CONSULTATIONS AND WORKSHOPS

Health Implications of Acrylamide in Food

Report of a Joint FAO/WHO Consultation
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FOOD SAFETY PROGRAMME
DEPARTMENT OF PROTECTION OF THE HUMAN ENVIRONMENT
WORLD HEALTH ORGANIZATION

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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.

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

1. BACKGROUND

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. Moreover, international initiatives to commence multidisciplinary research were viewed as urgently needed as the formation of acrylamide during the cooking process was likely to be a general 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. Dr Marvin Friedman, an expert in the field of acrylamide toxicity, who had worked for the acrylamide industry, did not participate in those sessions where the conclusions and recommendations were agreed. This course of action was agreed on, with WHO, prior to the Consultation.

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. Dr Nabarro 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 paucity of adequate data and the limited understanding of many of the processes involved.

2. OBJECTIVES OF THE CONSULTATION

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 is provided in Annex 3. Note that individual documents are not specifically referred to in these texts, nor are they exhaustively summarized in this report. A list of abbreviations used in this report is at Annex 4.

3. METHODS OF ANALYSIS

3.1 Introduction

The Consultation reviewed the methods of analysis available to test for acrylamide in foodstuffs and food ingredients, and for acrylamide and its metabolites as haemoglobin adducts in blood.

3.2. Foodstuffs and food ingredients

3.2.1. Sampling

Levels of acrylamide can vary considerably in foods, seemingly due to the processing or cooking conditions used and the temperature achieved. Consequently, there can be considerable variability from product to product and even concentration hot-spots within an individual food item. The whole food item or package should be homogenized before sub-sampling and a representative portion taken for analysis. For the foodstuffs investigated to date, there have been no problems reported of significant losses during storage and homogenization of the sample prior to analysis.

3.2.2. Extraction

Free acrylamide is extracted from the sample using cold or hot water. It has been demonstrated, by adding known amounts of acrylamide standard to the sample before extraction, that these extraction procedures give complete recovery. Many sample extracts can be analysed directly, however some sample types benefit from further cleanup and concentration of the extract. It is desirable to add an internal standard to the food sample at the outset, as an internal standard compensates for any recovery losses in these steps and helps to ensure that results are reliable.

3.2.3. Gas chromatography/mass spectrometry (GC-MS)

Although acrylamide can be analyzed as such, without derivatization, when using GC-MS, the molecule is normally brominated to form a derivative that has improved GC properties. The acrylamide derivative is identified by its retention time and by the ratio of characteristic MS ions. Once the identity of acrylamide has been established in a particular type of food, it may be possible to use gas chromatography with electron capture detection (ECD) or other selective detection techniques to routinely monitor levels, although with this analytical technique the identification rests on the retention time alone. The lowest level that can be measured when using GC-MS is in the range of 5 to 10 µg/kg.

3.2.4. Liquid chromatography/tandem mass spectrometry (LC-MS/MS)

Because there had been concerns about possible artefact formation during the bromination procedure, LC-MS/MS methods were developed for the direct analysis of acrylamide without the need to derivatize. Identification of the substance is by its retention time and by the relative ion intensities. The limit of measurement using LC-MS/MS is about 20 to 50 μg/kg.

3.2.5 Identification of acrylamide

When the same food sample is extracted and analyzed by both methods described, there is generally excellent agreement between the results and the putative acrylamide fulfils the identification criteria in both techniques. This provides added confidence in the qualitative and quantitative results to date. By modern standards of analytical evidence, the identification of acrylamide in foodstuffs is highly reliable.

3.2.6. Data quality

None of the methods used to measure acrylamide in foodstuffs has been fully validated by interlaboratory collaborative trials. However, some methods fulfil the requirements of single-laboratory ("in-house") validation and accreditation. Additionally, some samples have been analyzed by different laboratories using the same method, or by one laboratory using different methods, and there has generally been good agreement. It is considered that the measurement uncertainty is small in relation to the large variability that appears to occur even between different batches of the same product. Therefore, there seems to be no reason at this time to reject any of the limited data available on acrylamide concentrations in foods, or to exclude these data from a preliminary assessment of exposure.

3.3 Determination of biomarkers of exposure

Acrylamide and its metabolite, glycidamide, react readily with a number of biomolecules including haemoglobin. GC-MS methods for the determination of the adducts of acrylamide and glycidamide with haemoglobin have been reported. The sensitivity of these GC-MS methods is such that the adducts can be measured at concentrations in the blood that are relevant to possible dietary exposure to acrylamide. Consequently, the adducts can be used as biomarkers of exposure. In fact, it was the observation of unexplained levels of haemoglobin adducts that gave the first clue that there may be an unknown source of exposure, now generally agreed to be acrylamide in heated foods. The biomarker adducts can give a time-averaged estimate of exposure and are complementary to exposure estimates derived from food analysis and food consumption statistics. Where this comparison has been made the results from both approaches have been comparable. This adds further weight to the validity, both of the biomarker approach. The widespread use of this biomarker approach is limited at present because calibration standards are not generally available. Other approaches, such as using urinary biomarkers, may also lend themselves to possible use.

4.   FORMATION AND FATE OF ACRYLAMIDE IN FOOD

4.1   Introduction

Of the limited range and number of foods analysed to date, acrylamide levels are highest in potato and cereal-based products subjected to heat processing such as frying, grilling or baking. Lower levels have also been found in some other heat-processed foods. However, only a limited range of food types have been tested to date and these belong to the Western diet.

