Dioxins: Dutch/European historical perspective and current evaluation of human health risks

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1. WHY WAS IT A PROBLEM AND WHY HAVE CONTROL POLICIES BEEN DEVELOPED?

Dioxin-like substances are a problem since in the sixties it became clear that these compounds have a highly toxic potential and that nearly everybody is chronically exposed to them because of their widespread occurrence and their persistence. In Europe chemical accidents from 1953 till 1976 in West-Germany, France, The Netherlands, Czechoslovakia, the United Kingdom and Italy made clear that dioxin-like substances could be harmful for man, shown by skin lesions (acné), liver insuffication, central nervous system disturbances, elevated lipid and cholesterol levels in blood, hypertension and prediabetes.

In experimental animals dioxin-like substances also caused skin lesions and liver impairment. Besides that the so called 'wasting syndrome' appeared at high doses. Thymusatrophy, tumors and impairment of reproduction were also observed. Experimental animals show a manyfold difference in vulnerability. The LD50 value for 2,3,7,8-TCDD in male guinea pigs (0,6 μg/kg) is a factor 5000 smaller than the LD50 in male hamsters (3000 μg/kg). This made it difficult to decide what animal model and what extrapolation factors should be used to make a human health risk assessment.

2. WHAT PROGRESS HAS BEEN MADE DURING THE LAST 20-30 YEARS?

Polyhalogenated aromatic hydrocarbons are almost always present in the environment in the form of mixtures of isomers and congeners. This phenomenon, combined with the similarity in their working mechanism, has led to a group approach for these substances for the purpose of risk evaluation. The 2,3,7,8-tetrachloride dibenzo-*p*-dioxin (2,3,7,8-TCDD) acts as reference in assessing the toxic effect of those polyhalogenated aromatic hydrocarbons that have a similar effect. It is both the most thoroughly investigated and the most toxic of this class of compounds with a dioxin-like effect. So-called TEF values have been assigned to all polychlorinated dibenzo-*p*-dioxins and polychlorinated dibenzofurans with chlorine atoms in the 2,3,7 and 8 positions. These toxic equivalency factors indicate the toxic effectiveness of dioxin-like compounds compared with that of the reference compound 2,3,7,8-TCDD; the TEF of this latter compound is, by definition, 1.

In 1977 D.L. Grant was the first to apply weighing factors to grade the toxicity of the different congeners. During the 1980's, several countries and national and international institutions have developed separate models for TEF's like the Federal Swiss Government in 1982, the Danish National Agency of Environmental Protection in 1984, the Federal Republic of Germany's Office for the Environment in 1985. The scientific basis differed between the models. The Danish and Swiss models were based essentially on the relative potency for aryl hydrocarbon hydroxylase induction, whereas the German model was based on a weighing of all available quantitative data on toxicity of the different congeners. In 1987 a Nordic expert group developed a new set of weight factors based on the most recent toxicity data. In 1988, the North Atlantic Treaty Organization Committee on the Challenges of Modern Society (NATO/CCMS) used the Nordic model as the basis for the international toxicity equivalent factors (I-TEF's) and recommended to its member countries to adopt this model. It has indeed been adopted by Germany, Italy, The Netherlands, the United Kingdom, the Nordic countries and beyond Europe Canada and the United States. The I-TEF values for PCDD's and PCDF's have been derived from data originating from *in vitro* and *in vivo* research into acute toxicity,

subchronic and chronic toxicity, and carcinogenic and teratogenic effects.

During a meeting in 1993 held under the auspices of the World Health Organization (WHO) - and organized within the context of the International Program on Chemical Safety (IPCS) - the question of whether it was also possible to lay down internationally accepted TEF values for the dioxin-like PCB's was considered. The participants in that meeting have proposed interim TEF values. The criteria for including a PCB in the TEF scheme were that the structure of the relevant PCB resembles that of PCDD's and PCDF's, the PCB binds to the Ah receptor, the PCB causes dioxin-like biochemical and toxic effects and the PCB is not rapidly degraded in the environment and accumulates in the food chain. There is another proposal for TEF_{PCB}'s from mr Safe. Both proposals seem tenable in the light of the present state of scientific knowledge. In addition, the uncertainty in the exposure to PCB's is much greater than the difference in the calculated dose when using one or the other TEF_{PCB} list.

With the help of the TEF values, we can express the exposure to mixtures of PCDD's, PCDF's and dioxin-like PCB's in the form of the so-called toxic equivalency (TEQ). The TEQ value is arrived at by multiplying the concentration of each component in the mixture by the corresponding $TEF_{dioxins}$ or TEF_{PCB} value, and then adding together the products obtained.

