Food and Agriculture Organization of the United Nations

World Health Organization

JOINT FAO/WHO EXPERT COMMITTEE ON FOOD ADDITIVES
Seventy-second meeting
Rome, 16–25 February 2010

SUMMARY AND CONCLUSIONS

Issued 16th March 2010

A meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA) was held in Rome, Italy, from 16 to 25 February 2010. The purpose of the meeting was to evaluate certain contaminants in food.

Professor Ron Walker, Hampshire, United Kingdom, served as Chairperson, and Mrs Inge Meyland, National Food Institute, Technical University of Denmark, Søborg, Denmark, served as Vice-Chairperson.

Dr Annika Wennberg, Nutrition and Consumer Protection Division, Food and Agriculture Organization of the United Nations, and Dr Angelika Tritscher, Department of Food Safety and Zoonoses, World Health Organization, served as Joint Secretaries.

The present meeting was the seventy-second in a series of similar meetings. The tasks before the Committee were (a) to elaborate further principles for evaluating the health risk of food contaminants and (b) to evaluate six food contaminants.

The report of the meeting will be published in the WHO Technical Report Series. Its presentation will be similar to that of previous reports—namely, general considerations, comments on specific substances and recommendations for future work.

Monographs and monograph addenda on the substances that were considered, which will include information on analytical and other technical aspects, such as effects of processing, prevention and control, concentrations in food, as well as detailed toxicological and dietary exposure assessments, will be published in a joint FAO/WHO publication under WHO Food Additives Series No. 63/ FAO JECFA Monographs 8.

More information on the work of JECFA is available at:
http://www.fao.org/ag/agn/agns/jecfa_index_en.asp and
http://www.who.int/ipcs/food/jecfa/en/index.html

1. Summary of toxicological evaluations[1]

1.1 Acrylamide

Dietary exposure estimates:
Mean 0.001 mg/kg body weight (bw) per day
High 0.004 mg/kg bw per day

Effect	NOAEL/$BMDL_{10}$ (mg/kg bw per day)	MOE at		Conclusion/comments
		Mean dietary exposure	High dietary exposure	
Morphological changes in nerves in rats	0.2 (NOAEL)	200	50	The Committee noted that while adverse neurological effects are unlikely at the estimated average exposure, morphological changes in nerves cannot be excluded for individuals with a high dietary exposure to acrylamide.
Mammary tumours in rats	0.31 ($BMDL_{10}$)	310	78	The Committee considered that for a compound that is both genotoxic and carcinogenic, these MOEs indicate a health concern.
Harderian gland tumours in mice	0.18 ($BMDL_{10}$)	180	45	

$BMDL_{10}$, lower limit on the benchmark dose for a 10% response; bw, body weight; MOE, margin of exposure; NOAEL, no-observed-adverse-effect level.

[1] See section 3 for the more detailed toxicological, epidemiological and dietary exposure evaluations and recommendations.

1.2 Arsenic

The inorganic arsenic lower limit on the benchmark dose for a 0.5% increased incidence of lung cancer ($BMDL_{0.5}$) was determined from epidemiological studies to be 3.0 µg/kg bw per day (2–7 µg/kg bw per day based on the range of estimated total dietary exposure) using a range of assumptions to estimate total dietary exposure to inorganic arsenic from drinking-water and food. The Committee noted that the provisional tolerable weekly intake (PTWI) of 15 µg/kg bw (equivalent to 2.1 µg/kg bw per day) is in the region of the $BMDL_{0.5}$ and therefore was no longer appropriate. The Committee withdrew the previous PTWI.

1.3 Deoxynivalenol (DON)

As 3-acetyl-deoxynivalenol (3-Ac-DON) is converted to deoxynivalenol (DON) in vivo and therefore contributes to the total DON-induced toxicity, the Committee decided to convert the provisional maximum tolerable daily intake (PMTDI) for DON to a group PTMDI of 1 µg/kg bw for DON and its acetylated derivatives (3-Ac-DON and 15-Ac-DON). In this regard, the Committee considered the toxicity of the acetylated derivatives equal to that of DON. The Committee concluded that, at this time, there was insufficient information to include DON-3-glucoside in the group PMTDI.