4.2   Chemistry of formation

Acrylamide is a small and simple molecule. It could be formed in heated foods via several different mechanisms, which may involve reactions of carbohydrates, proteins and amino acids, lipids and possibly other minor food components. Some of the most commonly-proposed possibilities are:

- Formation via acrolein or acrylic acid which may be derived from the degradation of lipid, carbohydrates or free amino acids;

- Formation via the dehydration/decarboxylation of certain common organic acids including malic acid, lactic acid and citric acid; and

- Direct formation from amino acids.

In the first two cases the source of the nitrogen in the acrylamide molecule is possibly ammonia released in deamination processes.

As no systematic studies have yet been reported, there is no evidence to identify any specific routes of formation, nor to exclude any possibilities. Acrylamide could also originate from non-food sources. Most probably a multitude of reaction mechanisms is involved, depending on the food composition and processing conditions. This makes it difficult at present to draw conclusions on the influence of various food processes or make recommendations on how to minimise acrylamide levels.

The few observations that have been made strongly indicate that temperature and duration of heat processing are important factors. Acrylamide levels rise very strongly with time when potato chips are fried. Similarly, a 10 to 20-fold increase in acrylamide levels has been reported between cooked and over-cooked fried potatoes. In contrast, acrylamide formation has not been demonstrated at temperatures below 120°C.

The formation of acrylamide appears to be a surface phenomenon and water content may also be an important factor. In these two respects, there are similarities with the browning reactions that take place when heating foods (the so-called Maillard reaction) and this possible link should be investigated.

4.3   Fate in food

Acrylamide is known to be a highly reactive molecule. It can react by ionic and by free-radical mechanisms and its presence, in free form, in food, was therefore unexpected. The observation of relatively high levels in certain foods rich in carbohydrates, and lower levels in protein-rich foods, may reflect the relative ease of formation in the former, or it may be due to volatilization

or further reactions between acrylamide and food components in the latter. It is expected that acrylamide could react with any major or minor food component containing thiol, amino and, to a much lesser extent, hydroxyl groups. This complication, with the formation of acrylamide possibly being offset by disappearance pathways, means that it may be very difficult, if not impossible, to understand the mechanism(s) of formation based only on consideration of levels in foodstuffs. It will be necessary to conduct hypothesis-driven model studies, coupled with a systematic examination of the relationship between acrylamide levels and processing/cooking conditions.

5.   DIETARY EXPOSURE

5.1   Introduction

Although there are likely to be multiple sources of acrylamide exposure, this assessment focused on intakes due to the presence of acrylamide in foods. There has been intense activity in the two months since the April 2002 report by the Swedish National Food Administration that acrylamide is present in a range of fried, baked and heat-processed starchy foods at levels not previously determined. Other researchers have subsequently verified these findings successfully, providing additional information on the levels of acrylamide in different foods.

The amount of information does, however, remain both small in size – only around 250 data points – and limited in scope. Only a limited number of samples of starchy foods, not in any sense representative of the products available to consumers, have been analyzed. No data are available for many countries. The range of levels of acrylamide found in each of the several types of food (potato crisps, breakfast cereals, etc.) is broad and there is not a good understanding of the determinants of this variability. These foods only provide a part of the average energy intake in developed countries and the amount of information that has been collected on acrylamide in other types of foods is very limited. These missing data mean that the estimates of total long-term dietary exposure that have been calculated to date are likely to be underestimates by an undetermined degree and that the extent of underestimation will vary among countries. Also, foods not yet analyzed may emerge as significant contributors to total dietary exposure to acrylamide. The Consultation therefore echoes the warnings of researchers and national food authorities in different countries and cautions against drawing hasty conclusions from the very preliminary assessment below.

To date there has been selective sampling for only a few types of food items and the data are assigned to complete food groups that may not be adequate for accurate exposure estimation. However, an attempt has been made to use the available data to its fullest extent.

Filling the data gaps in a structured and prioritized way (particularly for staple foods consumed in developing countries, where there is a dearth of data), and understanding the determinants of variability in acrylamide levels in foodstuffs, are priorities for further research.

5.2   Description of submitted/available data

5.2.1   Acrylamide levels in food

Acrylamide concentration data for different food items or food groups were submitted to the Secretariat in advance of the Consultation. In some cases the food items analysed are well characterized, but in other cases the results were assigned to a product group and no further details regarding the specific food item were provided. Countries varied in their categorization of food items into food groups. Table 1 gives an overview of the range of acrylamide levels found (food grouping was undertaken at the Consultation according to the expertise available). Additional information about the analytical methods employed in generating these data is available in chapter 3.

Acrylamide was found in nearly all food items analyzed so far (Table 1), which raises the possibility that it might be present in other food items not yet analyzed. The highest average levels of acrylamide were found in crisps and chips, there was however a wide range, from not detectable to 3.5 mg/kg product.

Other foodstuffs that undergo similar processing may also contain acrylamide. However, no data were available for many commodities, such as meat (except as part of compound foods), milk, rice (other than a negative report for boiled rice), cassava, and soy products. No data were available for processed fruits (other than a single negative report for dried fruit) and vegetables (other than a small number of restaurant-prepared meals).

