

First Consensus Workshop on Food Safety

Environmental Issues and Food Safety – the Case of Dioxins

John Chr. Larsen

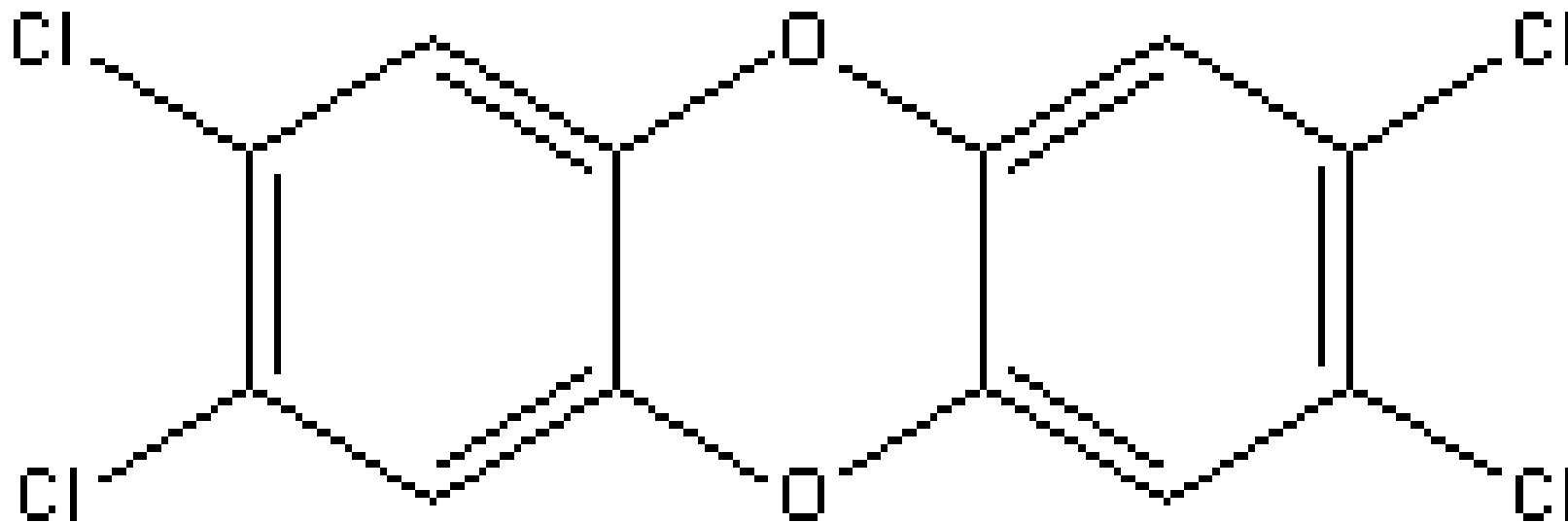
Institute of Food Safety and Nutrition

Denmark

Dioxins

- Polychlorinated dibenzo-*p*-dioxins (PCDDs)
- Polychlorinated dibenzofurans (PCDFs)
- Polychlorinated biphenyls (PCBs)
- 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) is the most toxic

2,3,7,8-TCDD



PCDDs and PCDFs

- Not produced by intention
- Formed during incomplete combustion processes, industrial as well as natural.
- Waste incineration is thought to be a major source.
- Manufacture of some chlorinated chemicals and chlorine bleaching of paper pulp.

Polychlorinated Biphenyls (PCBs)

