



FAO/WHO Consultation on the Health Implications of Acrylamide in Food Geneva, 25-27 June 2002

Summary Report¹

INTRODUCTION

In April 2002 the Swedish National Food Administration (NFA) and researchers from Stockholm University announced their findings that acrylamide, a toxic and potentially cancer-causing chemical, is formed in many types of food prepared/cooked at high temperatures. The NFA informed regional and international authorities and organizations about their findings in order to initiate international collaboration as a priority concern. Moreover, international initiatives to commence multidisciplinary research were viewed as urgently needed as the formation of acrylamide during the cooking process may be a widespread phenomenon.

In light of concern expressed by member countries, a Consultation was convened jointly by the Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO). The Consultation was held at WHO Headquarters in Geneva, Switzerland on 25-27 June 2002. A list of participants and agenda as adopted are provided in Annexes 1 and 2, respectively. Dr Dieter Arnold, Acting Director, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Berlin, Germany served as Chairman.

The Consultation was opened by Dr David Nabarro, Executive Director of the Cluster on Sustainable Development and Healthy Environments and Senior Policy Adviser to the WHO Director General, who emphasized that in addition to the evaluation of specific scientific aspects of acrylamide in food, governments, industry and consumers were looking forward to any interim advice that could be offered, particularly in the light of the lack of adequate data and the limited understanding of many of the processes involved.

¹ This summary report contains the collective views of an international group of experts, and does not necessarily represent the decisions or the stated policy of the Food and Agriculture Organization of the United Nations and the World Health Organization. The full report will be issued in due course.

The objectives of the Consultation were:

1. To review and evaluate new and existing data and research on acrylamide relevant to:
 - toxicology, especially carcinogenicity and neurotoxicity;
 - epidemiology;
 - exposure assessment;
 - analytical methodology; and
 - formation, fate and bioavailability of acrylamide in cooked food.
2. To identify needs for further information and studies; and
3. To develop and suggest possible interim advice for governments, industry and consumers.

The Consultation reviewed the health significance of the presence of acrylamide in foods on the basis of known international assessment reports, specific background papers prepared in advance by invited experts and on the available new data and publications. A list of the major documents available to the Consultation can be accessed on the WHO Web site (<http://who.int/fsf>). Note that individual documents are not specifically referred to in these texts, nor are they exhaustively summarized in this report.

EXECUTIVE SUMMARY

The FAO/WHO Consultation on Health Implications of Acrylamide in Food has undertaken a preliminary evaluation of new and existing data and research on acrylamide. The following main conclusions were reached:

Methods of analysis for acrylamide

By current standards of analytical science, the recent findings of acrylamide in foodstuffs are reliable. None of the methods used to measure acrylamide in foodstuffs has yet been fully validated by inter-laboratory collaborative trials. However, most methods fulfil the requirements of single-laboratory (“in-house”) validation and accreditation.

Formation and fate of acrylamide in food

Acrylamide has been found in certain foods that have been cooked and processed at high temperatures, and the levels of acrylamide increase with the time of heating. However, the mechanisms of formation of acrylamide in food are poorly understood.

Exposure assessment

Based on the available data, food is estimated to make a significant contribution to total exposure of the general public to acrylamide. Average intakes for the general population were estimated to be in the range of 0.3 to 0.8 microgram of acrylamide intake per kilogram of body weight per day. Within a population, it is anticipated that children will generally have intakes that are two to three times those of adults when expressed on a body weight basis. Dietary intakes of acrylamide by some consumers may be several times higher than the average.

Non-cancer toxicology

Neurotoxicity is the key non-cancer, non- genotoxic effect of acrylamide in humans and animals. No neurotoxic effects are to be expected from the levels of acrylamide encountered in food.

Genotoxicity

Acrylamide may induce heritable damage.

