesticide usage (GLP studies)
3. 3) Assess consumer risk assesment to ensure ADI level is not exceeded adding all food that may contain residues at the most probable level (STMR= supervised trials median residue) that could be consummed daily and for a lifetime.
4. 4) If the ADI is not exceeded, the MRL can be set and the use authorized

2 Enforce the **MRL**

Control sampling programmes:

1) By government (FVST in Denmark)
2) By suppliers/producers, internal quality control

ADI = Acceptable Daily Intake = Overall (lowest) NOAEL divided by safety factor of min 100*
*minimum 100 by EU law, regulation 1107/2009
MRL = Maximum Residue Level

Note! MRL may be far lower (but not higher) than ADI, as MRL set from the agronomically required use pattern