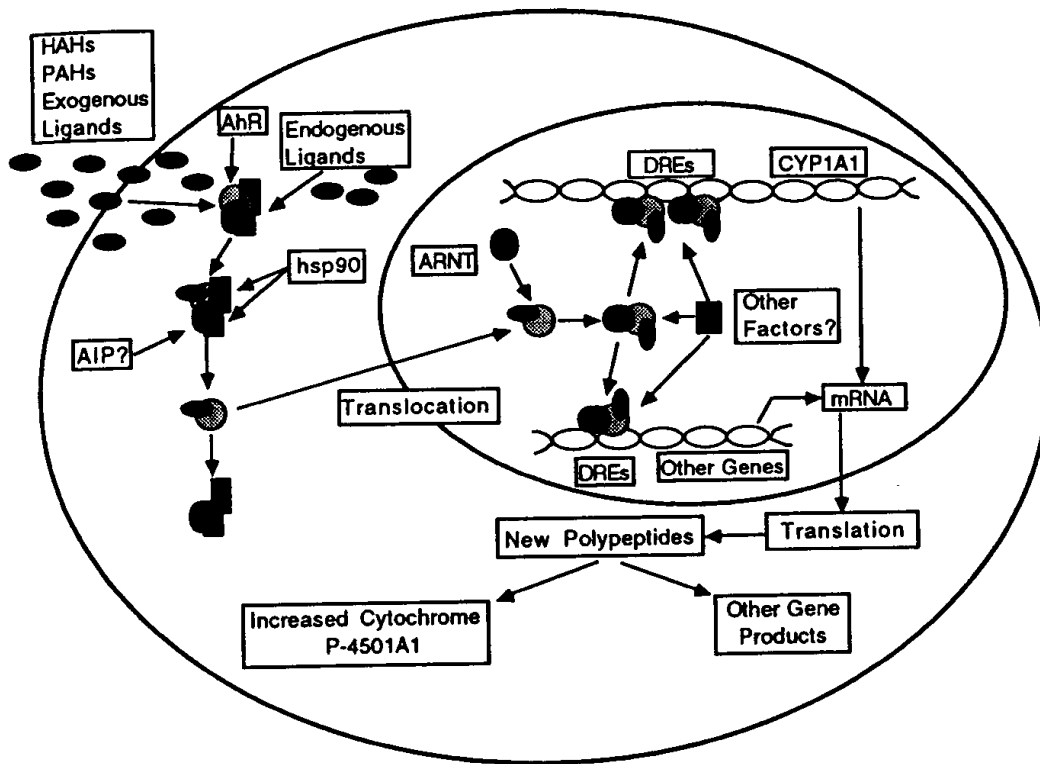
- Technical mixtures of PCBs have been widely used in a number of applications:
- Hydraulic and heat transfer systems
- Cooling and insulating fluids in transformers and capacitors.
- Used in pigments, dyes, repellents and carbonless copy paper or as plasticizers in paints, sealings, plastics and rubber products.
- The production and use of PCBs has been discontinued in most countries.

Dioxins

- Toxicological effects include dermal toxicity, immunotoxicity, reproductive toxicity and developmental effects, endocrine toxicity and carcinogenicity.
- WHO 1998: Tolerable daily intake (TDI) of 1-4 pg 2,3,7,8-TCDD /kg b.w. (extended to WHO-TEQ)

Toxic Equivalency Factors (TEFs)

- 2,3,7,8-substituted PCDDs, PCDFs and dioxin-like PCBs are assigned TEFs relative to the most toxic congener 2,3,7,8-TCDD (TEF = 1)
- The analytical results are converted into total toxic equivalents (TEQ) by multiplying the analytically determined amounts of each congener by the corresponding TEF and summing the contribution from each congener
- The most recent TEFs for PCDDs, PCDFs and dioxin-like PCBs were established by WHO in 1998.



Opinion of the SCF on the Risk Assessment of Dioxins and Dioxin-like PCBs in Food.

- Scientific Committee on Food
- Opinion Adopted November 2000
- Opinion Updated May 2001