The Committee derived a group acute reference dose (ARfD) of 8 µg/kg bw for DON and its acetylated derivatives using the lowest lower limit on the benchmark dose for a 10% response ($BMDL_{10}$) of 0.21 mg/kg bw per day for emesis in pigs. Limited data from human case reports indicated that dietary exposures to DON up to 50 µg/kg bw per day are not likely to induce emesis.

The Committee concluded that all of the mean estimates of national exposure to DON were below the group PMTDI of 1 µg/kg-bw. National reports showed dietary exposures that were above 1 µg/kg-bw per day in only a few cases, only for children at upper percentiles. For acute dietary exposure, the estimate of 9 µg/kg-bw per day, based on high consumption of bread and a regulatory limit for DON of 1 mg/kg food, was close to the group ARfD.

Group PTMDI: 1 µg/kg bw for DON and its acetylated derivatives
Group ARfD: 8 µg/kg bw for DON and its acetylated derivatives

1.4 Furan

Dietary exposure estimates:
Mean 0.001 mg/kg bw per day
High 0.002 mg/kg bw per day

Effect	$BMDL_{10}$ (mg/kg bw per day)	MOE at		Conclusion/comments
		Mean dietary exposure	High dietary exposure	
Hepatocellular adenomas and carcinomas in female mice	0.96	960	480	The Committee considered that these MOEs indicate a human health concern for a carcinogenic compound that might act via a deoxyribonucleic acid (DNA)-reactive genotoxic metabolite.

$BMDL_{10}$, lower limit on the benchmark dose for a 10% response; bw, body weight; MOE, margin of exposure.

1.5 Mercury

The Committee established a PTWI for inorganic mercury of 4 µg/kg bw. The previous PTWI of 5 µg/kg bw for total mercury, established at the sixteenth meeting, was withdrawn.

The new PTWI for inorganic mercury was considered applicable to dietary exposure to total mercury from foods other than fish and shellfish. For dietary exposure to mercury from these foods the previously established PTWI for methyl mercury should be applied. The upper limits of estimates of average dietary exposure to total mercury from foods other than fish and shellfish for adults (1 µg/kg bw per week) and for children (4 µg/kg bw per week) were at or below the PTWI for inorganic mercury.

PTWI: 4 µg/kg bw for inorganic mercury

1.6 Perchlorate

The Committee established a PMTDI of 0.01 mg/kg bw for perchlorate. The estimated dietary exposures of 0.7 µg/kg bw per day (highest) and 0.1 µg/kg bw per day (mean), including both food and drinking-water, are well below the PMTDI. The Committee considered that these estimated dietary exposures were not of health concern.

PMTDI: 0.01 mg/kg bw

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2. General considerations

2.1 Modelling of dose–response data

The present meeting used dose–response modelling to evaluate exposure-related effects and to derive a point of departure (POD) for the estimation of a margin of exposure (MOE) or health-based guidance value. The method used was based on that employed at the sixty-fourth meeting of the Committee. At the present meeting, the Committee proposed and followed the steps given below:

- The data are assessed for exposure-related responses.
- The biological relevance to human health of responses found in animal studies is assessed.
- In assessment of the data from epidemiological studies, it may be necessary to make adjustments to the data that involve both the dose (e.g. to take other sources of exposure into account) and the outcome (e.g. conversion of risk per person-year to risk per person over a lifetime).
- A benchmark response (BMR) for the effects to be modelled is selected. The sixty-fourth meeting of the Committee selected a BMR of 10% for carcinogenicity data from 2-year studies in rodents, but other BMRs may be more appropriate for epidemiological studies with large numbers of subjects, for other quantal end-points or for continuous data.
- The mathematical models appropriate for the chosen end-points (continuous or quantal data) are selected.
- The models are fitted to the selected data using suitable software (United States Environmental Protection Agency BMDS and the Netherlands National Institute for Public Health and the Environment PROAST have been used by the Committee in its evaluations).
- Results from the models that provide acceptable fits are used for derivation of the POD (e.g. when the BMDS was used for furan, a *P*-value of >0.1 for the goodness of fit was used to define an acceptable fit). At both the sixty-fourth meeting and the present meeting, the lowest lower confidence limit on the benchmark dose (BMDL) from the accepted models was used, except when data from a more robust or better-designed study measuring the same response resulted in less uncertainty and a slightly higher BMDL.