Table 1. 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 (μg/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

5.2.2 Food consumption data

Exposure assessments using different acrylamide concentration data (see Table 1) were provided by several national agencies and the International Agency for Research on Cancer (IARC). These included assessments using food consumption data from Australia, The Netherlands, Norway and USA. In addition the IARC EPIC[5] study used food consumption data from 10 different European countries. The foods for which residue data were submitted did not directly match the foods reported as consumed. Matching of residue data to food

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[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)
[5] The European Prospective Investigation into Cancer and Nutrition (EPIC), covers a large cohort of a half a million men and women from 23 European centres in 10 Western European countries (Denmark, France, Germany, Greece, Italy, Norway, Spain, Sweden, The Netherlands, United Kingdom). It is designed to study the relationship between diet and the risk of chronic diseases, particularly cancer.

consumption data was conducted according to the expertise available. This could be a source of uncertainty in the resulting exposure estimates. In the future, as additional data become available, standardization according to a well-recognized international food coding system would be useful in order to facilitate exposure assessments at the international level.

Foods of both plant and animal origin are consumed daily throughout the world. In most Western and Asian countries, many foods are fully or semi-processed prior to consumption. In other parts of the world, particularly Africa, traditional methods of food preparation are common and these methods can vary between communities and countries. For example, in most parts of Africa, cassava, yam, and maize are consumed directly or in semi-processed forms. In some communities/countries, maize, cassava, and yam are staple foods consumed on a daily basis. Therefore, an urgent assessment of the status of acrylamide (effects of processing parameters, storage conditions, and degradation) in staple foods across regions is needed to provide more global data on acrylamide in foods.

In 24-hour diet recalls, information on cooking methods is systematically collected for home-prepared meals. Heat treatments occurring during industrial processing can only be indirectly derived from the product category (e.g. breakfast cereals, bread, etc.). Further investigations using different food groupings according to cooking methods could be considered, once more specific information is available as to which cooking methods are actually associated with the presence/formation of acrylamide in foods.

5.3 Uncertainty regarding overall exposure to acrylamide

A substantial non-food source of exposure to acrylamide in people not occupationally exposed is tobacco smoke. Passive smoking is perhaps another source. In non-smokers the known food exposures did not appear to explain the levels of acrylamide-haemoglobin adduct observed. While further food survey work may account for more of the measured adduct levels, on the basis of the limited information available, it appears that non-food acrylamide exposures may be substantial for at least some populations. Exposure evaluations that exist in relation to polyacrylamide use in cosmetics, food packaging and water treatment, suggest that exposure levels from these known potential sources appear to be well below the intake levels implicated for foods and the overall exposure implicated by biomarker studies. Speculation regarding other potential sources of acrylamide exposure has included the possibility of endogenous acrylamide formation (i.e. in the body).

Biomarkers of exposure have been reported in only a handful of studies, and given that the sources of exposure other than food and smoking are largely unknown, the relative contribution of food-borne acrylamide to overall acrylamide exposure on a worldwide basis is unknown.

Evaluation of background acrylamide exposure levels, whether through food or other sources, should be assessed using biomarkers of exposure. Given the uncertainty as to whether acrylamide intake through food is sufficient to explain total exposures to acrylamide, as well as the suggestion that other known sources may not explain the full body-burden, population-based studies of broad scope would be most useful at this stage to identify other potential non-occupational, non-food sources of exposure.

5.4 Dietary intake of acrylamide

Preliminary analyses from existing limited data indicate that potato and potato products such as crisps, chips and other high-temperature cooked potatoes (e.g. roasted, baked) would contribute most to the total mean acrylamide intakes, particularly when considered together. This is observed in data from studies in Nordic, central European and Mediterranean countries (e.g. Spain and France (from EPIC data)) and other regions in the world (e.g. Australia, USA). However, other food groups with lower acrylamide concentration but consumed on a daily (or more regular) basis (e.g. bread, crispbread), and other foods in which levels of acrylamide are currently unknown, may also contribute substantially to the total intakes, with the magnitude varying across countries or study populations.

5.4.1 Estimation of short-term intake

Intake estimates using Monte Carlo statistical techniques were conducted using the available food consumption data for two populations (The Netherlands, USA) in order to provide an estimate of likely short-term intakes on the basis of the acrylamide residue data provided by Sweden. Although the matching of the residue data to foods consumed and the modelling methods varied slightly, the estimated exposures were similar. The resulting intake estimates ranged from 0.8 µg/kg bw per day for the average consumer, to 3 µg/kg bw per day for the 95th percentile consumer, and 6.0 µg/kg bw per day for the 98th percentile consumer.

5.4.2 Estimation of long-term intake

The Consultation considered whether estimates of exposure over longer periods of time, including chronic or lifetime exposures, could be assessed given the present state of knowledge for acrylamide. It was agreed that the sparse, unrepresentative data available on acrylamide occurrence in foods, limited the degree to which extrapolations could be made for subsets of populations based on either biologic (e.g. gender, age, ethnic background) or food consumption differences. Nonetheless, the data do allow uncertainty estimates for the typical or median exposures that occur through food for Western European, Australian and North American diets. The general agreement of the several methods used to estimate exposure using well described food consumption data from Australia, Norway, The Netherlands, Sweden, USA and from the IARC EPIC study indicate a lower bound estimate of typical exposures in the range of 0.3 to 0.8 µg/kg bw per day depending upon whether the average or median exposure is estimated and which age groups were evaluated.

Within a population, it is anticipated that children will generally have exposures that are two to three times those of adult consumers when expressed on a body weight basis. Although there is inadequate data to reliably estimate exposure for high consumers, their exposure could be several times the mean exposure.