Carcinogenicity

Acrylamide has a carcinogenic potency in rats that is similar to that of other carcinogens in food, but the intake levels for acrylamide are likely to be higher. For humans, the relative potencies of cancer-causing agents in food are not known. Only limited human population data are available for acrylamide and these provide no evidence of cancer risk from occupational exposure. All such studies have limited power to detect small increases in tumour incidence. The Consultation recognized the presence of acrylamide in food as a major concern in humans based on the ability to induce cancer and heritable mutations in laboratory animals.

Need for further information and provision of interim advice

The Consultation provided a range of recommendations for further information and new studies to better understand the risk to human health posed by acrylamide in food. The Consultation also provided some advice to minimize whatever risk exists, including avoiding excessive cooking of food*, choosing healthy eating, investigating possibilities for reducing levels of acrylamide in food, and establishing an international network on acrylamide in food.

* However, all food - particularly meat and meat products - should be cooked thoroughly to destroy foodborne pathogens.

CONCLUSIONS AND RECOMMENDATIONS

Methods of analysis

Sensitive and reliable methods are available to identify and measure acrylamide in foodstuffs. The measurement uncertainty of the methods is small in relation to the between-sample and the within-lot variability expected for acrylamide levels. Methods are also available to determine biomarker adducts as an alternative means to assess exposure. Interlaboratory validation of analytical methods and the preparation of reference materials and standards for proficiency testing, is desirable. There is a need to develop simple low-cost method(s) to be used for routine monitoring.

- Interlaboratory validation of analytical methods covering a range of different food types should be conducted.
- Reference materials and standards for proficiency testing should be prepared and distributed.
- Low-cost and simple method(s) for routine monitoring of acrylamide in food should be developed.

Modes of formation, fate and levels of acrylamide in food

Acrylamide is formed when some foods are cooked or processed at high temperatures. It seems to arise when different food components react together. These may be carbohydrates, proteins and amino acids, lipids, and possibly other minor food components also. The reaction is promoted by heating and increases with the time of heating. It is not yet clear what combinations of food components are involved and it may well be that the situation is complex with many mechanisms operating. The situation is further complicated by the fact that acrylamide is a volatile and reactive substance that could itself be partially lost after formation. With the limited data available so far, it is not possible to identify any specific routes of formation nor exclude any possibilities. To understand completely the formation and fate of acrylamide in heated foods it will be necessary to conduct hypothesis-driven model studies coupled with a systematic examination of the relation between acrylamide levels and processing/cooking conditions. This understanding would allow formulation, processing and cooking conditions to be optimised to minimise and possibly eliminate acrylamide levels in heated foods.

- The relation between acrylamide levels and processing/cooking conditions should be systematically examined.
- Hypothesis-driven model studies are needed to elucidate sources, mechanism(s) of formation and fate of acrylamide in heated foodstuffs
- Optimization of formulation, processing and cooking conditions to minimize and possibly eliminate acrylamide levels in foods prepared industrially and at home should be investigated
- The range of foods investigated needs to be extended to include staple foods from different regions and diets.

Dietary intake

The range of levels of acrylamide found in foods was broad and the determinants of variability unknown. The foods that have been analysed to date represent only a portion of the total diet and do not include foods representative of those consumed in developing countries (see Annex 3). Nonetheless, based on the available data, food appears to contribute a significant proportion of total exposure. Based on the estimates of biomarkers of exposure (haemoglobin adducts), it seems likely that there are other important sources as well. Additional foodstuffs may be found to contain residues.

The available data allowed the Consultation to make only an order-of-magnitude estimate of average long-term dietary intakes of acrylamide in developed countries, which would be 0.3 to 0.8 µg/kg body weight/day. Within a population, it is anticipated that children will generally have exposures two to three times those of adult consumers when expressed on a body weight basis. Although there was inadequate data to reliably estimate exposure for high consumers, their exposure could be several times the mean exposure.

