REPORT FROM A NORDIC MEETING ON THE 1998 WHO CONSULTATION ON ASSESSMENT OF THE HEALTH RISKS OF DIOXINS; RE-EVALUATION OF THE TOLERABLE DAILY INTAKE (TDI)

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Introduction

The Nordic countries have a long tradition of co-operation in dealing with the risk assessment of polychlorinated dibenzo-*p*-dioxins (PCDDs), dibenzofurans (PCDFs) and biphenyls (PCBs). A Nordic risk assessment on PCDDs and PCDFs was published in 1988[1] and one on PCBs in 1992[2]. In 1995 a Nordic expert group discussed the 1994 US EPA draft document covering exposure and health risk assessment of 2,3,7,8-TCDD and related compounds. The aim of the 1995 meeting was to critically review the document and to analyse to what extent new data and their evaluation would require a reconsideration of the earlier risk assessments from the Nordic countries[1,2] and WHO/EURO-IPCS[3]. The WHO has initiated several meetings on health risk assessment of dioxins. In May 1998 WHO-ECEH and IPCS jointly organised a consultation on the assessment of health risk of dioxins: re-evaluation of the tolerable daily intake (TDI). The report from this consultation was published in Food Additives and Contaminants[4]. Prior to the publication of this report an executive summary was available on the internet[5].

A Nordic expert group met in December 15-16 1999 in order to discuss "WHO assessment of the health risks of dioxins; Re-evaluation of the tolerably daily intake (TDI)" as given in the executive summary dated September 1999[5]. The aim of this meeting was to evaluate the result of the consultation in general and to investigate whether the results should give rise to any new proposals on risk reduction from a Nordic viewpoint.

Summary of the meeting

Since the meeting in 1995 no new important primary **sources** to dioxins have been identified. On the other hand dioxins have been found in a number of materials not investigated earlier that might be of importance for human exposure. Among these materials are different kinds of clay as bentonite and kaolin which was used in the "citrus pulp". Lately a number of incidences where dioxins and/or PCB have been found in a number of different animal foodstuffs have occurred. The accidental PCB and PCDD/F contamination in Belgium 1999 of different feed and subsequently human foodstuffs did demonstrate that routes of exposure could be difficult to predict. The Belgian accident has not caused any excessive levels of dioxins in food stuffs analysed in the Nordic countries. It is not clear as to whether citrus pulp or bentonite clay cattle feed has led to elevated levels of dioxins in meat or diary products.

Mechanism of action was intensely discussed. There are no strong evidence for non-Ah-receptor mediated effects that could influence the risk assessment. Thus, the critical effect of dioxins was assumed to most likely be mediated by the Ah receptor.

Toxicokinetics was one of the main parts of the discussion. In the report it is proposed that "body burden" should be used as a dose metric unit instead of daily intake. If the daily intake is known body burden can be calculated provided linear (1st order) kinetics. It was not clear whether such models have been used in the calculations of body burden. It is however also stated that "Metabolism is the rate limiting step for elimination" and "the apparent half-lives are not absolute but vary with dose". This indicates that the kinetics is not linear but obeying 0^{th} order kinetics as clearance varies with plasma concentration. If so, these simple pharmacokinetic models can not directly be used for an accurate calculation of body burden.

The Nordic group recognises the advantages of using body burden as it facilitates extrapolation across species and that it provides a better description of (free) concentration in the target tissue compared to daily intake. Thus body burden is likely to be a good marker of, or parameter to, effect(s). The body burden approach is also advantageous compared to daily intake as it emphasises the importance of long term exposure.

In order to reach reliable results of calculations of body burden from dosage it is important that the conditions are as close as possible to steady state. Many studies used for calculation of the new TDI are based on single dose exposure and thus the calculation of body burden is difficult to interpret. The conditions in close connection to a (high) single dose might be different to the conditions after long term administration of the same accumulated dose. It is not unlikely that the amount of free compound, available to target structures, for a limited time, can be higher after single dose administration compared to repeated exposure of the same total dose. This implies that the effects might be overestimated when body burden is calculated from a single dose administration.

Regarding **effects in laboratory animals and humans** the Group agreed that fetal exposure is important and that the risk assessment should be based on effects caused during this sensitive period of life. In addition, subtle effects related to prenatal dioxin exposure have been observed in the general human population of the Netherlands, which shows that the current exposure level is very close to the effect level. However, additional studies with repeated exposure are necessary for a reliable quantitative risk assessment. Also, such studies need to be confirmed so that the TDI will not be based on a single study. The Group emphasised that the situation is serious and that further measures have to be taken regarding further research on the critical effects of dioxins.

The Group agreed to recommend the use of the WHO-TEFs for dioxins and PCBs. However, the need for dose-response studies of the critical effects based on synthetic mixtures reflecting the human exposure situation was recognised.

Exposure of dioxins and dioxin-like substances to humans in Sweden has decreased during the last decades[6,7] and so has human body burden as illustrated by decreasing levels in human breast milk[7]. Similar trends have been reported from the other Nordic countries. However, environmental levels of PCB in biota from the Baltic Sea currently shows no, or only marginal, tendency to

decrease further. The average exposure in Sweden and Finland has recently been estimated to 2 pg TEQ/kg/d[6].

Recommendations

The current Nordic risk assessment (TDI 5 pg TEQ/kg) is still recommended. Although the studies that form the base for the WHO recommendations are not regarded as appropriate for quantitative risk assessment they are considered of such importance that they should result in increased activities aimed at both producing new data to fill identified gaps of knowledge as well as reducing the risk to humans and environment from current substances. The risk reduction should focus on limiting the emissions and reducing exposure.

- When body burdens are used as dose metrics for extrapolating critical effects from animals to humans, the safety margin between the lowest effect levels in animals and human exposures is small.
- A number of factors not completely known influence the extrapolation of animal data to humans so at present an exact quantification of human risk is difficult.
- Because of the uncertainty inherent in establishing TDI values and because the maximal tolerable intake set by WHO in 1998 (4 pg TEQ/kg) is not materially different from the Nordic TDI set in 1995 (5 pg TEQ/kg), the Group did not recommend a change of the Nordic TDI.
- However, since the safety margin in humans appears to be small and a certain part of the population probably is exceeding the TDI, the Group strongly recommended that exposure should be further reduced.

Research needs

- Studies on the critical effects during early development (of the reproductive, immune and nervous systems) using repeated dosing to the dam, preferentially including a period prior to mating,
- Dose-response studies of the critical effects based on mixtures relevant to current human exposure,
- Epidemiological studies on a Nordic basis on infant and child development,
- Mechanistical studies on how the Ah receptor leads to the critical effects, including identification of biomarkers for early effects,
- Kinetic studies on the influence of different factors (e.g. high acute exposure) on body burden and target organ concentrations,
- Continued monitoring of human exposure.

References

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