There is essentially no acrylamide occurrence data applicable to populations where the staple food consumption, or food preparation methods, differs substantially from the Western European or North American diet. Furthermore, the generally poor understanding of the mechanisms of formation of acrylamide in foods does not allow speculation as to the presence of acrylamide in foods that have not been sampled.

6. ABSORPTION, METABOLISM, DISTRIBUTION AND EXCRETION

6.1 Absorption

Acrylamide is absorbed from all routes of exposure. While data on the bioavailability from food matrices are limited, absorption is considered to be rapid and complete by the oral route in all species.

6.2 Metabolism and distribution

Animal studies have shown that acrylamide and glycidamide are widely distributed in all tissues of the body, including milk. The major metabolite of acrylamide, glycidamide, is an epoxide that may be more critical for carcinogenic and genotoxic properties in animals than the parent compound. Acrylamide, rather than glycidamide, probably accounts for its neurotoxic potential.

The major metabolic pathway for acrylamide is qualitatively similar in humans and laboratory animals, however, quantitative differences must be considered in assessing risk for humans. For the range of doses used in animal toxicology studies, the extent of conversion of parent compound to glycidamide is inversely related to the amount of acrylamide in the body – the lower the dose, the higher the proportion converted to glycidamide. Because metabolism and elimination involve pathways where there is genetic variability (e.g. conjugation and P450-mediated metabolism), there may be variation in the sensitivity of humans to the effects of ingested acrylamide.

6.3 Excretion

The elimination half-life of acrylamide and glycidamide is about two hours in rats. Pharmacokinetic data in humans are sparse.

7. NON-CANCER TOXICITY

7.1 Introduction

Neurotoxicity is the only recognized adverse effect of oral acrylamide exposure in humans[6]. Neurotoxicity is replicated in animal studies. Less is known about the effects of acrylamide on the developing nervous system, although major persistent structural or functional

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[6] Animal studies and human experience demonstrate that acrylamide is neurotoxic throughout postnatal life. Dysfunction of the central nervous system, especially the brain, dominates the acute toxic response to large single exposures. Brain dysfunction may present as seizures (overt poisoning only), or after prolonged exposure, in the form of sleepiness, changes in emotion and memory, hallucination, and tremor. These manifestations of acrylamide intoxication may precede and/or accompany signs of peripheral neuropathy (stocking-and-glove distribution of sensory loss, sweating, and muscle weakness) with or without the ataxia that characteristically results from repeated lower-level exposures to acrylamide. Peripheral neuropathy is a delayed response to acrylamide exposure and, depending on the dose received, may appear within weeks or months of daily exposures to small amounts, and up to several years in the event of chronic, low-level exposures. Rodent studies indicate that peripheral neuropathy develops more rapidly, and has greater severity and slower recovery in older versus young animals.

perturbations of the brain or behaviour resulting from in utero or post-natal exposure have not been found in animal studies. Animal studies demonstrate that acrylamide damages the testes and adversely affects fertility. Acrylamide is genotoxic *in vivo* in somatic cells and germ cells, and therefore has the potential to induce heritable damage at gene and chromosome level.

7.2   Single dose toxicity

Toxic effects on the nervous system of humans and animals, and on the male reproductive organs of rats, are known to occur after single oral doses of acrylamide that are equal to, or greater than, four to five orders of magnitude higher than the estimated daily intake of acrylamide from food (1-10 µg/kg bw per day from food, versus above 100,000 µg/kg bw per day).

7.3   Chronic toxic effects

7.3.1   Neurotoxicity

An earlier WHO risk assessment for chronic human exposure (Environmental Health Criteria Number 49, 1985) was based on experimental studies of acrylamide neuropathy in a sensitive species (rat). The assessment was based on the effects seen in rats treated orally with 1 mg/kg bw per day for 93 days. The report concluded that "applying a safety factor of 10 to the estimated minimal adverse neurological effect level for human beings would indicate a daily intake not exceeding 0.012 mg/kg body weight (from all sources)". The report emphasized that this assessment did not take into account toxic effects other than neurotoxicity.

The present Consultation considered these findings, the continued absence of dose-response data relevant to the human peripheral nervous system and the availability of additional published reports of experimental acrylamide neuropathy in rodents (chronic drinking water studies) and primates. The Consultation concluded that two chronic rat drinking water studies were most suitable for the purposes of risk assessment. These studies indicate that the LOAEL for peripheral neuropathy is 2 mg/kg/d, with a NOAEL of 0.5 mg/kg/d. The Consultation noted the primate NOAEL of 0.5-1.0 mg/kg bw per day for subcutaneous (6 days per week only) and oral dosing, respectively.

Workers in the People's Republic of China, who were exposed to acrylamide and acrylonitrile for 2 or more years, were assessed for neurological signs and haemoglobin acrylamide adducts. A correlation was demonstrated between levels of haemoglobin adducts and degree of peripheral neuropathy. These studies concluded that exposures greater than 1 mg/kg bw per day were associated with peripheral neuropathy. This is consistent with the primate and rodent data.

In sum, rodent studies (sub-chronic and chronic oral dosing), primate studies (oral and subcutaneous) and a human occupational study, support a NOAEL for acrylamide neuropathy of 0.5 mg/kg bw per day. Since the estimated average human daily intake for acrylamide in food is of the order of 0.001 mg/kg bw per day, there is a 500-fold margin between exposure and the NOAEL.