- Further data on the levels of acrylamide in food, particularly staple foods consumed in developing countries, needs to be obtained in order to refine the estimates of dietary exposure.
- An understanding of the mechanisms of formation and fate of acrylamide in foods would help identify those foods (in addition to the starchy foods analysed to date) that are likely to make a major contribution to dietary intakes of acrylamide.
- Information on how food is cooked and processed (domestic and industrial) should be collected to permit reliable estimation of acrylamide intake.
- In collecting data the emphasis should be on foodstuffs contributing most to exposure. In addition to food with the highest values, foods with lower values but high levels of consumption should be sampled. Attention should be paid to the sampling procedures to ensure that representative data are obtained.
- A consistent system for collecting and describing the available data should be used. The GEMS/Food Programme could provide a structure for data collection and reports and the GEMS/Food Regional Diets (<http://who.int/fsf/GEMS/index.htm>) could provide an indication of important staple foods in each of the regions of the world. National governments may collect data with additional details.
- Developing and other countries with insufficient information for determining population-level dietary exposures to acrylamide should consider generating interim information relevant to their own circumstances. This could include analysing total diet study samples, where they are available, for acrylamide, as the basis for estimating per capita dietary intake estimate; determining levels of acrylamide in a limited range of staple foods prepared in ways that reflect common domestic practice; and, analysing blood or urinary biomarkers of exposure.
- Given the state of knowledge on methods of formation and levels of acrylamide in food, biomarkers of exposure are likely to provide the most direct means of evaluating exposures to acrylamide from food and other sources. These biomarkers need to be evaluated and calibrated, and their correlation with dietary intakes should be investigated.
- Other sources of exposure to humans to acrylamide should be investigated to better define the relative contribution of food, smoking and other sources including the potential for endogenous formation of acrylamide.

Toxicology of acrylamide

Considered collectively, data on the absorption, metabolism, distribution and excretion of acrylamide suggest that toxicological findings in animals should be assumed to be relevant for extrapolation to humans.

The Consultation recognized neurotoxicity as the key non-cancer, non-genotoxic effect of acrylamide in humans. Effects on fertility have also been recognized in animals. Single exposures to large doses of acrylamide to humans and animals induce changes in the central nervous system while prolonged exposure to low levels (of relevance to the present risk assessment) result in peripheral neuropathy in the presence or absence of central nervous system involvement. Given the lack of dose-response data for human neurotoxicity, the risk assessment was based on rodent studies, and supported by primate studies of acrylamide neuropathy. Based on these data, the Consultation concluded that the no observed adverse effect level (NOAEL) for acrylamide neuropathy is 0.5 mg/kg body weight/day. The NOAEL for fertility changes is four times higher than for peripheral neuropathy. On the basis of current knowledge, controlling for peripheral neuropathy is expected to control for effects on fertility. The estimated average chronic human dietary intake is in the order of 1 µg/kg body weight/day. This provides a margin between exposure and the NOAEL of 500.

Greater understanding of the hierarchy of target organ toxicity would permit a refinement of the risk assessment for the non-cancer effects of acrylamide. In particular, the relative impacts of acrylamide on the peripheral nervous system, and the central nervous system and fertility would be helpful. Assessment of the impact of acrylamide on the endocrine system also warrants further investigation.

Acrylamide is genotoxic *in vivo* in somatic cells and germ cells, therefore acrylamide has the potential to induce heritable damage at gene and chromosome level. It is known to be metabolised to glycidamide, a chemically reactive epoxide that forms DNA adducts. The findings that acrylamide induces tumours both in rats and mice at a number of different sites are consistent with a genotoxic mode of action of the chemical. While suggestions have been made that additional modes of action might contribute to the observed spectrum of tumours seen in acrylamide treated rats, especially tumours of hormone-responsive tissues, these suggestions are speculative only. In conclusion, the Consultation endorsed the IARC classification Group 2A that acrylamide is probably carcinogenic to humans.