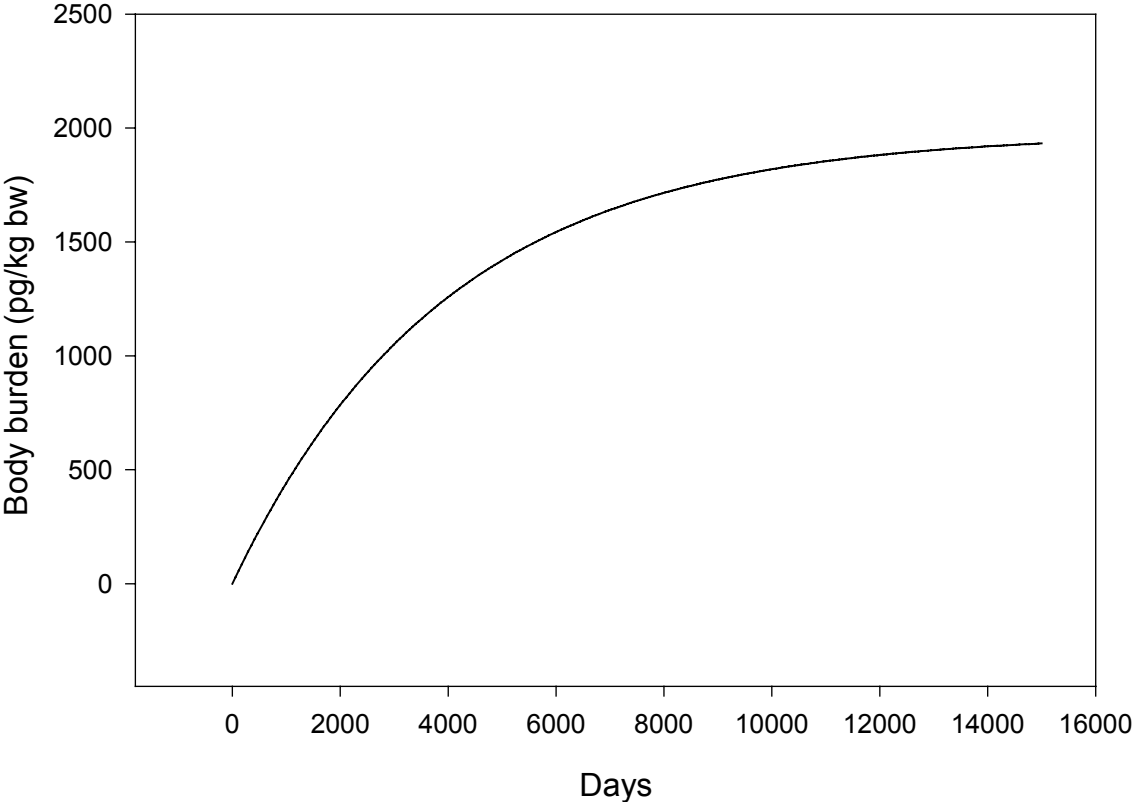
SCF Dioxin Assessment 2000

- As a starting point, the SCF assessment was based on the WHO (1998) evaluation.

SCF Dioxin Assessment 2000

- Body burdens used as dose metric to scale doses across species
- developmental, reproductive and hormonal effects following 2,3,7,8-TCDD exposure of female rats (and monkeys) were identified as the most sensitive adverse effects reported, i.e. the adverse effects occurring at the lowest body burdens

Dioxin TEQ body burden after 1 pg/kg bw/day



Dioxins

- Body Burden at steady state (ng/kg bw)
= $f * \text{Intake (ng/kg bw/day)} * \text{half-life in days} / \ln(2)$
- where f is the fraction of dose absorbed (assumed to be 50% for absorption from food for humans), and an estimated half-life for 2,3,7,8-TCDD of 2740 days (7.5 years).

SCF Dioxin Assessment 2000

- Estimate the 2,3,7,8-TCDD body burdens of the experimental animals in the studies providing the most sensitive LOAELs for 2,3,7,8-TCDD. From these estimated body burdens calculate the *associated estimated human daily intakes* (EHDI) using the equation given above.

SCF Dioxin Assessment 2000

- Effects considered but not used in final evaluation
- Effects in children following pre- and postnatal exposure?
- Carcinogenicity
- Biochemical changes, e.g. CYP1A1/2 induction, growth factors, oxidative stress

LOAELs for 2,3,7,8-TCDD

- Female monkeys fed 5 ng 2,3,7,8-TCDD per kg diet for 3.5 years and observed for another 10 years developed an increased incidence of endometriosis. Body burden 39 ng/kg bw (Rier *et al.*, 1993).
- A subtle non-persistent change in only one, among several, parameters related to cognitive recognition (object learning) was reported in the offspring delivered after 16.2 and 36.3 months by the female monkeys fed 5 ng 2,3,7,8-TCDD per kg diet. Body burden 25-37 ng/kg bw (Schantz & Bowman, 1989).

