



**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 9 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 certain 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](http://www.fao.org/ag/agn/agns/jecfa_index_en.asp) and  
<http://www.who.int/ipcs/food/jecfa/en/index.html>

*An edited version of this electronic summary report will be published as part of the report of the seventy-second meeting of JECFA in the WHO Technical Report Series. Main conclusions and evaluations are reproduced here in a shorter version so that the information can be disseminated quickly. This draft will be subject to further technical editing.*

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## 1. Summary of toxicological evaluations<sup>1</sup>

### 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 <sub>10</sub> (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 <sub>10</sub> )	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 <sub>10</sub> )	180	45	

BMDL<sub>10</sub>, lower limit on the benchmark dose for a 10% response; bw, body weight; MOE, margin of exposure; NOAEL, no-observed-adverse-effect level.

### 1.2 Arsenic

The inorganic arsenic lower limit on the benchmark dose for a 0.5% increased incidence of lung cancer (BMDL<sub>0.5</sub>) was determined from epidemiological studies to be 3.0 µg/kg bw per

<sup>1</sup> See section 3 for the more detailed toxicological, epidemiological and dietary exposure evaluations and recommendations.

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<sub>0.5</sub> 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 PMTDI 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<sub>10</sub>) 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 PMTDI: 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 <sub>10</sub> (mg/kg bw per day)	MOE at		Conclusion/comments
		Mean dietary exposure	High dietary exposure	
Hepatocellular adenomas and carcinomas in female mice	1.3	1300	650	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<sub>10</sub>, 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. 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.

**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 ( $\text{CH}_2=\text{CHCONH}_2$ , 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<sub>10</sub> (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<sub>10</sub> 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 there had been no reports of ill-effects among populations consuming large quantities of fish that result in organoarsenic intakes of about 0.05 mg/kg bw per day, but further investigation would be desirable to assess the implications for human health of exposure to naturally occurring organoarsenic compounds in marine products.

Inorganic arsenic has been evaluated on a number of occasions by the International Agency for Research on Cancer (IARC). In 2010, IARC concluded that arsenic in drinking-water causes cancers of the urinary bladder, lung and skin and that the evidence was “limited” for cancers of the kidney, liver and prostate.<sup>1</sup>

At its present meeting, the Committee was asked to consider all information related to the toxicology and epidemiology, exposure assessment, including biomarker studies, analytical methodology, speciation and occurrence in food and drinking-water, in order to re-evaluate and review the PTWI. The literature relating to arsenic is extensive, and the present Committee used three recent reviews<sup>2</sup> as the starting point for its evaluation and also took into account newer studies that were considered to be informative for the evaluation.

### **Evaluation**

From epidemiological studies measuring arsenic levels in drinking-water, inorganic arsenic has been identified as a human carcinogen. It is present naturally in food and water because of geochemical conditions, and consequently exposure varies significantly in different regions and even within regions, primarily through the presence or absence of arsenic in groundwater sources for drinking-water.

The approach to quantitative assessment of cancer risk from inorganic arsenic is limited, inter alia, by the lack of information on total exposure in the available epidemiological studies, in which only levels in drinking-water were measured. The inorganic arsenic BMDL for a 0.5% increased incidence of lung cancer (BMDL<sub>0.5</sub>) was determined by using a range of assumptions to estimate exposure from drinking-water and food, with differing concentrations of inorganic arsenic. The BMDL<sub>0.5</sub> was computed 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). The

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<sup>1</sup> IARC (2010) A review of human carcinogens. C. Metals, arsenic, dusts and fibres. Lyon, International Agency for Research on Cancer (IARC Monographs 100) (in press).

<sup>2</sup> ATSDR (2007) Toxicological profile for arsenic. Atlanta, GA, United States Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry (<http://www.atsdr.cdc.gov/toxprofiles/tp2.pdf>).

EFSA (2009) Scientific opinion on arsenic in food. European Food Safety Authority Panel on Contaminants in the Food Chain (CONTAM). EFSA Journal 7(10):1351 ([http://www.efsa.europa.eu/EFSA/efsa\\_locale-1178620753812\\_1211902959840.htm](http://www.efsa.europa.eu/EFSA/efsa_locale-1178620753812_1211902959840.htm)).

IARC (2010) See reference above.

uncertainties in this BMDL relate to the assumptions regarding total exposure and to extrapolation of the BMDL<sub>0.5</sub> to other populations due to the influence of nutritional status, such as low protein intake, and other lifestyle factors on the effects observed in the studied population. The Committee noted that the PTWI of 15 µg/kg bw (2.1 µg/kg bw per day) is in the region of the BMDL<sub>0.5</sub> and therefore was no longer appropriate, and the Committee withdrew the previous PTWI.

