THL Comment on EFSA Dioxin risk assessment

On 14th June 2018 EFSA adopted a confidential draft document "*Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food*". In the document the data from experimental animal and epidemiological studies were reviewed and it was decided to base the human risk assessment on effects observed in humans and to use animal data as supportive evidence. The critical effect was on semen quality, following pre- and postnatal exposure. The critical study showed a NOAEL of 7.0 pg WHO2005-TEQ/g fat in blood sampled at age 9 years based on PCDD/F-TEQs. No association was observed when including DL-PCB-TEQs. Using toxicokinetic modelling and taking into account the exposure from breastfeeding and a twofold higher intake during childhood, it was estimated that daily exposure in adolescents and adults should be below 0.25 pg Total TEQ/kg bw/day. Based on this daily exposure the CONTAM Panel established a TWI of 2 pg Total TEQ/kg bw/week.
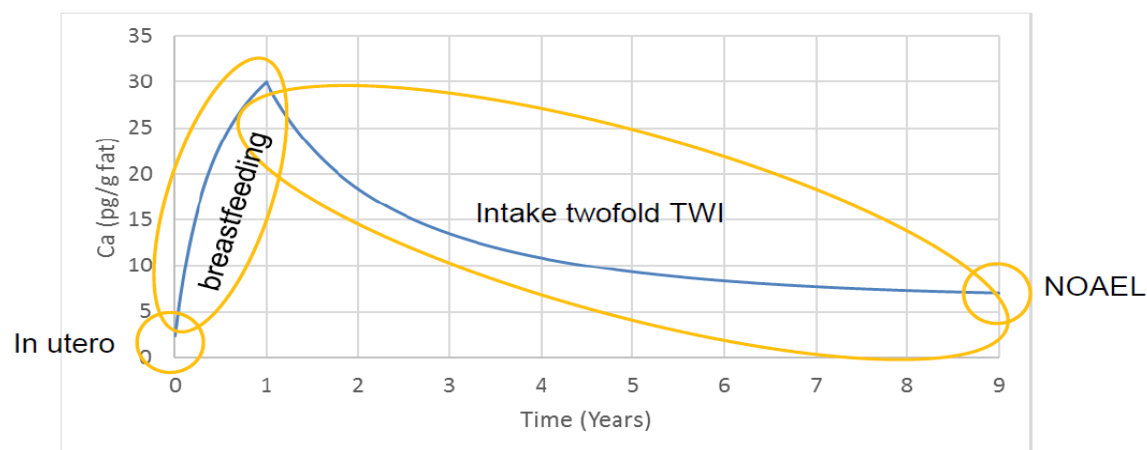
In THL we performed two separate of evaluations on the EFSA Risk Assessment. In the first one we used our existing data on PCDD/F and PCB level in human milk (1987 to 2010) and our estimates of human intake during the same time period to evaluate the plausibility of the PCDD/F and PCB accumulation modelling to human body conducted by the CONTAM Panel. We termed this part of our "*Evaluation of Accumulation Model*". In the second one we rerun our health benefit-risk assessment model constructed during the BONUS GOHERR from April 2018 with the new outcomes prosed by the CONTAM Panel. We termed this part of our evaluation "*Goherr health benefit-risk assessment update*".

Evaluation of Accumulation Model

Background

In the presentation of Roon Hoogenboom at Dioxin 2018 conference on 29.08.2018 on the main outcomes of the risk assessment, the following modeling for boys was presented (Figure 1).
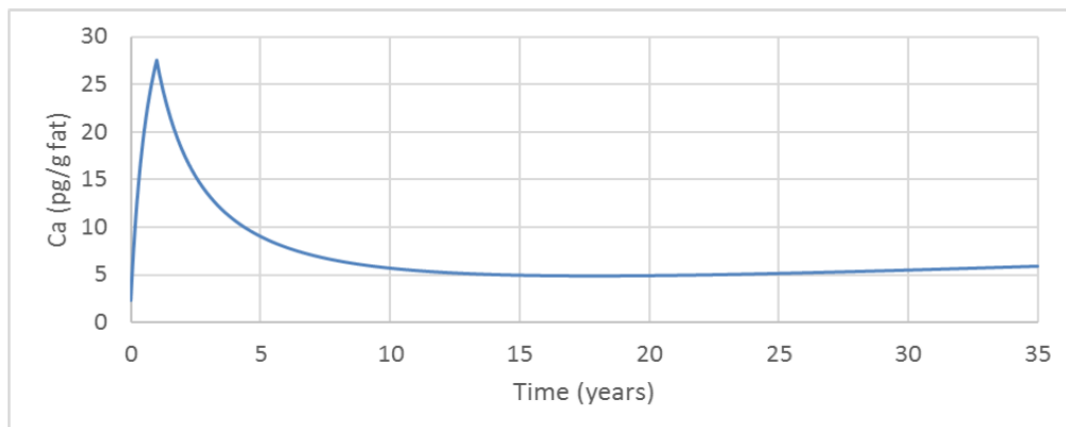

Serum level (Ca) in boys, breastfed for 12 months with milk with **5.9** pg/g fat (800 mL per day, 3.5% fat), followed by an intake of **0.5** pg/kg bw per day for an additional 8 years, resulting in a serum level of 7 pg/g fat.

Figure 1. Modeling of boys serum PCDD/F-TEQ (pg/g fat) based on intake during breast feeding from 0-1 years and intake from food from 1 - 9 years.

Respective modeling was preformed also for mothers on the exposure needed (0.25 pg/kg bw/day) to reach the input level of 5.9 pg/g fat for boys' exposure (Figure 2).