LOAELs for 2,3,7,8-TCDD

- Gavage administration of a single bolus dose of 50 ng 2,3,7,8-TCDD/kg bw to pregnant Long Evans rats on GD15 produced accelerated eye opening and a decrease in sperm counts in their male offspring. Body burden 30 ng/kg bw (Gray *et al.*, 1997a).

LOAELs for 2,3,7,8-TCDD

- Gavage administration of a single bolus dose of 100 ng 2,3,7,8-TCDD/kg bw to pregnant F344 rats on GD14 suppressed a delayed type hypersensitivity response to bovine serum albumin in the male offspring at 14 months of age. Body burden 60 ng/kg bw (Gehrs & Smialowicz, 1998, 1999)

SCF Dioxin Assessment 2000

LOAELs

- Animal body burdens in the range of 25 – 60 ng 2,3,7,8-TCDD/kg bw
- EHDIs (estimated human daily intake) in the range of 12.5 to 30 pg 2,3,7,8-TCDD/kg bw,
- Given the uncertainty, all contribute to the derivation of a tolerable intake.
- Applying the 10-fold uncertainty factor suggests a tolerable intake in the range 1 to 3 (rounded figures) pg 2,3,7,8-TCDD/kg bw/day.

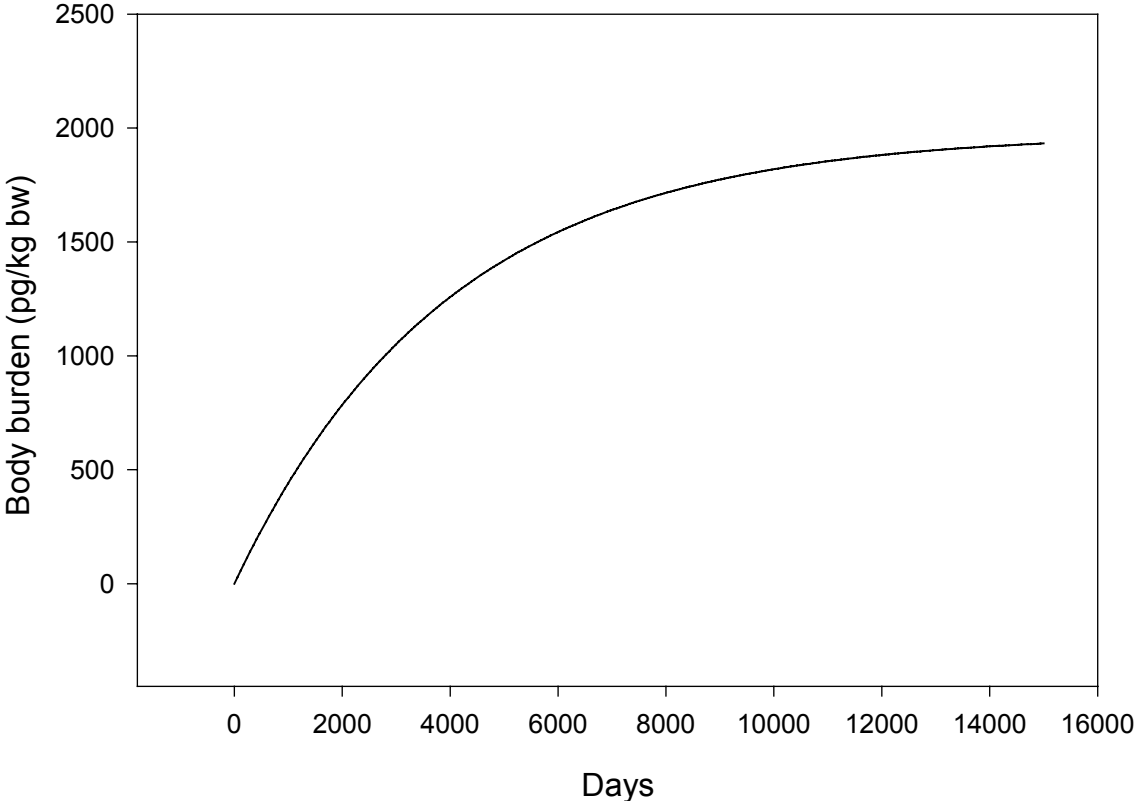
SCF Dioxin Assessment 2000

- There are currently no scientific data to guide the Committee on selection of a single value from the range of 1 to 3 pg 2,3,7,8-TCDD/kg bw/day. However, because of the acknowledged uncertainties the Committee concluded that the lower end of the range, i.e. 1 pg/kg bw/day, should be considered as a temporary tolerable intake.