Generally, introduction of genotoxic and carcinogenic substances into food during manufacturing is prohibited by regulations. However, certain carcinogens are formed in food as a result of cooking, such as benzo[*a*]pyrene and heterocyclic aromatic amines, and because of their formation in domestic settings such chemicals cannot always be controlled. It has recently been discovered that acrylamide is also formed in food cooked in certain ways. These are all genotoxic and carcinogenic substances and are considered to be without a threshold for their action on DNA. For such compounds it is generally recommended that exposures should be as low as reasonably achievable (ALARA). Another approach is to estimate carcinogenic risks. Ideally, such an assessment should be based on extensive epidemiological data that contain both accurate determinations of exposure and the tumour incidence in the exposed human population. Such data are rarely available.

All epidemiological studies have limited power to detect small increases in tumour incidence. Negative epidemiological studies may therefore provide an upper-bound to possible carcinogenic

effects, rather than proof that no such effects exist. Only limited epidemiological data are available for acrylamide, and these provided no evidence of increased cancer risk from occupational exposures.

If experimental animal carcinogenicity data are to be used to estimate human cancer risk, extrapolation has usually to be done over several orders of magnitude down to the human exposure level arising from food. To do so, different mathematical models have been used. The Consultation noted, however, that it is not known whether a given model actually reflects the underlying biological processes. The numerical estimate of risk obtained is critically dependent on which model is used.

The Consultation noted that several efforts have been made to use such models to quantify the risk posed by acrylamide in food. The Consultation did not reach consensus on how quantitative risk assessment based on animal data should be used to estimate human cancer risk from acrylamide in food.

Acrylamide has a carcinogenic potency in rats that is similar to that of other carcinogens in food as mentioned above, but the intake levels for acrylamide are likely to be higher. For humans, the relative potencies of cancer-causing agents in food are not known. The Consultation recognized the presence of acrylamide in food as a major concern in humans, given its ability to induce cancers and heritable mutations in laboratory animals.

- More data are required on the absorption, metabolism, distribution and excretion of acrylamide in humans by the oral route to permit more informed estimates of risk to humans
- The formation of glycidamide and binding to DNA as a marker of toxicity and carcinogenicity risk needs to be better defined.
- The bioavailability of acrylamide from food should be determined.
- Risk factors of susceptibility such as genetically-based differences in metabolism and the impact of age, sex or other factors that contribute to risk should be characterized.
- Cancer epidemiology and testicular toxicity in populations of known high exposure, such as occupationally exposed workers with neurotoxic signs and high levels of haemoglobin adducts, should be studied.
- Quantitative risk assessment models should be investigated on the basis of scientific merit and uncertainty of estimates.
- The toxicity and carcinogenicity of glycidamide need to be studied.
- The dose-response characteristics of acrylamide and glycidamide relative to toxicity, disposition, and binding to DNA and macromolecules need to be further assessed.
- Mechanisms of action and dose response characteristics for the effects of acrylamide and glycidamide on germ cell damage should be studied.
- Genotoxic effects on somatic and germ cells using genome-wide expression profiling should be studied.
- The relationship between adducts with haemoglobin and DNA in different organs should be explored.
- Application of new methods in biological research may be helpful in clarifying whether it is possible to establish a threshold for the genotoxicity of acrylamide.

Interim advice

The information on the levels of acrylamide in food is far from complete. Although the magnitude of the cancer risk posed by acrylamide in food was not quantified, the Consultation noted that several principles can be applied now to minimize whatever risk exists:

- Food should not be cooked excessively, i.e. for too long or at too high a temperature. However, all food - particularly meat and meat products - should be cooked thoroughly to destroy foodborne pathogens.
- The information available on acrylamide so far reinforces general advice on healthy eating. People should eat a balanced and varied diet, which includes plenty of fruit and vegetables, and should moderate their consumption of fried and fatty foods.
- The possibilities for reducing the levels of acrylamide in food by changes in formulation, processing and other practices should be investigated.
- An international network "Acrylamide in Food" should be established inviting all interested parties to share relevant data as well as ongoing investigations.

Risk communication

The Consultation would encourage transparent and open risk assessment and risk management processes and recognises the importance of involving interested parties (consumer, industry, retail etc.) in this process at some stages. Risk communication policy could facilitate the crucial communication process between risk assessor and risk manager and among all parties involved.