Outcome modelling mothers

Serum levels (Ca) in a woman, breastfed for 12 months in infancy with milk containing **5.9** pg/g fat, and then being exposed to **0.25** pg/kg bw per day for 34 years.

So milk and fat level at birth of son and start of breastfeeding at 35 years: 5.9 pg/g fat: **input for modelling boys**

Figure 2. Modeling of mothers' serum PCDD/F-TEQ (pg/g fat) based on intake during breast feeding from 0-1 years and intake from food from 1 - 35 years.

Objective

As THL has measured the levels of PCDD/Fs and PCBs in human milk from 1987 to 2010 and also conducted studies on the dietary intake of dioxins and PCBs during the same time period, we wanted to study how our measurements compare to the toxicokinetic modeling made by the CONTAM Panel.

Materials

Three studies have been conducted on the dietary intake of PCDD/Fs and PCBs in Finland.

Table 1. Estimated dietary daily intake of PCDD/Fs and PCBs in Finland (pg/kg bw/day, bw = 76 kg).

Concentration unit	PCDD/Fs	PCBs	Total TEQ	Sampling years	Reference
N-TEQ	1.25			1992	Hallikainen et al 1995
2005-TEQ	1.22	**0.80-1.0***	**2.0-2.2***		
1998-TEQ	0.79	0.74	1.53	1997-1999	Kiviranta et al 2004
2005-TEQ	0.67	0.45	1.13		
I-TEQ	0.86	0.71	1.57	1998-2000	Kiviranta et al 2001
2005-TEQ	0.84	0.43	1.25		
2005-TEQ	**0.30-0.40***	**0.20-0.25***	**0.50-0.65***		Estimate of 2018 exposure

*Backward and forward estimated concentrations based on intake and fish data

We have no measurements of PCB intake in the early 1990's. However, we have measured time trends from 1978 to 2009 of PCDD/Fs and PCBs in Baltic herring that as fatty Baltic fish is one of the most important sources of exposure for Finnish population. Total-TEQ approximately halved during the 1990's in

herring (Figure 3) and have again halved from 2000 to present as approximated from Baltic salmon (Figure 4) that shows very similar time trend as herring.
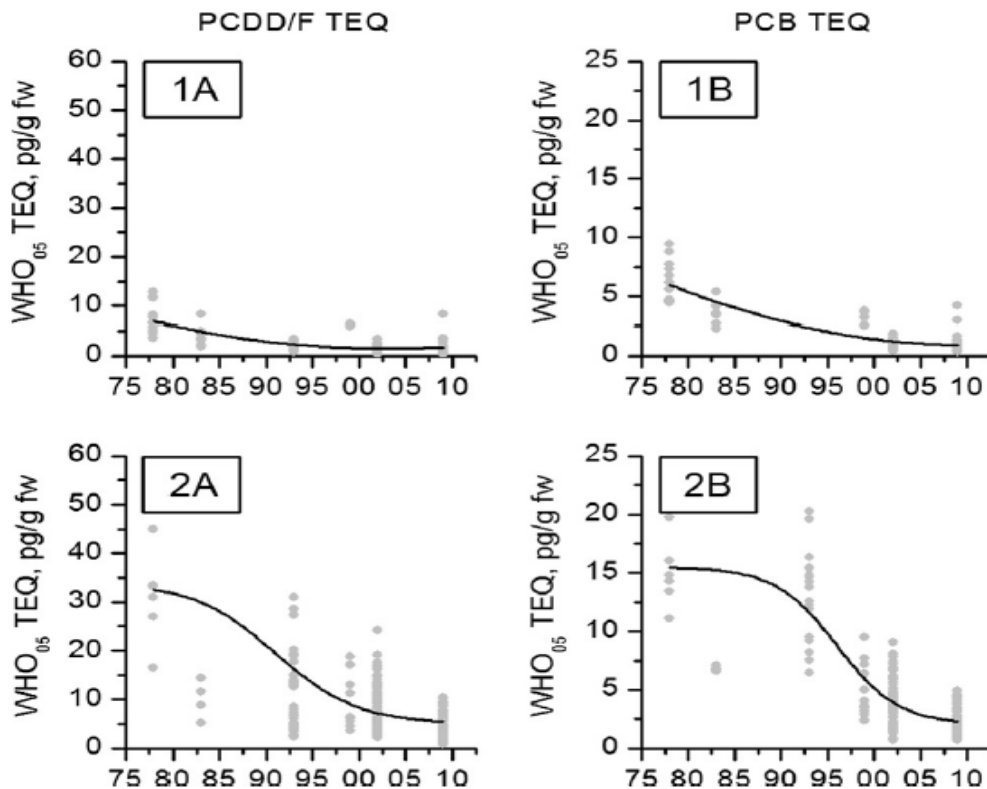