In the report, the BMR(s) and software used are stated, and the effects selected for modelling and the ranges of BMDs and BMDLs estimated by the different acceptable fits are tabulated.

In the monograph, the output of the models is given in tabular and graphical forms. The table of results shows the model, the *P*-value of the goodness of fit test, the benchmark dose (BMD) and the BMDL. Ideally, the graph should show results for the model resulting in the lowest BMDL, the dose–response data with the fitted curve and the confidence intervals at different dose levels and should indicate the position of the BMD; the graph should also show the curve for the lower bound on the BMD and indicate the position of the BMDL.

The Committee recognized that use of the lowest BMDL from the accepted models could result in a POD from a less robust data set being used in preference to the BMDL from a better data set that showed a better fit and higher BMDL in the presence of a comparable BMD. The Committee was aware of developments in combining the outputs of different models to generate an average model, the output of which includes all models weighted according to their goodness of fit.

The Committee recognized that the use of dose–response modelling is a developing field and recommends to the Joint FAO/WHO Secretariat that an expert working group be established to review progress and develop detailed guidance for the application of the methods most suitable to the work of the Committee. The working group should, inter alia, address the following aspects:

- the use of constraints when modelling;
- the weighting of model outcomes and model averaging;
- goodness of fit criteria;
- how human data might be used for dose–response modelling to derive a POD;
- presentation of modelling outcomes in JECFA publications.

2.2 Dietary exposure estimates in epidemiological studies

The Committee noted that epidemiological studies sometimes rely on responses to a food frequency questionnaire (FFQ) to estimate dietary exposure to a chemical contaminant. An important limitation in the use of FFQ responses for this purpose is the potential for random exposure misclassification (also referred to as non-differential exposure misclassification). This is a non-systematic error, in that dietary exposure to the contaminant will be overestimated for some individuals and underestimated for others, but the direction and magnitude of the error are unrelated to true dietary exposure to the contaminant. Several factors contribute to this error:

- An FFQ designed to assess consumption patterns or to estimate nutrient intake might not be well suited to estimate dietary exposure to a contaminant because of the ways in which foods are grouped into categories or if the FFQ was not designed to capture information about aspects of food preparation that can affect contaminant concentration.
- An FFQ provides data only on the frequency with which a respondent consumes a particular food during a specified interval. If no information on portion size is requested from the respondent, the frequency of consumption needs to be converted to an amount of food consumed by use of standard portion sizes.
- The concentration of a contaminant in samples of a particular food is defined by a distribution rather than by a single value. The larger the variance of this distribution, the greater the error in estimating dietary exposure to a contaminant if a single (e.g. average) concentration is assigned to each food consumed.

Under most circumstances, random exposure misclassification will decrease the statistical power of hypothesis testing and bias effect estimates, such as a relative risk or an odds ratio, towards the null value (i.e. indicating the absence of association). In other words, even if a true association exists between exposure to the contaminant and the risk of an adverse health outcome, the magnitude of the association derived using FFQ responses will tend to underestimate the true magnitude of the association and to estimate it with less precision (i.e. produce a wider confidence interval). This will increase the risk of a Type II error of inference (i.e. a false negative).

As long as mean intakes are estimated correctly (i.e. the errors are not skewed in either direction), exposure misclassification will not greatly influence the dose–response relationship. However, because values in the lowest exposure category (and sometimes also in the highest exposure category) are bounded only in one direction, the most common impact of exposure misclassification is that the dose–response relationship will appear to be flatter than it really is, particularly at the low end of exposure. Background response rates and outcomes for low-dose groups will tend to be overestimated, whereas rates at high

doses may be underestimated. If the degree to which exposure misclassification occurs is known, it is possible to represent the potential impact of misclassification on dose–response modelling by conducting a bootstrap analysis in which each individual dose is treated as a source of uncertainty.

When evaluating the results of studies in which FFQ responses provided the basis for estimates of dietary exposure to a contaminant, the extent to which random exposure misclassification might have influenced the conclusions drawn must be considered.