This analysis has been developed from an assessment of the sensory or sensory-motor deficits induced by acrylamide. This does not include an assessment of autonomic dysfunction, an

early feature of acrylamide neuropathy. Humans and animals develop a low-grade peripheral neuropathy with the advance of age, and aged animals are more susceptible to acrylamide neuropathy. Additionally, the NOAEL has been developed from studies of acrylamide neuropathy and does not consider effects of the substance on the brain because quantitative data are lacking. Clear involvement of this organ is found in humans and animals at higher exposure levels, but impact on the brain cannot be ruled out at low dose levels over a prolonged period of acrylamide exposure.

The molecular mechanisms of acrylamide neuropathy, specifically degeneration of nerve fibre axons, is unknown. Evidence points to protein targets involved in axonal transport, including microtubule-associated proteins and the motor proteins kinesin and dynein.

7.3.2 Effects on fertility

Impaired fertility has been demonstrated in male rats exposed to 15 mg/kg bw per day or more for 5 days and in mice exposed to up to 12 mg/kg bw/day for 4 weeks. The impaired fertility may have been associated with effects on sperm count and sperm motility. Degeneration of spermatids and spermatocytes was observed in one repeated-exposure study in which animals received approximately 36 mg/kg bw per day by the oral route for 8 weeks. In other studies, effects on fertility were less clear, with impaired copulatory ability possibly arising as a secondary result of hind limb weakness caused by acrylamide neuropathy. Overall, there is sufficient evidence to conclude that acrylamide impairs male fertility, and NOAELs may be identified from some studies: 2 mg/kg bw per day from a two-generation rat study (10-11 weeks of treatment), and 9 mg/kg bw per day from a 27 week mouse study.

Based on the rat study, a NOAEL for reproductive toxicity of 2 mg/kg bw per day is 4-fold higher than that for chronic neurotoxic effects in the form of peripheral neuropathy. Controlling for chronic neurotoxic effects of acrylamide is therefore expected to control for effects on fertility. However, testicular toxicity may also develop rapidly after large doses of acrylamide, and detailed studies to assess the differential vulnerability of nervous versus testicular tissue appear not to have been performed.

The molecular targets of acrylamide in relation to testicular toxicity are not known. Interest has focused on protein targets, notably microtubules.

8. CARCINOGENICITY (INCLUDING GENOTOXICITY AND MECHANISMS OF CARCINOGENICITY)

8.1 Carcinogenicity

8.1.1 Animal data

Acrylamide is carcinogenic in laboratory rats in standard 2 year bioassays, producing increased incidences of a number of benign and malignant tumours identified in a variety of organs (for example thyroid, adrenals, tunica vaginalis). Two separate, independent studies have confirmed this phenomenon at a dose of 2 mg/kg per day, administered in drinking water. There is also a suggestion of tumours in brain and spinal cord, and in other tissues.

In a series of non-standard carcinogenicity bioassays in mice, acrylamide induced lung and skin tumours.

8.1.2   Human data

Epidemiological studies have been conducted on a cohort of more than 8 000 workers exposed to acrylamide in monomer and polymer production plants during 1925 – 1976. An evaluation performed in 1983 revealed no statistically significant excess risk of cancer in any organ, and no trend in cancer mortality was seen with increasing cumulative exposure.

Data for this cohort were subsequently updated for the period 1984 – 1994, and again no statistically significant excess cancer risks were observed, with the single exception of pancreatic cancer for which a doubling of risk was found in workers most heavily exposed. The statistical power of this study was adequate to have detected a 75% excess incidence of brain cancer, a 40% increase in pancreatic cancer, a 15% increase in lung cancer, or a 9% increase in all cancers combined. All epidemiological studies have limited power to detect small increases in tumour incidence. Therefore, the absence of positive results found in most studies on acrylamide cannot be interpreted as proof that the substance cannot induce cancer in humans.

Levels of exposure in this study are expressed as concentrations in air, multiplied by duration of exposure (by inhalation). Dermal exposure, which was also likely to have occurred, was not quantified. It is difficult to compare the resulting daily intake with levels of acrylamide that have been measured in food.

8.2   Genotoxicity

Acrylamide does not induce gene mutations in bacteria, but the epoxide metabolite glycidamide does in the absence of metabolic activation. Acrylamide showed equivocal, negative, or weakly positive results when tested for the induction of gene mutations in mammalian cells. Acrylamide induces chromosomal aberrations, micronuclei, sister chromatid exchanges (SCE), polyploidy, aneuploidy and other mitotic disturbances (e.g. C-mitosis) in mammalian cells in the absence of metabolic activation. Acrylamide was unable to induce unscheduled DNA synthesis (UDS) in rat hepatocytes. Glycidamide induced UDS in human mammary cells, with equivocal results in rat hepatocytes. For micronuclei induction, a mixed breakage (prevalent)-aneuploidy mechanism was shown.

Acrylamide was positive in the mouse spot test, in the bone marrow chromosome aberration assay and in particular in the bone marrow micronucleus assay. In a transgenic mouse model (MutaMouse) acrylamide induced a small increase in mutation frequency.

Acrylamide induced somatic mutations as well as sex-linked recessive lethal mutations in *Drosophila*.

In germ cells acrylamide produced several genetic effects such as chromosome aberrations, micronuclei (derived both by breakage and, to a lesser extent, by aneuploidy), SCE, UDS, single-strand breaks in DNA, dominant lethal mutations, specific locus mutations and heritable translocations. Glycidamide also induces dominant lethal mutations.