SCF Dioxin Assessment 2000

- Recognising that compounds like 2,3,7,8-TCDD and related substances have very long half-lives in the human body, the Committee found it more appropriate to express the tolerable intake on a weekly rather than a daily basis. Therefore the Committee established a temporary tolerable weekly intake (t-TWI) of 7 pg 2,3,7,8-TCDD/kg bw.

Dioxin TEQ body burden after 1 pg/kg bw/day



SCF Dioxin assessment 2000

- The Committee extended the t-TWI to include all 2,3,7,8-substituted PCDDs and PCDFs, and the dioxin-like PCBs, expressed as WHO TEQ.

SCF Dioxin Assessment 2000

- Reservations about using single dose gavage studies for the assessment
- The critical determinant of the reproductive effects is the foetal concentration on GD15, which is likely to be higher following a single bolus dose on this day than that resulting from lower level chronic exposure.

SCF Dioxin Update 2001

- Hurst *et al.* (2000a and 2000b) measured the radioactivity in both the maternal and foetal tissues of pregnant Long Evans dams at GD 16 following single bolus administration and at GD 9, 16, and 21 following subchronic administration of ³H-2,3,7,8-TCDD.

SCF Dioxin Update 2001

- As expected, acute single gavage doses at GD 15 produced considerably higher foetal concentrations at GD 16 than subchronic administration of low daily doses leading to maternal steady state body burdens of similar magnitude.

SCF Dioxin Update 2001

- New studies of the rhesus monkey dams used by Schanz and Bowman (1989) for behavioural testing of offspring, and by Rier et al. (1993) for study of endometriosis was published. They throw doubts about the earlier studies (Rier et al. 2001)

