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Author:	Director of the Office for Risk Assessment of the Food and Consumer Product Safety Authority
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Opinion of the Director of the Office for Risk Assessment
To the Minister of Health, Welfare and Sport and the Minister of Agriculture, Nature and Food Quality

Subject
Opinion on children and chemical substances in their diet

Introduction
In 2006 a national food consumption survey was conducted commissioned by the Minister of Health, Welfare and Sport. This food consumption survey was focused on the intake of food by young children. RIVM (National Institute of Public Health and the Environment) and RIKILT-Institute for Food Safety will use the data to calculate the exposure of children to a number of chemical substances (contaminants) and to analyse whether the exposure complies with health-based guidelines.

Request for opinion
At the request of the Ministry of Health, Welfare and Sport, the results of the food consumption survey will be used to calculate the exposure of children to different chemical substances. Ahead of this, the Ministries of Health, Welfare and Sport and Agriculture, Nature and Food Quality asked the Office for Risk Assessment of the Food and Consumer Product Safety Authority (VWA) in 2006 how to carry out an assessment of the health risks of chemical substances in the diet of children (see Annex 1 of the attached panel report).

The usual manner of a closer appraisal of health risks of chemical substances in the diet on the basis of an acceptable or tolerable daily intake (ADI or TDI) is possibly not adequate for children for several reasons. An exceedance of the ADI or TDI by children with their lower body weight may have different implications compared to adults. Also there may be a short-term exposure, while the ADI and TDI are intended for the assessment of a life-long exposure. In addition, children are still growing and body structures, organs and physiological processes have not yet been fully developed, as a result of which a specific sensitivity for external influences can occur. These aspects may not be fully covered by the ADI or TDI.

Given the importance of this subject, the question has been presented to a multidisciplinary panel of experts, chaired by Professor Dr G.J. Mulder. The panel has limited itself to the assessment of health risks for children aged from six months to twelve years. In the period up to a half year after birth a child mainly receives breastfeeding or is bottle-fed. Also the panel only considered chronic exposure to those chemical substances for which an ADI or

TDI has been derived. The most important conclusions of the panel are given below. The complete report of the panel is attached.

Detailed risk assessment in children
The panel concluded that a case by case approach by a committee of independent experts is required for a detailed assessment of possible health risks when an ADI or TDI is exceeded. According to the panel, it was not possible to develop a generic approach to assess the risk of exposure of children to chemical substances. To support the case by case approach for risk assessment when an ADI or TDI is exceeded, the panel has established a decision tree.

For a risk evaluation in children, the toxicity associated with the human developmental stage is important to consider. For this all data must be collected which are available concerning toxicokinetics, toxicodynamics, uncertainty factors and windows of exposure[1]. It is preferred to use dose response data[2] of (potential) effects in children. Nearly always, these data will not be available and animal data need to be used. To estimate the potential risk the panel considers one or two generation studies with laboratory animals the most suitable model for developing humans.

In order to assess the risk for children with these data, the panel has made a pragmatic cut-off between children aged six months up to and including four years and those of five to twelve years old. This was done because most development of children takes place before the age of five years. When evaluating health risk, special attention must be paid to possible neurological, endocrine and immunological effects in children aged six months to five years. For the period from five years special attention must be paid to the sensitivity for neurological and endocrine effects of a chemical substance.

When an assessment is made, a possible extra margin of a factor of two that is sometimes included in the ADI or TDI could be taken into account. In chronic animal tests, including the one and two generation studies, the substance under study is frequently mixed in a constant concentration in feed or drinking water. This means that the administered quantity of the test substance per kilogram body weight is twice the amount in young, weaned animals than that administered to adult animals. The ADI or TDI derived from these studies contains then in fact an additional safety factor of approximately two for young individuals.

The panel has also searched for an approach if substance-specific dose-response data are lacking or limited available and concludes that the following assumption could be justified for a toxicological effect on a continuous scale: a limited exceedance of the ADI or TDI with a factor of two to four will results in an increased size of the effect with a similar factor. This statement is based on a risk estimate using the benchmark dose method. Research has indicated that for continuous data the classic NOAEL on average corresponds with the lower confidence limit of the benchmark dose at a benchmark response of 5%. For children this assumption needs to be further supported with reproduction toxicity data.

To arrive at conclusions with respect to risks, for each situation it must be assessed with which factor the ADI or TDI is exceeded, whether there is an (additional) safety margin for young individuals (children) included in the ASDI or TDI and whether the database contains data that indicate a health risk in cases of exceedance. If no adequate reproduction toxicity data are available, the health risk in children cannot be assessed.

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1 Windows of exposure are time periods during the development of the child in which an increased sensitivity for external influences can occur.

2 Dose response data are data about the relationship between the extent of the exposure to a chemical substance (dose) and the strength of the associated health effect (response).

Recommendations
I advise you to:
- adopt the recommendations of the panel. Because of the diversity of substances, characteristics and effects, a case by case approach is required when an ADI or TDI is exceeded. An independent committee assessing the risk can use the decision tree.
- request an explanation and proper description of the uncertainties and assumptions made by the assessors for each risk assessment. This will contribute to a proper interpretation of the risk and it will increase the consistency and transparency of the policy measures that will be taken.
- generate more data relevant for children (toxicological endpoints) to support the assumption that a limited exceedance of the ADI or TDI with a factor of two to four, will result in an increased size of the toxicological, continuous effect with a similar factor.
- create an infrastructure, which will enable (confidential) data exchange, so that dose-response data that are part of non-public admission files in the medical, veterinary or phytosanitary sectors become available for this type of risk assessments.

In addition, it is important considering all relevant data when assessing the health risk of exceedances of ADIs or TDIs. Not only data obtained from studies with laboratory animals is important, also data from research into the developmental stages and toxicity in humans needs to be considered.

The Office for Risk Assessment of VWA will evaluate the use of the decision tree in the near future. The risk assessments of chemical substances in the diet of children, which will be published, by RIVM and RIKILT-Institute for Food Safety in the beginning of 2009 will be used for this evaluation. I will report on the outcome of the evaluation in 2009.

Yours sincerely,

Prof. Dr E.G. Schouten
Director Office for Risk Assessment

Attached:
- Panel report Children and chemical substances in the diet