HEALTH RISKS FROM DIOXINS AND RELATED COMPOUNDS: PRINCIPAL CONCLUSIONS AND RECOMMENDATIONS OF A FRENCH EXPERT ADVISORY GROUP (2000)

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Introduction

In 1999 and 2000, the French Institute for Health and Medical Research (INSERM) brought together a group of 15 experts to: i) review existing knowledge about the public health risks presented by exposure to dioxins and dioxin-like compounds; ii) formulate recommendations for action by decision-makers. The participants' fields of expertise were chemistry, cancer biology, molecular physiology, (food, immunological, molecular, and pharmacological) toxicology, (environmental and occupational) epidemiology, and risk assessment. This project was actively supported by the Ministries of Health and of the Environment. The following questions were presented by INSERM and these Ministries:

1. What is the physico-chemistry of dioxins? How are they formed?

2. What are their reservoirs and sources? What are their effects on the environment? By what pathways is the food chain contaminated?

3. What assay methods exist? By what metrics can the results be expressed?

4. How are dioxins distributed throughout various tissues? How does this differ between species? What biomarkers are sensitive to and specific for dioxin exposure?

5. What biological and toxic effects are observed in different animal species? What effects are observed in humans from exposure to high and to low doses? What are the consequences of mother-child transmission?

6. By what mechanisms do dioxins act? How important is the mechanism involving the Ah receptor? How can the variability of dioxin action from species to species and sometimes even within a single species be explained?

7. What toxicokinetic parameters must be considered in assessing the toxicity of dioxins for animals and for people? What models can be used to assess the risks of dioxin exposure?

Methods

INSERM (Common Services 14) furnished to the participants more than 1600 articles, supplemented by the participants' own bibliographies, when applicable, and 13 national or international reviews of dioxin emission sources, exposure, and the health risks.[e.g.1-5] During 9

working sessions, the experts presented a critical analysis and synthesis of the available knowledge. The last 3 sessions were devoted to drafting the principal conclusions and recommendations. Each expert wrote a chapter on the knowledge available in his or her area of expertise. These chapters are not signed.

Principal points of the review

PCBs were excluded from this assessment because i) the questions raised by the sponsors essentially concerned PCDD and PCDF; ii) those PCBs that are not dioxin-like do not seem to have the same mechanism of action, and they represent a major exposure source. For these two reasons, the risk that they may represent for public health should be the object of a specific study. We therefore did not discuss them except when the circumstances (e.g., of exposure) made it impossible to consider only the effects of PCDDs/PCDFs.

Mechanisms of formation and decay, sources and contamination of environmental compartments

The mechanisms of PCDD/PCDF formation and their theoretical sources were discussed, and it was concluded that the principal production pathway is *de novo* synthesis during the combustion process. The very low vapor pressure of PCDDs/PCDFs means that they disperse only slightly as a gas, but their strong absorption onto particles containing organic materials enables them to be dispersed through the air. The decay reaction most important to the environment appears to be photodechlorination. It involves especially the most chlorinated congeners and may lead to the formation of 2,3,7,8-tetrachlorodibenzo-para-dioxins (TCDD) from octachlorodibenzo-*p*-dioxin (OCDD), the leading compound in dioxin emissions. Several studies of the biodegradability of PCDD/PCDFs shows that some microorganisms (bacteria, yeast, and fungi) can metabolize them.

The data available about the contribution of various sources (in particular, natural formation) were discussed. It was concluded that the principal sources of emissions in France were the incineration of household and municipal waste and metallurgy; these emissions are now diminishing because of technological improvements. The available data indicate that contamination of the environmental compartments in France is essentially of the same order of magnitude as in other Western countries.

Assay Methods

Advances in analytic chemistry now enable PCDD/PCDF to be assayed in 10-15 ml of blood, or even less if relatively high levels are present. These may help make it possible to conduct epidemiologic studies in chronically exposed general populations, but reaching such a level of sensitivity will require substantial skills . Nonetheless, no correlation has yet been established between the body burden and the quantity of dioxin binding to the Ah receptor (the effective dose). Laboratory assay methods (e.g., CALUX) enable the degree of activation of the Ah receptor to be determined. These appear to complement the analytic PCDD/PCDF assay for epidemiologic purposes. Analysis of the concentrations of each of the congeners remains essential for the identification of the sources of contamination.