Reported mean dietary exposure to inorganic arsenic in the United States of America (USA) and various European and Asian countries ranged from 0.1 to 3.0 µg/kg bw per day. Drinking-water was a major contributor to total inorganic arsenic dietary exposures and, depending on the concentration, can also be an important source of arsenic in food through food preparation and possibly irrigation of crops, particularly rice. The proportion of total exposure to inorganic arsenic arising from food relative to the proportion from water increases as the concentration of inorganic arsenic in the water decreases. At the lower end of the exposure range, food can also be a major contributor to total inorganic arsenic exposure.

For certain regions of the world where concentrations of inorganic arsenic in drinking-water exceed 50–100 µg/l, some epidemiological studies provide evidence of adverse effects. There are other areas where arsenic concentrations in water are elevated (e.g. above the World Health Organization guideline value of 10 µg/l) but are less than 50 µg/l. In these circumstances, there is a possibility that adverse effects could occur as a result of exposure to inorganic arsenic from water and food, but these would be at a low incidence that would be difficult to detect in epidemiological studies.

The Committee noted that more accurate information on the inorganic arsenic content of foods as they are consumed is needed to improve assessments of dietary exposures of inorganic arsenic species. Analytical constraints to achieving this goal include the lack of validated methods for selective determination of inorganic arsenic species in food matrices and the lack of certified reference materials for inorganic arsenic in foods. The proportion of inorganic arsenic in some foods was found to vary widely, indicating that dietary exposures to inorganic arsenic should be based on actual data rather than using generalized conversion factors from total arsenic measurements.

### **3.3 Deoxynivalenol (DON)**

#### **Explanation**

Deoxynivalenol (12,13-epoxy-3,4,15-trihydroxy-trichothec-9-en-8-one; DON; CAS No. 51481-10-8) is a type B trichothecene mycotoxin produced mainly in cereals by various *Fusarium* species. In addition to DON, 3-acetyl-deoxynivalenol (3-Ac-DON; CAS No. 50722-38-8) and 15-acetyl-deoxynivalenol (15-Ac-DON; CAS No. 88337-96-6) are also naturally occurring fungal secondary metabolites, whereas DON-3-glucoside is a naturally occurring conjugate of DON formed in plants.

DON was previously evaluated by the fifty-sixth meeting of the Committee. The Committee established a provisional maximum tolerable daily intake (PMTDI) of 1 µg/kg bw on the basis of the no-observed-effect level (NOEL)<sup>1</sup> of 100 µg/kg bw per day for decreased body weight gain reported in a 2-year feeding study in mice and application of a safety factor of 100. The

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<sup>1</sup> At the sixty-eighth meeting of the Committee, JECFA decided to differentiate between NOAEL and NOEL. This NOEL would now be considered a NOAEL.

Committee concluded that intake at this level would not result in effects of DON on the immune system, growth or reproduction. The Committee noted that the available data did not suggest that DON presents a carcinogenic hazard.

DON was on the agenda of the present meeting at the request of the Second Session of the Codex Committee on Contaminants in Food (CCCF), which asked the Committee to assess exposure on a more global basis, taking new data into account; to review the toxicological data and consider the need for an acute reference dose (ARfD), taking into account data in finished products, but also in raw wheat and other commodities as they are traded internationally, and consideration of processing factors; and assess the toxicity of 3-Ac-DON and 15-Ac-DON.

The Committee reviewed several new studies on metabolism and toxicokinetics, acute toxicity, genotoxicity, mechanisms of toxicity and developmental toxicity of DON and/or its acetyl derivatives. The Committee also took note of the data previously evaluated at the fifty-sixth meeting. Emphasis was given to studies in which pure DON or acetylated DON was added to defined diets in mammalian species, because naturally contaminated feed commonly contains multiple mycotoxin contaminants. Also, new information on occurrence, processing, prevention and control, and dietary exposure was considered.

### **Evaluation**

Repeated-dose short-term studies considered in the present evaluation indicated that the no-observed-(adverse-)effect level (NO(A)EL) established at the fifty-sixth meeting remains appropriate.

Since 3-Ac-DON is converted to DON in vivo and therefore contributes to the total DON-induced toxicity, the Committee decided to convert the PMTDI for DON to a group PMTDI 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 ARfD for DON and its acetylated derivatives using the lowest BMDL<sub>10</sub> of 0.21 mg/kg bw per day for emesis in pigs. The Committee considered that because DON-induced emesis is a systemic effect and more dependent on the maximum concentration in plasma ( $C_{max}$ ) than on the area under the plasma concentration–time curve (AUC), it would be appropriate to apply an uncertainty factor of 25, which is the value used by the Joint FAO/WHO Meeting on Pesticide Residues (JMPR) for acute  $C_{max}$ -dependent effects.<sup>1</sup> The Committee established a group ARfD for DON and its acetylated derivatives of 8 µg/kg bw. 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.