**FAO/WHO Consultation on the
Health Implications of Acrylamide in Food
25 - 27 June 2002, Geneva, Switzerland**

List of Participants

- Dr G. Adegoke**, Professor, Department of Food Science and Technology, University of Ibadan, Ibadan, Nigeria
- Dr D. Arnold**, Acting Director, Federal Institute for Health Protection of Consumers and Veterinary Medicine, Berlin, Germany (Chairman)
- Dr R.A. Canady**, Toxicologist, Hazard Assessment Branch, Division of Risk Assessment, Center for Food Safety and Applied Nutrition, US Food and Drug Administration, College Park, Maryland, USA
- Dr A. Carere**, Istituto Superiore di Sanita, Laboratorio de Tossicologia comparata ed Ecotossicologia, Rome, Italy
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- Dr M.A. Friedman**, Consultant Toxicologist, Oviedo, Florida, USA
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- Dr M. Hirose**, National Institute of Health Sciences, Tokyo, Japan
- Dr A.G.A.C. Knaap**, Centre for Substances and Risk Assessment, National Institute of Public Health and the Environment, Bilthoven, Netherlands
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Ms C. Vickers, Chemical Safety, World Health Organization, Geneva, Switzerland (WHO Co-Secretary)

**FAO/WHO Consultation on the
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25 - 27 June 2002, Geneva, Switzerland**

Agenda

Tuesday, 25 June

9:00 - 12:30

Welcome
Introduction of Participants
Election of Chair and Appointment of Rapporteur
Housekeeping announcements
Adoption of Agenda
Introduction of Background Papers
Briefing for Working Groups

14:00 - 17:30 Working Groups on:

- Toxicology, in particular neurotoxicology
- Carcinogenicity, including epidemiology
- Methods of analysis, formation and fate of acrylamide in food
- Dietary exposure, including levels in food, as well as other potential exposures

Wednesday, 26 June

9:00 – 9.30

Plenary progress report from Working Groups

9.30 –12:30

Working Groups continued

14:00 - 17:30

Plenary discussion of draft Working Group reports and interim risk management advice to governments, industry and consumers

Thursday, 27 June

9:30 - 12:30

Plenary discussion of recommendations, including data needs and further studies

14:00 - 15:30

Adoption of report and other communication outputs of the meeting
Next Steps

ANNEX 3

Acrylamide levels in different foods and food product groups from Norway, Sweden, Switzerland, the United Kingdom and the United States of America

Food/Product Group	Acrylamide levels ($\mu\text{g}/\text{kg}$) ¹			
	Mean ²	Median ²	Minimum – Maximum	Number of samples
Crisps, potato/sweet potato ³	1312	1343	170 - 2287	38
Chips, potato ⁴	537	330	<50 - 3500	39
Batter based products	36	36	<30 - 42	2
Bakery products	112	<50	<50 - 450	19
Biscuits, crackers, toast, bread crisps	423	142	<30 - 3200	58
Breakfast cereals	298	150	<30 - 1346	29
Crisps, corn	218	167	34 - 416	7
Bread, soft	50	30	<30 - 162	41
Fish and seafood products, crumbed, battered	35	35	30 - 39	4
Poultry or game, crumbed, battered	52	52	39 - 64	2
Instant malt drinks	50	50	<50 - 70	3
Chocolate powder	75	75	<50 - 100	2
Coffee powder	200	200	170 - 230	3
Beer	<30	<30	<30	1

¹ The limits of detection and quantification varied among laboratories; values reported as less than a value are below the limit reported by the laboratory.

² Mean and median were calculated where individual data were available; samples sizes were extremely small particularly for some food categories; where the mean and median are different it reflects the skewed distribution of the underlying data that were collected in different countries and may represent different food items within the larger category.

³ Products that are thinly sliced and fried (Includes foods called potato chips in some regions including North America)

⁴ Products that are more thickly sliced (Includes foods called French fries in some regions including North America)