Figure 3. PCDD/F TEQ, PCB TEQ, indicator PCBs, and PBDEs in young (<5 years, 1A–B) and old (P5 years, 2A–B) Baltic herring off the coast of Finland during 1978–2009 (Airaksinen et al 2014).
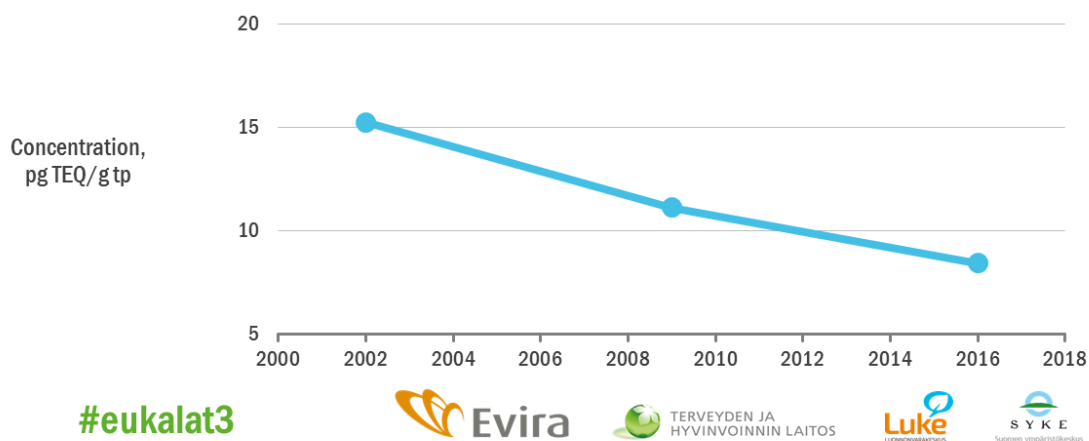

Figure 4. Change in Total TEQ in the Baltic Salmon from 2002 to 2016 (Airaksinen et al 2018).

Thus, we estimate that the intake of PCDD/Fs and PCBS has decreased 65%-80% from 1990 to present values 0.50 - 0.65 pg/kg bw/day (Table 1). This estimate is in good agreement with Swedish data where

Total TEQ intake in 2015 was estimated to be 40 pg TEQ/day (i.e. 0.53 pg/kg bw/day using 76 kg bw) and intake in Sweden was also estimated to be halved from 2000 (Livsmedelverket 2017).

We have also measured the levels of PCDD/Fs and PCBs in primiparas' human milk from the time period 1987 to 2010 the result of which are presented Table 2.

Table 2. Levels of PCDD/Fs and PCBs in primiparas' human milk from 1987 to 2010

Sum measure	Year	1987	1994	2005	2010	1987-2010	Annual
	n	84	42	90	85	decrease (%)	decrease (%)
PCDD/Fs-TEQ	Average	24.3	15.6	4.8	3.8	84	7.8
	Median	23.3	14.5	4.2	3.5	85	8.0
	10th percentile	14.9	8.0	2.4	1.8	88	8.7
	90th percentile	33.2	24.0	7.8	5.9	82	7.2
PCB-TEQ	Average	18.4	7.5	2.6	2.0	89	9.1
	Median	15.4	7.0	2.1	1.8	89	9.0
	10th percentile	6.1	3.5	1.0	0.9	86	8.1
	90th percentile	31.5	12.8	4.7	3.3	89	9.3
Total-TEQ	Average	42.6	23.1	7.4	5.8	86	8.3
	Median	38.6	21.1	6.4	5.1	87	8.4
	10th percentile	26.1	11.4	3.4	2.7	90	9.4
	90th percentile	62.6	36.2	12.1	9.1	85	8.0

These measurements show that during this 23 year time period median/average concentrations of PCDD/Fs and PCBs have decreased 82-90% and annually 7-9%. At 2010 even the 90th percentile of PCDD/F-TEQ was at the "*input for modeling boys*" –level (see Figures 1 and 2) despite that the estimated median PCDD/F exposure (see Table 1) for was about 5-fold at 1990, about 3-fold at 2000 and about 1.5-fold at 2010 as compared to 0.25 pg/kg bw/day exposure used by the CONTAM Panel.

Extrapolating the general decreasing trend from 2010 to 2018 with declined decrease rate of 6%, it can be estimated that in 2018 at least 99% of the Finnish primipara mothers are below the PCDD/F-TEQ level of 5.9 pg/g fat and similarly at least 90% of mothers in Total-TEQ terms are below the same 5.9 pg/g fat level. This continuing decrease has taken place despite the fact our best 2018 estimate of maternal PCDD/F exposure is slightly higher (0.3 – 0.4 pg/kg bw/day) and Total TEQ exposure is still about 2-fold higher (0.5 – 0.65 pg/kg bw/day) as compared CONTAM Panel exposure of 0.25 pg/kg bw/day. In other words, a hypothetical girl born in 1987 was exposed during 1 year lactation to 2.5 to 5.6 fold (10perc – 90 perc) PCDD/F-TEQ burden and 4.4 to 10.6 fold (10pers – 90 pers) Total-TEQ burden and then during the following 30 year (1988-2018) to 5 to 1 fold PCDD/F-TEQ and 8 to 2 fold Total-TEQ compared to CONTAM Panel estimates of 5.9 pg/g fat in maternal milk followed by 0.25 pg/kg bw/day dietary exposure. Yet her milk levels at 31 years of age in 2018 are below 5.9 pg/g fat in PCDD/F-TEQ term as calculated from 99th percentile of the 2010 distribution and 6% annual decrease.

Conclusions
Our data and calculations clearly show that the model used by the CONTAM Panel overestimated the real life accumulation of PCDD/Fs and PCBs from human milk and from the diet. There is no reason to believe that similar overestimation of accumulation (or underestimation of exposure needed to reach critical level of 7 pg/g fat PCDD/Fs) would not be the case also for boys. Thus, the very low daily exposure in adolescents and adults of 0.25 pg Total TEQ/kg bw/day recommended by the CONTAM Panel is not justified based on

our data because in real life conditions much higher exposures are likely needed to accumulate the critical level of 7 pg/g fat PCDD/F-TEQ in boys at the age of 9 years.