Estimation of dietary exposure was made using data from 42 countries, representing 10 of the 13 Global Environment Monitoring System – Food Contamination Monitoring and Assessment Programme (GEMS/Food) consumption cluster diets, and was therefore considered to be more globally representative than the previous evaluation. 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

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<sup>1</sup> FAO/WHO (2009) Pesticide residues in food—2008. Report of the Joint Meeting of the FAO Panel of Experts on Pesticide Residues in Food and the Environment and WHO the Core Assessment Group. FAO Plant Production and Protection Paper, 193.

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.

The acetylated derivatives have not been included in the estimates of dietary exposure to DON prepared at this meeting. The Committee noted that, in general, they are found at levels less than 10% of those for DON, and inclusion would not be expected to significantly change the estimates of dietary exposure to DON. Data are limited on the occurrence of DON-3-glucoside, which might be an important contributor to dietary exposure; this derivative was also not included in the dietary exposure estimates.

### **3.4 Furan**

#### **Explanation**

Furan (C<sub>4</sub>H<sub>4</sub>O) (CAS No. 110-00-9) is a highly volatile cyclic ether that can be formed unintentionally in foods during processing from precursors that are natural food components. Information available to the Committee at its present meeting suggested that the major route of exposure to furan in the human population is through consumption of heat-treated foods and beverages.

Furan has not been evaluated previously by the Committee. The request for a full evaluation of furan originated from the Second Session of CCCF.

#### **Evaluation**

MOEs were calculated at dietary exposures of 0.001 mg/kg bw per day, to represent the average dietary exposure to furan for the general population, and 0.002 mg/kg bw per day, to represent the dietary exposure to furan for consumers with high dietary exposure. This estimate will also cover dietary exposure of children. Comparison of these dietary exposures with the BMDL<sub>10</sub> of 1.3 mg/kg bw per day for induction of hepatocellular adenomas and carcinomas in female mice gives MOEs of 1300 and 650 for average and high dietary exposures, respectively. The Committee considered that these MOEs indicate a human health concern for a carcinogenic compound that might act via a DNA-reactive genotoxic metabolite.

The furan levels can be reduced in some foods through volatilization (e.g. by heating and stirring canned or jarred foods in an open saucepan). However, there is currently a lack of quantitative data for all foods, and no information is available on other mitigation methods.

### **3.5 Mercury**

#### **Explanation**

Mercury occurs naturally in the earth's crust, usually in the form of the mineral cinnabar (mercury(II) sulfide). It can be released into the global environment through a number of processes, both natural and anthropogenic. While relatively chemically inert, mercury occurs in three valence states: elemental mercury (also known as metallic mercury), the monovalent mercurous ion and the divalent mercuric ion, elemental mercury and the divalent ion being the most important in nature. There are several organic mercury compounds; by far the most common in the environment and in the aquatic food-chain is methylmercury.

Mercury has previously been evaluated by the Committee. At its sixteenth meeting, the Committee established a PTWI of 0.3 mg of total mercury (5 µg/kg bw), of which no more than 0.2 mg (3.3 µg/kg bw) should be in the form of methylmercury, based primarily on the

relationship between the intake of mercury from fish and mercury levels in blood and hair associated with the onset of clinical disease. The sixteenth meeting of the Committee noted that almost all dietary exposure to methylmercury is from fish and seafood and that methylmercury is probably by far the most toxic form of mercury in food; therefore, other forms of mercury could be given less weight when establishing a tolerable intake for mercury. The original PTWI for methylmercury (3.3 µg/kg bw) was revised at the sixty-first meeting to 1.6 µg/kg bw, based on an assessment of results from various epidemiological studies involving fish-eating populations and developmental neurotoxicity. At the sixty-seventh meeting, the Committee provided further clarifications as to the relevance of the new methylmercury PTWI for different subgroups of the population.

At the sixty-first meeting, the Committee recommended that the total mercury PTWI be reviewed.

### **Evaluation**

The Committee noted that there was a lack of quantitative data on methylmercury in non-fish products and on inorganic mercury in foods in general.