Toxicological and Epidemiologic Data

The current state of knowledge in these fields was examined. It was concluded that i) inter- and intra-species sensitivity is variable; ii) it is impossible to define an immunotoxicological profile valid for all the species considered (including humans), the immunotoxic mechanisms have not been elucidated, and the data do not support the hypothesis that PCDD/PCDF action causes autoimmune diseases ; iii) in experiments, females have been shown to be more sensitive than males to the carcinogenic action of TCDD, action based on a non-genotoxic mechanism; iv) there are few precedents for carcinogens that induce, as TCDD does, a non-specific increase in the tissues or organs at risk of cancer; v) the effect of bias or confounding factors cannot be totally ruled out in the epidemiologic studies that have reported the greatest effects on cancer mortality; vi) the conclusions of epidemiologic studies on the cardiovascular risk are not entirely consistent; and the epidemiologic studies on the hormonal and neuropsychological effects are based on only a few observations; vii) the epidemiologic observations about reproduction and development are not entirely consistent, and in the case of alleged problems in neurobehavioral development, they may be related more to prenatal exposure than to breast-feeding; it is not possible to determine the specific respective ? effects of PCBs and PCDD/PCDFs.

Molecular Cascade Involving the Ah Receptor

Knowledge of the molecular mechanism responsible for toxic manifestations has advanced substantially and was examined in detail. The binding affinity of 2,3,7,8-TCDD varied only slightly between species (1-10 nM) and does not explain the differences in sensitivity by species. The consequences of cytochromes P450 induction were examined to assess the role and mechanism of oxidant stress in PCDD/PCDF toxicity. We also sought to determine what can be deduced from this about individual sensitivity related to genetic polymorphisms. The possible toxicological consequences of Ah receptor involvement in the alterations of sexual and thyroid endocrine function and in the expression of growth factors were highlighted, including when taking into account the action of a possible natural ligand.

Human Exposure and Body Burden

More than 95% of human exposure comes from food. In 1999, the median food intake was estimated at 1.3 g/kg/d with a 95th percentile of 2.6 g/kg/d.[2] Compared with 1990, this intake has therefore fallen by almost 50%. In France, a recent national study of 244 individual samples showed that the median PCDD/PCDF (TEQ) concentration in breast milk was 16.4 pg/g of fat (range 6.5-34.3)[3].

Toxicokinetic Models for Risk Assessment

The analysis of human data indicates that the half-life of 2,3,7,8-TCDD is approximately 8.5 years for occupational cohorts, and 15.5 years for the general population. It varies from one individual to another (for example, according to their weight) and increases with age; it can reach 30 years. The toxicokinetic data partly explain the inter-species differences in sensitivity. They justify the use of the body burden as the basis of risk assessments.

Risk Assessment

The approaches proposed by the US EPA[6] and the WHO[5] were examined. The expert group commended the effort undertaken under the aegis of the US EPA to model dose-response relations at low doses for carcinogenicity and other effects. At current levels of public exposure, Ah receptor occupancy is sufficient to induce some level of target-gene transcription, with a linear dose-response relation. It is nonetheless not possible to establish a causal link with the risk of cancer. Some experimental data and results from modeling them, as well as epidemiologic data (for cancers), are compatible with a no-threshold linear dose-response relation for low doses. WHO applies a carcinogenic mechanism with a threshold to its modeling; this leads to the conclusion that the risk of cancer associated with PCDD/PCDFs in the general population is very probably zero. The US EPA proposes a stochastic approach with a no-threshold linear dose-response relation that foresees a high level of risk of cancer attributable to TCDD exposure in the general population. No definitive argument makes it possible to reject one or the other of these approaches.

Recommendations

The principal recommendations of the expert advisory group are to i) improve our knowledge of the sources of PCDD/PCDF emissions so that we may to continue to try to reduce these emissions into the environment; ii) monitor environmental contamination, to reconstruct its past course and to intensify research on the transfer between environmental compartments; iii) monitor contamination of the food chain; iv) monitor the changes in the dioxin burden in the population by assays of PCDD/PCDF in blood and in breast milk; v) encourage both research into the molecular mechanisms of dioxin's action and epidemiologic studies, most especially on the neurobehavioral development of children; vi) develop new assay methods.

It is further recommended that, in the case of brief overexposures (e.g., the chicken feed crisis in Belgium), a toxicokinetic model should be applied to estimate the resulting excess body burden as a basis for health decisions (e.g., medical follow-up, detoxification treatments).

Conclusion

The 406-page document summarized in this article is available in French.[7] An English version of the review and recommendations will be available soon.

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