Recommendations

- Changes to current guidelines on the safe consumption of fish, the main source of PCDD/Fs and PCBs in Finland, are not justified as the accumulation model used by the CONTAM Panel appears to overestimate the real life accumulation of PCDD/Fs and PCBs from human milk and from the diet.
- However, it is justified to:
  - Continue monitoring the levels of PCDD/Fs and PCBs in mother's milk in 2019
  - Perform a survey on the levels of PCDD/Fs and PCBs in the serum of 9 years old boys in 2019 that, to the extent possible, are the sons of those mothers that participated to 2010 round human milk collection
- These surveys enable us to:
  - Verify the continued decrease of PCDD/Fs and PCBs in human milk
  - Verify the accumulated levels of PCDD/Fs and PCBs in 9 year old boys using human milk (Table 2) and dietary (Table 1) exposure that especially in Total-TEQ terms are very close to those that CONTAM Panel used in their modelling to reach the critical level of 7 pg/g fat.

References

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Airaksinen et al. Changes in the levels of enviromental contaminants of Finnish wild caught fish. Prime Minister's Office, 2018. URL: http://julkaisut.valtioneuvosto.fi/bitstream/handle/10024/161079/51-2018-EU-kalat%20III.pdf

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Kiviranta et al. Dietary intakes of polychlorinated dibenzo-p-dioxins, dibenzofurans and polychlorinated biphenyls in Finland. Food Additives and Contaminants, 18 (2001) 945-953

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Goherr health benefit-risk assessment update

On 28th August, 2018, EFSA committee released a new assessment of the tolerable weekly intake (TWI) of dioxin. The committee suggests that the TWI is reduced from the current 14 pg/kg/week to 2 pg/kg/week, so a sevenfold decrease. The reason for a new tighter recommendation is that there is new information about a sensitive endpoint: sperm concentrations in men that were exposed before the age of 9 years. The data comes from two sources: Seveso accident (Mocarelli 2008, 2011 at EHP) and Russian children's study (Minguez-Alarcon, EHP 2017). Sperm concentrations go down even by 40 % when the dioxin concentration in boy's serum fat exceeds 10 pg/g and stay at lower level permanently. This was used as the main criteria to update TWI.

Based on this, BONUS GOHERR project reran its health benefit-risk assessment model from April 2018 (documented in detail at http://en.opasnet.org/w/Goherr_assessment) with these new outcomes. The exceedance of the new TWI is called *TWI2018* while the current recommendation is called *Dioxin TWI*, and the sperm concentration was converted into infertility based on knowledge about how much more difficult it will be to get a child when the sperm concentration goes down to certain levels. The results are in this figure.

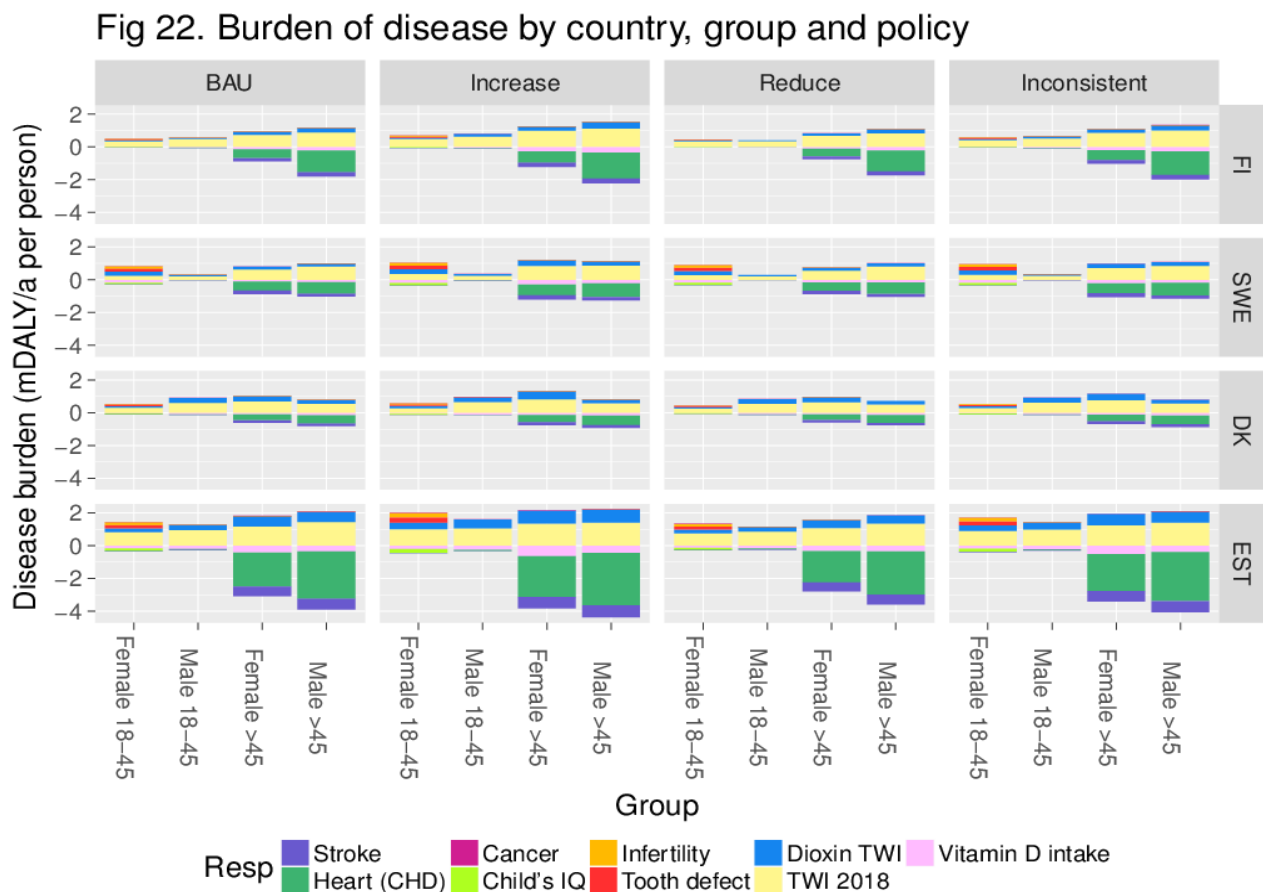Fig 22. Burden of disease by country, group and policy