The TEF concept is a usable and uniform instrument in the estimation of the risks associated with exposure to PCDD's, PCDF's and dioxin-like PCB's.

During the 1980's a number of regulatory bodies throughout the world generated separate assessments of the risks posed by 2,3,7,8-TCDD. While all of these assessments relied on essentially the same experimental data, they differed in the extrapolation methods. In 1982 The Netherlands based its exposure limit on hepatotoxic effects at 1 ng per kg with a safety factor of 250, resulting in a value of 4 pg per kg per day. Comparable approaches in the United Kingdom, Germany and Switzerland resulted in values from 1 to 10 pg per kg per day. No effect levels for carcinogenicity, reprotoxicity and immunotoxicity were established. In 1989 a tolerable weekly intake has been set by the International Program on Chemical Safety (IPCS) on the basis of rodent cancer studies. The proposal from the IPCS was based on the cancer responses at doses 1, 10 and 100 ng per kg per day in the animal lifetime feeding study of Kociba and coworkers.

An uncertainty factor of 200 was applied to the no-observed effect level (considered to be a threshold) of 1 ng per kg per day and thus a tolerable weekly intake for man turned out to be 35 pg per kg body weight per week. This value coincides with the value given by a Nordic Council working group in 1988.

Since then more about the working mechanism of dioxin-like compounds became known. Techniques to assess other endpoints than death and tumor formation in experimental animals were used to perform studies on developmental and reprotoxicity, neurotoxicity and immunotoxicity. Sampling and analytical techniques became standardized in the EU member states. Food and breastmilk concentrations were measured on a European scale. Epidemiological studies on incidentally high and chronically low exposed populations were reported. Scientific and political discussions about health risk evaluation and lowering of exposure took place on the international level of the WHO, the IARC and the EU. WHO-discussions resulted in 1990 in an acceptable daily intake of 10 pg per kilogram bodyweight per day on a life time base. This was based on both human data of Seveso residents and animal experimental data on carcinogenicity and reprotoxicity. The internal concentration of the liver was taken as the basis for deriving an acceptable daily intake because the liver was considered to be a primary target organ. Using a pharmacokinetic model it was calculated that 1 ng per kg per day during 2 years (the NOAEL for rats) equalled an intake of 100 pg per kg per day during 70 years for humans (the calculated NOAEL for humans). Because of uncertainty about interhuman variability and reprotoxicity a safety factor of 10 was applied. This resulted in a tolerated daily intake of 10 pg per kg per day for humans.

3. WHICH WERE THE 'DRIVING FORCES' BEHIND THE PROGRESS OBTAINED?

Depending on what exposure limit was chosen in a country, the exposure of people was under or above this limit. In The Netherlands, by adopting the WHO-limit there was a larger margin of safety then with the first Dutch exposure limit. Also the extreme low American exposure limit value became known. This gave rise to much concern in citizen

groups. It pressed governments to pay scientists to investigate the potential effects of these compounds and to perform risk evaluations.

4. CURRENT SITUATION

As scientists went on with their toxicological and epidemiological research they now come to the conclusion that the health based exposure limit should be lowered. This was stated in an advisory report of the Health Council of The Netherlands to the Dutch government in august 1996 as follows.

In experimental animal studies NOAEL's or LOAEL's have been found that are lower than 1 ng per kg per day. The induction of the enzymes CYP1A1 and CYP1A2, and a more obviously adverse effect such as the increase of endometriosis, serve to illustrate that. According to the Committee, the experiments reported by Bowman and Schantz (1989), by Neubert (1992) and Rier (1993) are the most relevant basis for the derivation of a health-based recommended exposure limit because the laboratory animals were primates (and therefore are relatively close to man) and the observed effects are adverse. In the one study a change in cognitive development in baby Rhesus monkeys was noted; the effect arose in the case of a 2,3,7,8-TCDD dose of 0.1 ng per kg per day in the mothers (which themselves developed endometriosis). The other study showed a change in lymphocytes in Marmosets at a dose of 0.13 ng per kg per day. So 0.1 ng per kg per day was taken as a LOAEL in non-human primates. To accomplish the transition to a NOAEL the dose-effect relationship for all kinds of effects within the dosage range between 0.1 and 1 ng per kg per was extrapolated. This resulted in a factor of 2 lower than the corresponding LOAEL's so 0.05 ng per kg per day. Pharmacokinetic characteristics of PCDD's and PCDF's indicate that, in certain respects (e.g. the way in which these substances are distributed between the liver and the fatty tissue), the monkey occupies a position somewhere between the rat and man. Therefore the Committee proposes a interspecies safety factor of 5. The intraspecies variation (the possible difference in sensitivity within a species and, in this case therefore, between humans) is, according to the Committee, adequately taken into account when the standard safety

factor of 10 is used. Accordingly, the Committee derives as a health-based recommended exposure limit for man of 0.001 ng per kg per day (or 1 picogram of 2,3,7,8-TCDD per kg per day). Given the similarity of their effects, the Committee considers this recommended exposure limit to be applicable also to the intake of mixtures of diverse dioxin-like compounds expressed in the TEQ.