Acrylamide is a germ cell mutagen in rodents, with the potential to induce heritable genetic damage at gene and chromosomal level. Acrylamide impairs fertility in male rats, most likely through a direct toxic effect. Whether acrylamide has an adverse effect on fertility through genetic damage is unclear.

8.3   Cell transformation

Positive results were reported for acrylamide in four different cell transformation assays with mammalian cells *in vitro*.

8.4   Adduct formation

Acrylamide contains an electrophilic α,β-unsaturated system, that reacts via a Michael addition with nucleophilic compounds. Within proteins the sulfhydryl group of cysteine is the major site of reaction, although reaction also occurs to a lesser extent with amino groups, such as those at the N-terminal position of the protein.

Haemoglobin adducts are used as a measure of human exposure to electrophilic compounds over the previous 4 months (i.e. the life span of human red blood cells), but are not an indicator of toxicity. Adduct formation at the N-terminal valine of haemoglobin has been used as a marker of *in vivo* exposure to acrylamide, using an analytical procedure employing a modified Edman degradation. A similar analytical approach is used for measurement of haemoglobin adducts of glycidamide. The detection of this latter adduct in rat and human haemoglobin after exposure to acrylamide confirms the formation of this metabolite *in vivo*. Binding of acrylamide to other proteins in nervous and testicular tissue may be relevant to the toxic action of acrylamide to these tissues.

Adduct formation of acrylamide with DNA also occurs, however the reaction is slow. Amongst the products formed *in vitro* are formamidoethyl or carboxyethyl adducts with exocyclic amino groups or ring nitrogens in DNA bases. The mutagenic significance and repair capabilities of these adducts is unknown. The only adduct detected in mice and rats exposed to acrylamide has been reported to be an adduct of the epoxide metabolite glycidamide with guanine. At present there are no data on DNA adduct formation after acrylamide exposure in humans. Glycidamide is expected, because of its structure, to be of more significance than acrylamide to the genotoxic effects of acrylamide *in vivo*.

8.5 Mode of carcinogenic action

Acrylamide is genotoxic *in vivo* in somatic cells and germ cells, and is known to be metabolized to glycidamide, a chemically reactive epoxide that forms DNA adducts. The finding that acrylamide induces tumours at a number of different sites in both rats and mice is consistent with a genotoxic mode of action of the chemical. The existence of adducts in experimental systems is supportive of a genotoxic mechanism of carcinogenesis of acrylamide. 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 for acrylamide for Group 2A (probably carcinogenic to humans).

9.   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 minimize 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 analyzed to date represent only a portion of the total diet and do not include foods representative of those consumed in developing countries (see Table 1). 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 analyzed 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 Global Environmental Monitoring System/Food Contamination Monitoring and Assessment Programme (GEMS/Food) 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 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.

Toxicity 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 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. The Consultation therefore concluded that no neurotoxic effects are to be expected from the levels of acrylamide encountered in food.

Greater understanding of the hierarchy of target organ toxicity would permit a refinement of the risk assessment for the non-cancer, non-genotoxic 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. The influence of background acrylamide exposure from food was not evaluated in these studies, since at this stage there was no knowledge of the importance of this source of exposure.

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

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**FAO/WHO Consultation on the
Health Implications of Acrylamide in Food
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

List of major documents used by the Consultation

To assist the FAO/WHO Consultation, WHO called on organizations and individuals that had information relevant to acrylamide in food to submit it to WHO for consideration by the Consultation. Information sought included, but was not limited to, the following:

- Toxicological data, in particular data on the potential carcinogenicity and neurotoxicology of acrylamide;

- Information relevant to elucidating the mode/s and mechanism/s of toxicity of acrylamide;

- Epidemiological data, including occupational studies;

- Information relevant to dietary exposure, including levels in food, as well as exposures through cosmetics and drinking water;

- Methods of analysis, particularly in food;

- Information on the formation and fate of acrylamide in food during cooking (all types) and other types of processing;

- Information on the binding of acrylamide and acrylamide precursors to food matrices, and their bioavailability; and

- Information relevant to risk management.

The attached tables include a list of the documents received, along with other major documents used. These tables can also be accessed via the Food Safety webpage of WHO: www.who.int/fsf. In addition, a reference collection of papers on the toxicology of acrylamide was available to the Consultation.

Table 1   WHO call for data on acrylamide: Submissions received (up to 24.6.02)

No.	Date of submission	Sent by	Title of paper/information item	Comments
1	17.05	Joint Research Centre European Commission (Sazan Pakalin)	European Union risk assessment report (final draft)	Available to the Consultation as a final draft
2	29.05	Tapan Chakrabarti National Environmental Engineering Research Institute, India	Data on Acrylamide	Unreferenced and unpublished review.
3	29.05	Peter Ungeheuer Acrylamide Monomer Producers Association, Germany	1. Crump, K. S., 1999. Consideration of the Potency Classification of Acrylamide Based on the Incidence of Tunica Vaginalis Mesotheliomas (TVMs) in Male Fischer 344 Rats. The K. S. Crump Group, 602 East Georgia, Ruston, LA 71270. 2. Crump, K. S., 1999. Mechanism of Acrylamide Induction of Benign Mammary Fibroadenomas in the Aging Female Fischer 344 Rat: Relevance to Human Health Risk Assessment. The K. S. Crump Group, 602 East Georgia, Ruston, LA 71270 3. Crump, K. S., 2000. The Biological Role of Acrylamide-Induced Astrocytomas in the Aging Fischer 344 Rat to Human Health Outcomes. The K. S. Crump Group, 602 East Georgia, Ruston, LA 71270.	All documents cleared by data provider for use by the Consultation.