Figure 1 (22 in Goherr assessment). Burden of disease in subpopulations and after different policy options. Infertility and TWI2018 (tolerable weekly intake of dioxin based on the August 2018 recommendation by an EFSA expert group) are endpoints that were not considered in the Goherr health benefit-risk assessment in April 2018. Negative numbers are health gains.

What does this mean? First, the TWI2018 is fairly large in all groups, but not as large as the cardiovascular benefit in age groups older than 45 years. It should be noted, that the TWI is only relevant for young women (who expose their sons during pregnancy and breast feeding), because other groups cannot get the health outcome that was the criteria for TWI2018.

Second, having both infertility and TWI2018 on the same figure is double counting, and infertility is the more relevant health outcome. Actually showing also the previous TWI (called Dioxin TWI on graph) is triple counting. The three endpoints are shown together to reflect the fact that they imply very different magnitude for the same dioxin effect, namely reduction of sperm concentration in males exposed before age nine.

Third, infertility as a new outcome does turn the balance towards higher risks and makes Goherr project rethink its recommendations. However, if the focus is on health outcomes rather than TWI's, the changes in disease burden are surprisingly low, considering that the TWI change from 14 to 2 pg/kg/d sounds really dramatic.

Disease burden of sperm concentration effects

In humans, sperm concentrations have been shown to decrease permanently if boys are exposed to dioxins before nine years of age. The results come from Seveso[2][3] and a Russian children's study[4].

EFSA recently assessed this risk and derived dose-response from the Russian children's study. In the study, the boys were divided into quartiles with PCDD/F TEQ values 7.0, 10.9, 15.2, and 32.8 pg/g fat. Sperm concentration mean was 65 (95 % CI 50-80) million/ml in the lowest quartile, while in all other quartiles the concentration was 40 (96 % CI 30-55) million/ml. (Numbers are approximate because they have been read from a figure.)

According to a review[5], sperm concentrations have declined from 120 to 60 million/ml between 1930 and 1990. At the same time, the fraction of men in "subfertile" range (sperm concentrations below 40 million/ml) has increased from 20 to 40 %. Above 40 million/ml, the success rate of couples who try to get pregnant is 65 % in 6 months. Below that concentration, the probability is fairly proportional to the sperm concentration.

Based on this, Goherr project estimated that there is an exposure-response function of dioxin on sperm concentration that has the non-linear shape of relative Hill and reduces the sperm count by at most 39 % (I_{max}), i.e. from 65 to 40 million/ml, and the exposure causing half of the maximal effect is 10.5 pg/g fat (the concentration of the second quartile in the Russian children's study). In five years (assuming independent probabilities between 6-month periods), the probability of *not* getting pregnant follows this curve:

P(infertility after 5 a) = (1 - 0.65*min(40M /ml,s)/40M /ml (1+(-0.39d)/(d + 10.5 pg/g)))^(2y),

where d is the dioxin concentration in boy's fat tissue, s is the sperm concentration, and y is the number of years of trying.
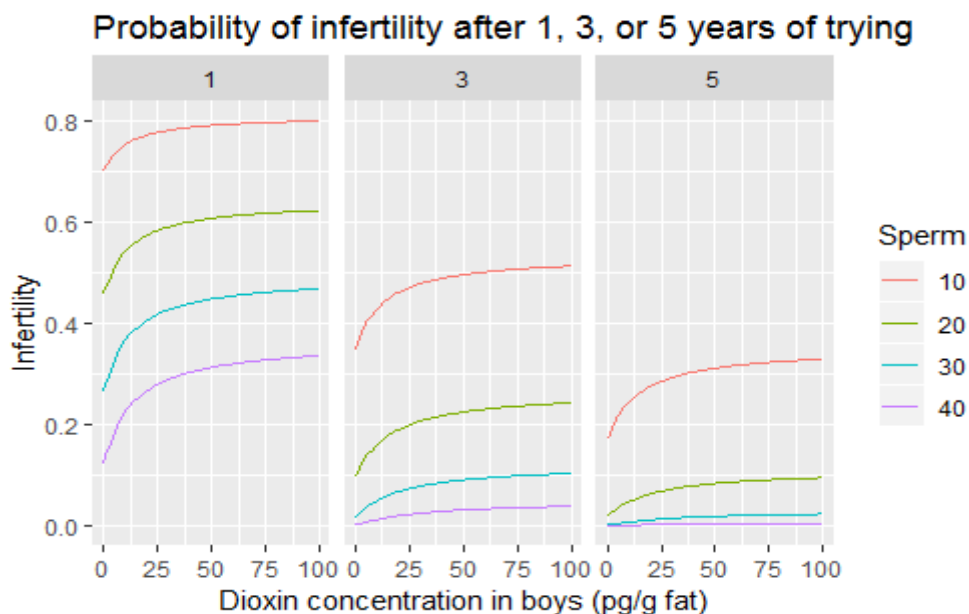
Figure 2. Probability of infertility after 1, 3, or 5 years of trying as a function of dioxin concentration at age 9 and sperm concentration (before possible effects of dioxin) at adult age.