Among the most important epidemiological studies concerning exposure to PCDD's, PCDF's and dioxin-like PCB's are that of industrial accidents in the sixties and seventies in Europe and that of Vietnam veterans. The Committee attaches much importance to the results of the research conducted among infants in Rotterdam and Groningen, first because the study deals with the consequences of long-term exposure to low doses - the situation to which the health-based recommended exposure limit relates - and, second, on account of the (as is generally assumed) increased sensitivity of infants (and foetuses) to harmful substances. Effects associated with the building up and development of organ systems are among the first that become apparent. The first point to make from the reported studies from Huisman (1995), Koopman-Esseboom (1994, 1995) and others is that no link has been found between serious, clinically relevant abnormalities in the development of new-born children and their degree of exposure to PCDD's PCDF's and PCB's. However, the infants with the highest prenatal exposure over a period of some time did have a lower neurological optimality score, a lower psychomotor score, and an altered immune function parameter. Among the infants with the highest postnatal exposure, the same subtle signs of a suboptimal development were observable, as well as changes in the thyroid hormone status. Although all the differences referred to fall within the range of the clinical reference values, the Committee thinks that their harmlessness to health in the longer term has not been established. In conformity with the definition of adverse effect such effects are in the Committee's opinion undesirable. The median daily dose expressed in the form of TEQ in the case of the mothers of the infants suffering the highest exposure levels amounts to 0.003 ng per kg per day. The fact that, at this dose, effect arise in infants offers in the opinion of the Committee, further support for the health-based recommended exposure limit of 0.001 ng per kg per day. In the mother themselves, physiological effects related to the exposure to dioxin-like PCB's were also observed, i.e. changes in thyroid hormone levels. The significance of this for health is, in

the Committee's opinion, still unclear.

The Council concluded that the possibility that the ingestion of dioxin-like compounds causes adverse health effects in the Dutch population cannot be excluded with reasonable certainty.

5. WHICH PROBLEMS REMAIN AND WHY?

The group of dioxin like compounds contains so many congeners it remains difficult to assess their relative potencies. As the half time of these compounds in humans is 7 years, one should like to know more about the relation of body burden and health effect as a base for setting a daily intake limit. The broad spectrum of effects of these substances remains a problem. There is only a small number of studies at chronic low exposure levels in humans, so inter- and intra species extrapolationfactors are uncertain and large. Besides extrapolation from high to low doses is necessary.

The main problem concerning health risk assessment of dioxin-like compounds is the fact that governments more and more a quantitative risk assessment using the bench mark dose approach. Because it is very expensive to mitigate exposure they need to make a cost/benefit analyses. This is in contrast with the past where scientists were asked to set a level of exposure for chemicals that was safe in the first place, a more qualitative approach.

6. WHAT RELATIONSHIP EXISTS WITH OTHER ENVIRONMENTAL EFFECTS AND VARIOUS SOURCES OF POLLUTION/'CAUSING FACTORS'

There are some other compounds were the same problem causes a lot of ongoing discussion like particulate matter and radon. For these agents it is difficult to extrapolate health effects to the level of the actual exposure. At the same time it is clear that measures to bring down these exposures have a big economical impact.

7. WHICH PROMISING SOLUTIONS ARE AVAILABLE? CAN ADDITIONAL BENEFIT BE OBTAINED FROM VARIOUS LEVELS OF INTEGRATION?

In the health risk evaluation field there are some tendencies to cope with this problem of risk quantification. One of them is the design of sophisticated physiology based pharmacokinetic and pharmacodynamic models to perform more accurate extrapolations from high to low dose and for different experimental animals to humans. In practice this could mean tighter safety or uncertainty margins.

To validate these models it is important to get more data of the exposure - effect and the exposure - response curve.

For dioxins there is already a tendency to standardize and harmonize analytical techniques through Europe to get an European wide exposure assessment that should prove that the source reduction measures that have been taken within the framework of the 5th European Environmental Action Plan do work.

Discussions about exposure limits are going on at the WHO and about carcinogenicity at the International Agency of Research on Cancer. Apart from the progress in international cooperation national stimulation programs like that in the nineties in The Netherlands are very fruitful by building interdisciplinary centers of excellence.

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