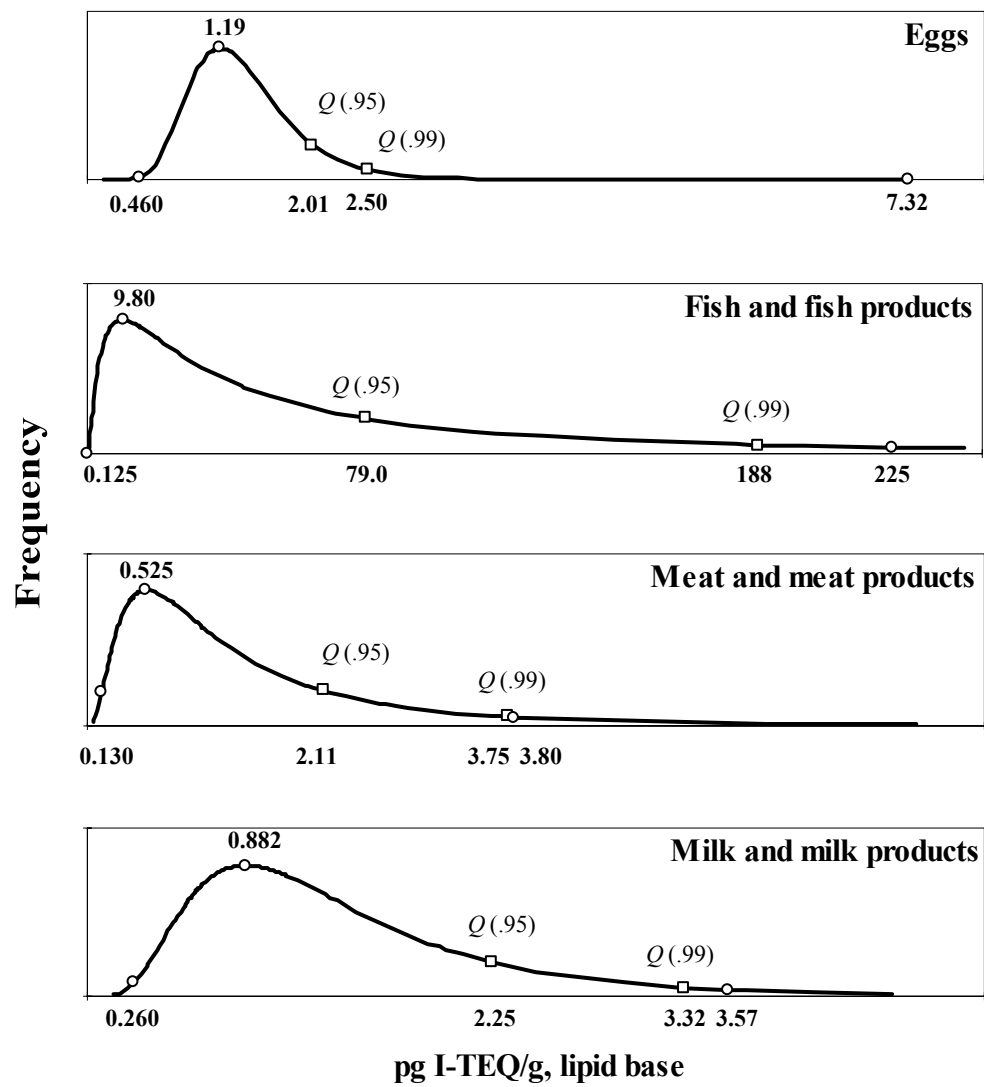
Study	Endpoint	NOAEL	LOAEL	Estimated maternal steady state body burden¹⁾ (ng/kg bw)	Associated EHDI (pg/kg bw)
Mably <i>et al.</i> , 1992c	Holzman rats: Decreased sperm count in male offspring		64 ng/kg bw single bolus dose by gavage	99 ³⁾	49.5
Gray <i>et al.</i> , 1997a	Long Evans rats: Accelerated eye opening and decreased sperm count in male offspring		50 ng/kg bw single bolus dose by gavage	79 ³⁾	39.5
Faqi <i>et al.</i> , 1998	Wistar rats: Decreased sperm production and altered sexual behavior in male offspring		Maintenance of 25 ng/kg bw by subcutaneous injections	39 ³⁾	19.5
Ohsako <i>et al.</i> , 2001	Holzman rats: Decreased anogenital distance in male offspring	12.5 ng/kg bw single bolus dose by gavage		19 ⁴⁾	9.5
			50 ng/kg bw single bolus dose by gavage	79 ⁴⁾	39.5

SCF Dioxin Update 2001

- The LOAEL body burdens of 39 – 99 ng TCDD/kg bw in animals were related to EHDIs of 19.5 – 49.5 pg TCDD/kg bw/day.
- The NOAEL body burden of 19.5 ng TCDD/kg bw corresponded to a EHDI of 9.5 pg TCDD/kg bw/day.
- A TWI of 14 pg WHO-TEQ/kg bw was established.

Levels of dioxins in food

- PCDDs and PCDFs in eggs, fats and oils, meat (products), and milk (products) in the order of 1 pg TEQ/g, lipid basis, or less.
- Fish in the order of 10 pg TEQ/g, lipid basis.
- Fruits, vegetables, and cereals relatively low, generally close to the limits of determination.
- Average TEQ contributions from dioxin-like PCBs one to three times the TEQ contribution of PCDDs and PCDFs.