This curve is pretty linear below 25 pg/g and sperm concentrations more than 20 million/ml with slope ca. 0.00006 g/pg, meaning that for each 1 pg/g increase in dioxin concentration the boy's fat tissue (or serum fat), there is an incrementally increased probability of 0.00006 that he cannot get a child even after five years of trying. Let's assume that five years is a critical time window, and after that the boy will be childless. Childlessness is said to be "tragedy of life", so the disability weight could be in the order of 0.1 DALY per year permanently (50 years). However, the disability weight applies to only half of the children (boys), and we can fairly assume that half of the couples get a satisfactory solution via adoption, in-vitro fertilisation or other treatments. Therefore, the impact is 0.1*50*0.5*0.5 DALY/case = 1.25 DALY/case, with rather high uncertainty (say, 0-2.5 DALY/case)

We can also consider men that have already decreased semen concentrations from an unrelated reason. Dioxin is likely to reduce that even further. For example, if the concentration is 10 million/ml, the probability of infertility in five years is 0.17, and that increases to 0.24 and 0.33 at dioxin concentrations 10 and 100 pg/g, respectively. If ten percent of the population had this low semen concentration and if 20 % of boys exceed 10 pg/g (as seems to be the case with Goherr assessment), then we would see for example in Finland 25000 boys/year * 0.1 with low fertility * 0.2 with high dioxin * (0.24-0.17 absolute increase in infertility) = 35 cases per year and thus 44 DALY/year.

In another scenario, we can look at male population at subfertile range (40 % of population, see above). If their average sperm concentration is 30 million/ml, this would give 0.0066 probability of infertility with exposure concentration 10 pg/g, compared with 0.0013 with no dioxin exposure. Thus, we get 25000 boys/year * 0.4 with low fertility * 0.2 with high dioxin * (0.0066-0.0013) = 10.6 cases/year and thus ca. 13 DALY/year. In either case, the disease burden is far from the most important environmental health risks.

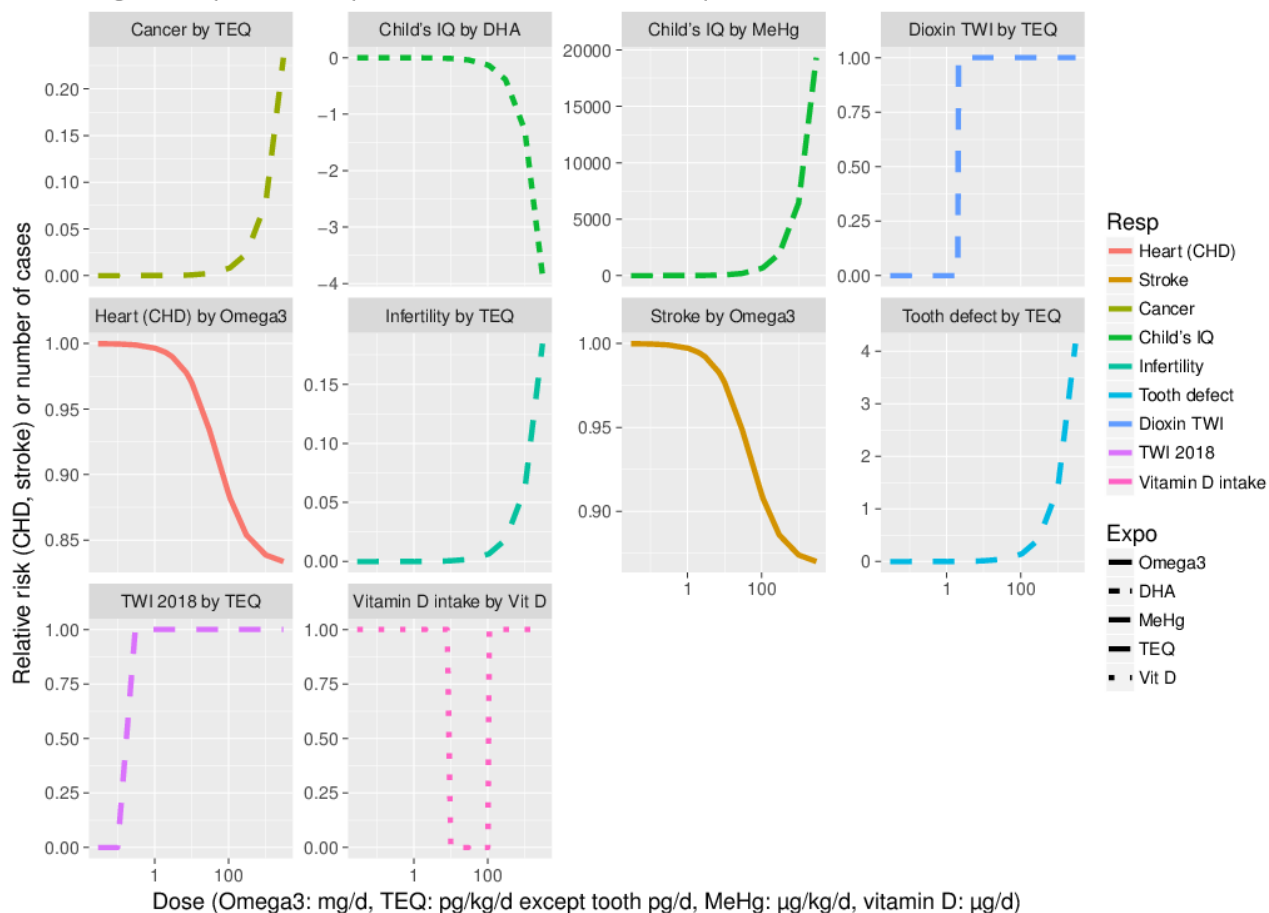Fig 17. Exposure–response functions for health impacts