4. Crump, K. S., 2000. The Biological Role of Acrylamide-Induced Thyroid Follicular Cell Tumors in the Aging F344 Rat to Human Health Outcomes. The K.S. Crump Group, 602 East Georgia, Ruston, LA 71270.

5. Crump, K. S., 2001. Hazard Analysis and Dose Response Identification for acrylamide. The K.S. Crump Group, 602 East Georgia, Ruston, LA 71270.

6. Crump, K. S., 2001. Estimates of Acrylamide Intake from the Use of Personal Care Products Containing Polyacrylamide: A Monte Carlo Analysis. The K.S. Crump Group, 602 East Georgia, Ruston, LA 71270.

7. Tyl, R. W., Marr, M. C., Myers, C. B., Ross, W. P. and Friedman, M. A., 2000. Relationship between acrylamide reproductive and neurotoxicity in male rats. Reprod Toxicol: 14(2), 147-157.

8. Tyl, R. W., Friedman, M. A., Losco, P. E., Fisher, L. C., Johnson, K. A., Strother, D. E. and Wolf, C. H., 2000. Rat two-generation reproduction and dominant lethal study of acrylamide in drinking water. Reprod Toxicol: 14(5), 385-401.

9. Friedman, M. A., Tyl, R. W., Marr, M. C., Myers, C. B., Gerling, F. S., and Ross, W., 1999. Effects of lactational administration of acrylamide on rat dams and offspring: Reprod Toxicol 13(6), 511-520.

10. Tyl, R. W., and Friedman, M. A., submitted. Review: Effects of Acrylamide on Rodent Reproductive Performance. Reprod Toxicol.

11. Sickles, D. W., Stone, J. D., and Friedman, M. A., 2002. Fast Axonal Transport: A Site of Acrylamide Neurotoxicity? Neurotoxicology 122: 1-29.

12. Damjanov, I., Friedman, M. A., 1998. Mesotheliomas of tunica vaginalis testis of Fischer 344 (F344) rats treated with acrylamide: a light and electron microscopy study. *In vivo*: 12(2), 495-502.

13. Sumner, S. C. J., Asgharian, B., Williams, C. C. and Fennell, T. R., 2001. Acrylamide: Metabolism, Distribution, and Haemoglobin Adducts in Male F344 Rats and B6C3F1 Mice Following Inhalation Exposure and Distribution and Haemoglobin Adducts Following Dermal Application to F344 Rats. Research Triangle Park, NC

14. Sumner, Susan C. J., Williams, Carla C., and Fennell, Timothy R., 1999. Characterization of Urinary Metabolites of [1,2,3-13C]Acrylamide in Male F344 Rats Following Dermal Application and IP Injection. Research Triangle Park, NC CIIT-Center for Health Research

			15. Diembeck, W., Dusing, H.-J., and Akhiani, M., 1998. Dermal Absorption and Penetration of Acrylamide ([C14]-Acrylamide as Tracer) in different Cosmetic Formulations and polyacrylamide-solution after Topical Application to Excised Pig Skin. Beiersdorf. 16. Marty, J-P, 1998. *In Vitro* Percutaneous Absorption of Acrylamide Across Human Skin. Faculty of Pharmacy, University of Paris Sud, Paris, France. 17. Park, J., Kamendulis, L. M., Friedman, M. A. and Klaunig, J.E., 2002. Acrylamide-induced cellular transformation. Toxicol Sci: 65(2), 177-183. 18. Fennell, T. R., Snyder, R. W., Krol, W. K. and Susan C. J. Sumner S. C. J. (in preparation). Comparison of the Haemoglobin Adducts Formed by Administration of N-Methylolacrylamide and Acrylamide to Rats. Tox. Sci.	
4	30.05	Tore Sanner The Norwegian Radium Hospital, Oslo, Norway	Opinion of the scientific Committee on Cosmetic Products and non-food products intended for consumers concerning acrylamide residues in cosmetics	Full opinion, cleared by data provider for use by the Consultation.
5	31.05	Anders Tromborg, Matforsk Norway	Suggested plan for further work connected to acrylamide in Norway	.
6	31.05	European Commission Secretariat Scientific Committee on Food (Taina Sateri)	Acrylamide (CAS No. 79-06-1) as a food contact material in the relevant legislation of the European Union (31 May 2002)	Cleared by data provider for use by the Consultation.