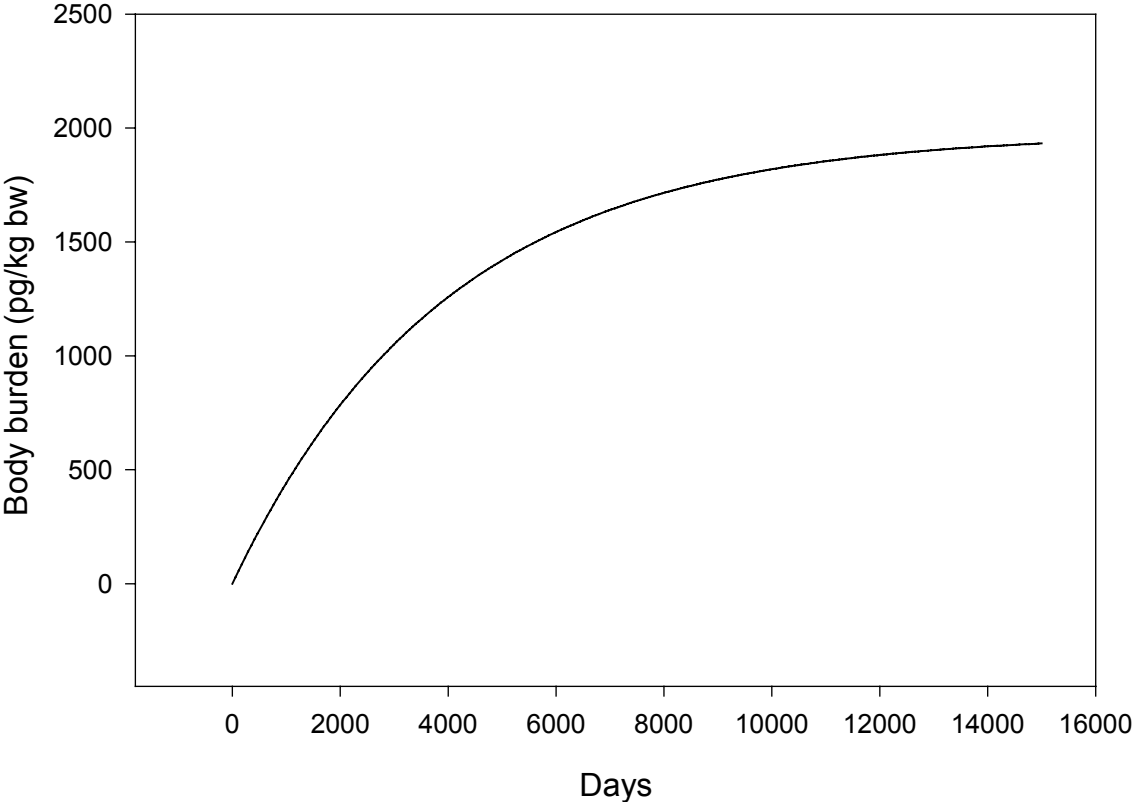
EU Scientific Cooperation (EU SCOOP) Task 3.2.5.

- Assessment of Dietary Intake of Dioxins and Related PCBs by the Population of the EU Member States, June 7th, 2000
- PCDDs/PCDFs: 0.4 - 1.5 pg I-TEQ/kg bw/day
- Dioxin-like PCBs: 0.8 - 1.8 pg PCB-TEQ/kg bw/d

Dioxin intake

- The average intake of TEQ is close to the TWI of 14 pg TEQ/kg bw/week (2 pg TEQ/kg bw/day).
- Therefore, a considerable proportion of the European population would exceed the group t-TWI of 14 pg WHO-TEQ/kg bw.
- TWI is not a lower bound of toxicity.
- However, exposure above the TWI leads to an erosion of the protection embedded in the TWI.

Dioxin TEQ body burden after 1 pg/kg bw/day



Dioxins in human milk

- For the period before 1995, the national average levels ranged from 10 to 34 pg TEQ/g, lipid basis.
- For the period 1995-1999, the national average concentrations appear to range from 7.9 to 19 pg TEQ/g, lipid basis.
- For some countries clearly indicating a downward trend.
- Mean PCB-TEQ concentrations comparable to the TEQ contributions of PCDDs and PCDFs

Dioxins in human milk

- Breast-fed infants may have intakes estimated to be 1 to 2 orders of magnitude higher than the average adult intake.
- The studies used for the derivation of the TWI mimic the situation with breast-feeding.
- SCF reiterated the conclusions of WHO meetings that the current evidence does not justify altering recommendations on the promotion of, and support for, breast-feeding.

Recommendation

- Continuing efforts should be made to limit release of PCDDs, PCDFs and dioxin-related compounds to the lowest levels that are technically achievable. This is the most efficient way to reduce the presence of these compounds in the food chain and to ensure continued reductions in human body burdens.

Recommendation

- SCF recommended to set *action thresholds* and *target values* for those food groups that contribute most to the human body burden.
- Target values indicate the average levels of contamination of food products required to bring the exposure down to the TWI value.
- An action threshold is a level of contamination that triggers specific risk management actions.
- Action thresholds are higher than target values.