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3. Toxicological, epidemiological and dietary exposure evaluations and recommendations on specific contaminants

3.1 Acrylamide

Explanation

Acrylamide (CH_2=CHCONH$_2$, CAS No. 79-06-01) is a water-soluble vinyl monomer that is formed during cooking in many common foods. Acrylamide is also a component of tobacco smoke. It is readily polymerizable. Polyacrylamide has multiple applications in chemical and manufacturing industries—for example, as a flocculant for clarifying drinking-water, as a sealant for construction of dams and tunnels, as a binder in the paper and pulp industry and in dye synthesis.

The sixty-fourth meeting of the Committee evaluated dietary acrylamide and recommended that it should be re-evaluated once additional information on its occurrence in food, biomarkers and toxicity became available. At the present meeting, the Committee reconsidered the studies described in the monograph of the sixty-fourth meeting as well as new information on occurrence, mitigation and dietary exposure. Additionally, the Committee considered recently completed toxicity studies, which included studies on metabolism, genotoxicity and neurodevelopmental effects following exposure to acrylamide as well as long-term/carcinogenicity studies on acrylamide and glycidamide. There were also many new epidemiological studies available for review.

Evaluation

The Committee noted that mitigation after 2003 has been reported for food types with high acrylamide levels or single products that contain higher levels within their food type. Although this might significantly reduce the exposure for some individuals or population subgroups, the Committee noted that this will have little effect on the dietary exposure of the general population in all countries. In line with this, neither the estimated average acrylamide exposure for the general population (0.001 mg/kg bw per day) nor the exposure for consumers with high dietary exposure (0.004 mg/kg bw per day) had changed since the sixty-fourth meeting. The MOE calculated relative to the no-observed-adverse-effect level (NOAEL) of 0.2 mg/kg bw per day for the most sensitive non-carcinogenic end-point—namely, morphological changes in nerves, detected by electron microscopy, in rats—therefore remains unchanged. For the general population and consumers with high dietary exposure, the MOE values are 200 and 50, respectively. Consistent with the conclusion made at the sixty-fourth meeting, the Committee noted that while adverse neurological

effects are unlikely at the estimated average exposure, morphological changes in nerves cannot be excluded for individuals with a high dietary exposure to acrylamide.

When average and high dietary exposures are compared with the $BMDL_{10}$ (the BMDL for a 10% response) of 0.31 mg/kg bw per day for the induction of mammary tumours in rats, the MOE values are 310 and 78, respectively. For Harderian gland tumours in mice, the $BMDL_{10}$ is 0.18 mg/kg bw per day, and the MOE values are 180 and 45 for average and high exposures, respectively.

The Committee considered that for a compound that is both genotoxic and carcinogenic, these MOEs indicate a human health concern. The Committee recognized that these MOE values were similar to those determined at the sixty-fourth meeting and that the extensive new data from cancer bioassays in rats and mice, physiologically based pharmacokinetic modelling of internal dosimetry, a large number of epidemiological studies and updated dietary exposure assessments support the previous evaluation.

The Committee noted that there was a poor correlation between the estimated dietary exposure and internal biological markers of acrylamide exposure (acrylamide–valine and glycidamide–valine haemoglobin adducts) in humans and that worker cohort epidemiological studies did not provide any evidence that exposure to acrylamide resulted in an increase in the incidence of cancer. To better estimate the cancer risk from acrylamide in food for humans, the Committee recommended that longitudinal studies on intra-individual levels of acrylamide and glycidamide haemoglobin adducts be measured over time in relation to concurrent dietary exposure [see also section 2.2, general considerations on dietary exposure estimates in epidemiological studies]. Such data would provide a better estimate of acrylamide exposure for epidemiological studies designed to assess the risk associated with consumption of certain foods.

3.2 Arsenic

Explanation

Arsenic is a metalloid that occurs in different inorganic and organic forms found in the environment both from natural occurrence and from anthropogenic activity. Arsenic was previously evaluated by the Committee at its tenth, twenty-seventh and thirty-third meetings. At its thirty-third meeting, the Committee assigned a provisional tolerable weekly intake (PTWI) of 0.015 mg/kg bw for inorganic arsenic, “with the clear understanding that the margin between the PTWI and intakes reported to have toxic effects in epidemiological studies was narrow”. The Committee noted that the organic forms of arsenic present in seafood needed different consideration from the inorganic arsenic in water. It concluded that