			Determination of Acrylamide in food simulants	http://europa.eu.int/comm/food/fs/sc/sccp/out95_en.html
			Opinion of the scientific committee on cosmetic products and non-food products intended for consumers concerning Acrylamide residues in cosmetics (1999)	http://europa.eu.int/comm/food/fs/sc/sct/out88_en.html
			Opinion of the CSTEE on the EU Risk Assessment Report on Acrylamide (2001)	
7	14 .05	Lars Hagmar University Hospital Lund, Sweden	Hagmar L, Törnqvist M, Nordander C, Rosén I, Bruze M, Kautiainen A, Magnusson A-L, Malmberg B, Aprea P. and Axmon A. Health effects of occupational exposure to acrylamide using Hb adducts as biomarkers of internal dose. Scand J Work Environ Health 2001;27:219-226.	.
	16.05	Lars Hagmar (continued)	Application for research grant: The impact of food habits on haemoglobin adducts of acrylamide.	
8	31.05	Erland Brathen Marforsk, Norway	Comment on formation of acrylamide in food.	
9	3.06	Margareta Törnqvist, Department of Environmental Chemistry Wallenberg Laboratory Stockholm University Stockholm Sweden	Summary of studies on acrylamide at Dept. of Environmental Chemistry at Stockholm University	

10	5.06	Warholm et al. Sweden	Improved risk assessment of acrylamide and similar compounds by studies on genetic susceptibility, Report to the Swedish Council for Working Life and Social Research, Stockholm, April 25 2002.	
11	7.06	Wendy Matthews UK Food Standards Agency	Acrylamide in Food – June 2002	UK data on acrylamide levels in food.
12	7.06	Rob M.C. Theelen Ministry of Agriculture, Nature Management and Fisheries The Netherlands	First results of a study of the formation of acrylamide in foods by the RIKILT Institute, Wageningen, The Netherlands	Submitted in Dutch.
13	10.06	Peter Spencer, Oregon Health &Science University's Centre for Research on Occupational and Environmental Toxicology	Miller M. S. and Spencer P. S. The Mechanisms of acrylamide axonopathy. Ann. Rev. Pharmacol. Toxicol. 1985. 25.643-66 Schaumburg H. H, Arezzo J. C. and Spencer P. S. Delayed onset of distal axonal neuropathy in primates after prolonged low-level administration of a neurotoxin. Annals of Neurology, 1989; 26: 576-579. Sabri M. I. et al. Effect of exogenous pyruvate on acrylamide neuropathy in rats. Brain Research, 1989; 483: 1-11.	
14	12.06	NICNAS, Australia	National Industrial Chemicals Notification and Assessment Scheme Priority Existing Chemical Report on Acrylamide 2002 (Australian Risk Assessment Report)	

15	7.06	Norwegian Food Control Authority (M Widme)	Results of acrylamide in thirty Norwegian food samples. Risk Assessment of acrylamide intake from foods with special emphasis on cancer risk. Report from the Scientific Committee of the Norwegian Food Control Authority, 6 June 2002.	
16	14.06	Australian and New Zealand Food Authority (Tracey Hambridge)	Acrylamide Dietary Exposure Assessment Report	Australian dietary exposure assessment based on Swedish and UK analytical data.
17	18.06	Bingheng Chen	Translated abstracts of a number of articles published in the Chinese scientific literature.	

Table 2 Other Information Collected

Item	Title of paper/information item	Comments
1	Material from Swedish National Food Administration (NFA) website: • Press Release by NFA • Acrylamide in foodstuffs, consumption and intake • Individuals results for all tested samples • Analytical methodology and survey results for acrylamide in foods • Acrylamide – Cancer studies and comparisons of risk • Recommendations regarding acrylamide in Food • Toxicological aspects of acrylamide	Source: NFA website http://www.slv.se/HeadMenu/livsmedelsverket.asp

2	Press Release UK Food Standards Agency – Levels of acrylamide in food.	Source: internet http://www.foodstandards.gov.uk/news/newsarchive/60581
3	Press Release of Swiss data on levels of acrylamide in food.	Source: internet, select item 13/6 from below site. http://www.bag.admin.ch/verbrau/aktuell/d/index.htm In German and French, (English translation of table of data provided). .
4	Tareke, E. et al. (2000) Acrylamide: A cooking carcinogen? *Chem Res Toxicol* 13, 517-522	.
5	Törnqvist M. and Ehrenberg L. (2001) Estimation of cancer risk caused by environmental chemicals based on *in vivo* dose measurement. *J Env Pathol, Toxicol, Oncol,* 20(4), 263-271	
6	US Report on Carcinogens Evaluation of Acrylamide	Source: internet http://ntp-server.niehs.nih.gov/htdocs/8_RoC/RAC/Acrylamide.html
7	IPCS INCHEM Pesticide Information Monograph on Acrylamide, 1999	Source: internet http://www.inchem.org/documents/pims/chemical/pim652.htm
8	IARC evaluation of Acrylamide: Summary of data reported and evaluation	Source: internet http://monographs.iarc.fr go to 'search IARC agents and summary evaluations'
9	Data on acrylamide levels in food from two Swiss retailers (independently submitted)	
10	Comment on analytical issues from Japan (National Institute of Health Sciences)	

11	Results on acrylamide contents in various foods (Official Food Control Authority of the Canton of Zurich, Switzerland)	
12	Acrylamide in US Foods (Center for Science in the Public Interest, US)	
13	Selected excerpts from *Health risk assessment of acrylamide (IMM report February 1998)*, Institute of Environmental Medicine, Karolinska Institut	Translation provided.
14	WHO (1985) Acrylamide. Environmental Health Criteria 49, WHO, Geneva.	

ABBREVIATIONS

ALARA	As Low As Reasonably Achievable
bw	Body Weight
DNA	Deoxyribonucleic Acid
ECD	Electron Capture Detection
GC	Gas Chromotography
LC	Liquid Chromatography
LOAEL	Lowest Observed Adverse Effect Level
MS	Mass Spectrometry
NOAEL	No Observed Adverse Effect Level
SCE	Sister Chromatid Exchange
UDS	Unscheduled DNA Synthesis