Figure 3 (17 in Goherr assessment). Exposure-response functions of different fish-relevant compounds and health endpoints. The new TWI suggested by EFSA is clearly the most sensitive. For details, see http://en.opasnet.org/w/ERF_of_dioxin .
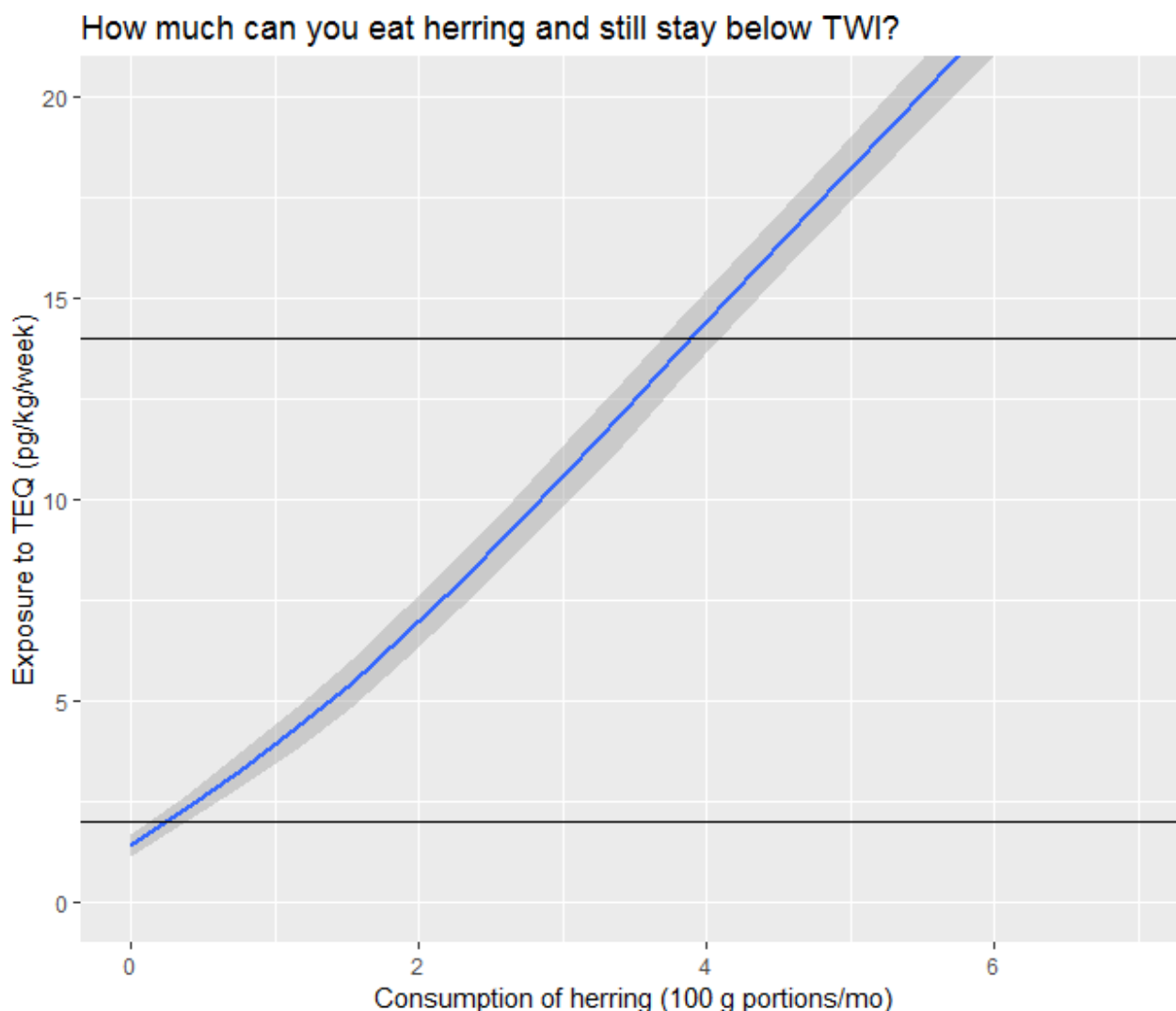
Dietary implications of the suggested TWI2018

Figure 4. Amount of Baltic herring that can be eaten without exceeding TWI values according to the Goherr model results, if one wants to comply with EFSA's current (14 pg/kg/week) or the new suggested TWI (2 pg/kg/week).

In practice, the lower tolerable weekly intake means that Baltic herring can be used 3-4 times per year at most. But suggesting such restriction would go against the main Goherr results based on net health benefit. Thus, it is a major policy decision whether decisions are based on tolerable weekly intakes rather than net health benefit.

In the figure below (Fig 5), we see that the whole Baltic fish issue is not even close to the major environmental health problems in Finland. Air pollution, indoor radon and UV radiation are clearly larger problems. This comparison is based on burden of disease, in other words disability-adjusted life years (DALY). In this figure, the dioxin TWI and TWI2018 are double counting the same health problem, and both are also allocated to all population subgroups although the TWI is based on infertility, which only occurs when young women are exposed to dioxin and then expose their sons during pregnancy and breastfeeding.