The Committee assumed that the predominant form of mercury in foods other than fish and shellfish is inorganic mercury. Although data on speciation of inorganic mercury in foods are limited, the Committee agreed that the toxicological database for mercury(II) chloride was relevant for assessing the health risk of foodborne inorganic mercury. The United States National Toxicology Program bioassay provided limited evidence for carcinogenicity; however, direct reaction of mercury(II) chloride with deoxyribonucleic acid (DNA) has not been demonstrated. Therefore, setting a health-based guidance value was considered appropriate.

The lowest BMDL<sub>10</sub> for relative kidney weight increase in male rats was calculated to be 0.11 mg/kg bw per day as mercury(II) chloride. This corresponds to 0.06 mg/kg bw per day as mercury, adjusted from a 5 day per week dosing schedule to an average daily dose and for the percent contribution of inorganic mercury to dose. After application of a 100-fold uncertainty factor, the Committee established a PTWI for inorganic mercury of 4 µg/kg bw (rounded to one significant figure).

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

In the absence of evidence to the contrary, the new PTWI for inorganic mercury was considered applicable to dietary exposure to total mercury from foods other than fish and shellfish. 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.

## **3.6 Perchlorate**

### **Explanation**

The perchlorate ion (ClO<sub>4</sub><sup>-</sup>) is very stable in water, and its salts are highly soluble in water. Perchlorate occurs naturally in the environment, in deposits of nitrate and potash, and can be formed in the atmosphere and precipitate into soil and groundwater. It also occurs as an environmental contaminant arising from the use of nitrate fertilizers and from the manufacture, use and disposal of ammonium perchlorate (CAS No. 7790-98-9) used in rocket propellants, explosives, fireworks, flares and air-bag inflators and in other industrial

processes. Perchlorate can also be formed during the degradation of sodium hypochlorite used to disinfect water and can contaminate the water supply. Water, soil and fertilizers are considered to be potential sources of perchlorate contamination in food. Potassium perchlorate (CAS No. 7778-74-7) has been used as a human therapeutic medicine to treat thyroid disease.

Perchlorate has not been previously evaluated by the Committee. It was referred to the Committee for evaluation on request of the Second Session of CCCF.

### **Evaluation**

The primary effect of perchlorate is its ability to competitively inhibit uptake of iodide by the thyroid gland.

As perchlorate has a very short half-life and is rapidly cleared from the body, it is considered appropriate to derive a PMTDI. The BMDL<sub>50</sub> of 0.11 mg/kg bw per day for inhibition of uptake of radiolabelled iodide by the thyroid in a clinical study in healthy adult volunteers was chosen as the POD for derivation of a PMTDI. As it is based on human data, there is no need to apply any interspecies uncertainty factor.

The Committee noted that the BMDL<sub>50</sub> was derived from a study of relatively short duration but that there are efficient homeostatic mechanisms to cope with short-term and long-term inhibition of iodide uptake, up to (at least) 50%, in healthy children and adults. The Committee also noted that there is at least a 4-fold margin between the value of the BMDL<sub>50</sub> and the estimate of >0.4 mg/kg bw per day that would probably be necessary as a sustained exposure in order to trigger hypothyroidism in normal adults. The Committee therefore concluded that it was not necessary to apply an uncertainty factor to account for the short duration of the pivotal study.

In considering the size of any necessary uncertainty factor for inter-individual human differences, the Committee took account of the fact that the effect of perchlorate on inhibition of iodide uptake by the thyroid and on the subsequent synthesis of thyroid hormones in potentially vulnerable groups—such as pregnant women, fetuses, neonates and young infants, those with iodine-deficient diets and those with clinical or subclinical hypothyroidism—may differ from that in healthy adults. The Committee concluded that an uncertainty factor of 10 would be appropriate to cover any differences in the general population, including those in potentially vulnerable subgroups. Applying this 10-fold factor to the BMDL<sub>50</sub> and rounding to one significant figure, a PMTDI of 0.01 mg/kg bw was established 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.

## Annex 1: Participants

### Seventy-second meeting of the Joint FAO/WHO Expert Committee on Food Additives Rome, 16–25 February 2010

#### Members

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Mrs I. Meyland, National Food Institute, Technical University of Denmark, Søborg, Denmark (*Vice-Chairperson*)  
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Professor A.G. Renwick, School of Medicine, University of Southampton, Ulverston, United Kingdom (*Joint Rapporteur*)  
Dr S. Resnik, Tecnología de Alimentos, Departamento de Industrias, Facultad de ciencias Exactas y Naturales, Ciudad Universitaria, Buenos Aires, Argentina (*unable to attend*)  
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Dr G.S. Shephard, Programme on Mycotoxins and Experimental Carcinogenesis, Medical Research Council, Tygerberg, South Africa (*Joint Rapporteur*)  
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