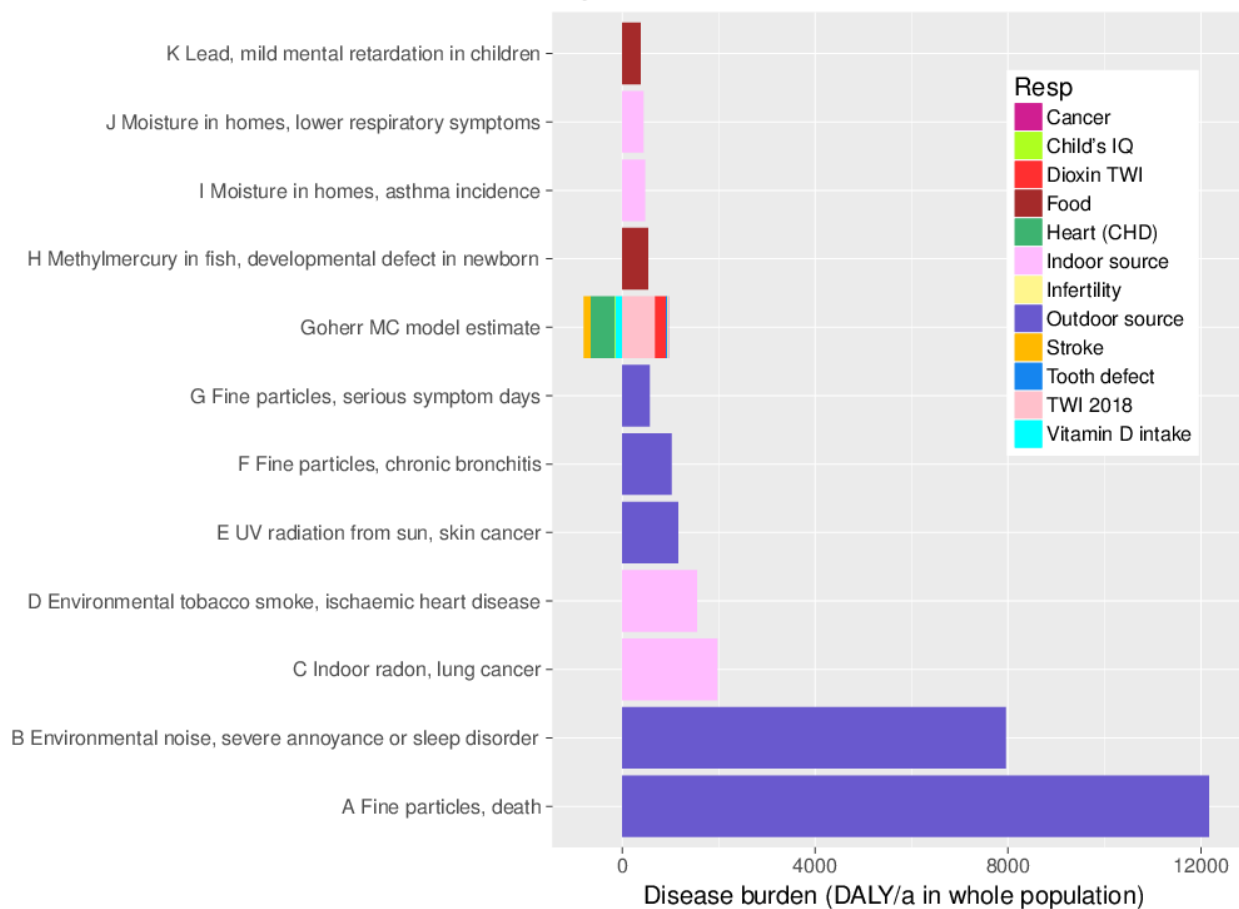Fig 28. Environmental burden of disease in Finland

Figure 5 (28 in Goherr assessment). Disease burden caused by various environmental pollutants in Finland.

Conclusions

The current TWI of 14 pg/kg/week implies clearly higher a risk than when risk is estimated using disease burden (especially if health benefits of the most common dioxin source, namely fish, is included in consideration). In other words, the most important uncertainty is whether we use net health benefit or tolerable weekly intake as our decision criterion. All scientific uncertainties are fairly small compared with this.

Interestingly, the choice between the current TWI and the new suggested TWI is not very important as they both lead to rather similar decisions: a fair fraction of population is exposed to intolerable amounts of dioxin, and therefore intake should be reduced eg. by restricting intake of Baltic fish. The conclusion is similar even if the fraction of population that exceeds TWI is rather different, being ca a fifth with the current TWI but increasing to a vast majority of people who consume Baltic herring at all, if the new recommended TWI is applied.

Recommendations

THL thinks that net health benefit, when available, should be used as the main policy criterion rather than tolerable weekly intake. Thus, in the most important practical situation, i.e. with Baltic and other fish contaminated by dioxin, health benefits of fish override in most subpopulations the risks of dioxin. Making

even stricter TWI recommendations related to fish intake would lead to increased health harm and is therefore not advised.

References

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3. Mocarelli P. et al. Perinatal exposure to low doses of dioxin can permanently impair human semen quality. Environmental Health Perspectives 2011: 119(5).
4. Minguez-Alarcon L. et al. A longitudinal study of peripubertal serum organochlorine concentrations and semen parameters in young men: the Russian children's study. Environmental Health Perspectives 2017: 125(3).
5. Sharpe1, RM. Sperm counts and fertility in men: a rocky road ahead. EMBO Rep. 2012 May; 13(5): 398–403. doi:10.1038/embor.2012.50 [2].

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