Summary

The unexpected discovery of acrylamide in some foodstuffs has caused considerable concern for public health. During the past year researchers from industry, national authorities, the EU Commission and academia have gained increasing insight in understanding the presence, formation and potential risk to public health posed by this finding. In spite of this endeavour, significant gaps in our knowledge remain. On March 28 2003 a workshop was held in Brussels, bringing together approximately 70 experts from the EU and North America, to discuss the state of the science and knowledge, to identify the gaps and to recommend actions where appropriate and possible. These actions concentrate on coordination of research aimed at minimising the presence of acrylamide in food without adding other health risks, estimating the human cancer risk associated with exposure to acrylamide(-rich) foods, risk communication and the establishment of a mechanism for information exchange.

Outcome of the acrylamide workshop held in Brussels on March 28, 2003
Introduction

Acrylamide is classified by the International Agency for Research on Cancer (IARC) as “probably carcinogenic to humans” based on results from animal studies. Acrylamide is also a known neurotoxin. At present it is unclear to what extent the results of these animal studies can be extrapolated to humans. Reviewing the available evidence, the World Health Organisation (WHO) deems acrylamide in food to be “a serious problem” and recommends further research. This point of view was endorsed by the EU Scientific Committee on Food.

Almost one year ago the Swedish National Food Administration announced the finding of acrylamide in some starch-rich baked and fried foods. By now there are an estimated 100 research projects underway, within the EU and beyond, addressing a wide range of issues concerning the formation, dietary intake, epidemiology and toxicity of acrylamide in food. The types of foods in which acrylamide has been detected, basically all foods that contain reducing sugars and free asparagine and are fried or baked at high temperatures, have traditionally been part of the basic diet of most people. No conclusive studies correlating exposure to acrylamide and occurrence of cancer are currently available.

On the 28th of March 2003, a workshop to discuss acrylamide in food was held in Brussels. This workshop was a joint initiative of industry, the CIAA (Confédération des Industries Agro-Alimentaires) and regulators, the UK FSA (Food Standards Agency) and the Dutch VWA (Voedsel en Waren Autoriteit). The meeting was organised in close cooperation with DG SANCO and the EFSA. The aims of the workshop were:

- To review the present knowledge on the formation, epidemiology and toxicology of acrylamide in food
- To catalogue the research being conducted
- To formulate a plan for future action.

The discussions during the workshop were based on information presented at the JIFSAN Workshop on acrylamide (Chicago, October 2002), the WHO Consultation on acrylamide (Geneva, June 2002), ILSI Europe workshop (December 2002), surveillance of research exposure in Europe (European Commission, DG SANCO March 2003), overviews of research by the industry and the outcome of the recent FAO/WHO seminar during the 35th Codex Committee on Food Additives and Contaminants in Tanzania (March 2003). This information is mostly available in the public domain and will therefore not be repeated here. The overview lectures presented information on acrylamide research in the US, surveillance of exposure in Europe, research by the industry and the FAO/WHO seminar in Tanzania, which is for the same reason also not reiterated here.

Two sets of 3 parallel brainstorm sessions were held. The first series concentrated on an exchange of views regarding 1) toxicology, 2) epidemiology and exposure and 3) formation. The second series dealt with 1) practical possibilities for action, 2) demarcation of responsibilities between EFSA, national authorities, industry and research institutes and 3) a permanent mechanism for discussions and the exchange of information. The results of these sessions form the foundations of the present white paper, which describes the most desirable course of action in the view of the participants. It is based primarily on the European perspective, but takes the ongoing activities elsewhere, in particular in the US, into account.
Three draft versions of the white paper have been circulated to the participants of this workshop and the final version reflects their opinions of the group.

Current knowledge

Toxicology

Acrylamide is classified in IARC’s Group 2A ‘probably carcinogenic to humans’, this classification indicates that there is insufficient evidence that acrylamide is carcinogenic in humans for it to be classified in Group 1 (agent is carcinogenic to humans) but sufficient evidence of carcinogenicity in animals to classify it higher than Group 2B (agent is possibly carcinogenic to humans). The basis for a quantitative risk assessment is very small and the mechanism behind the tumour formation is not understood.

The current consensus is that acrylamide is a genotoxin in addition to a carcinogen. There is, however, a need for long-term studies on the effects of acrylamide exposure on the incidence of cancer in different strains of rats. The relationship between protein and DNA adducts and the relevance of DNA-adduct formation and cancer need further study. In addition, research is needed on the extrapolation of data in rats to the human situation. Studies of acrylamide exposure on foetal development suggest it is not more detrimental to the developing animal than to the adult. Transfer of acrylamide to breast milk has not been demonstrated, but a study on this subject is required.

The hormonal and neurotoxic effects are better documented than the carcinogenic effects, having been studied in animals and workers exposed to acrylamide. The neurotoxic effects observed at high levels of exposure were found to be completely reversible. It seems unlikely that levels high enough to cause neurotoxic effects in humans can be reached through uptake from food. In general, the uptake, bioavailability and metabolic pathways of acrylamide are understood substantially in animals and studies in humans are under way to complete the information needed for risk assessment.

With respect to the uncertainties regarding endogenous formation of acrylamide it was recognized that Maillard reactions occur in vivo. In animals that have been fed on feed that does not contain acrylamide, some acrylamide is detected in the blood, indicating endogenous formation. The observation of haemoglobin adducts in hares also supports this suggestion. At present no knowledge is available on potential endogenous formation, either in animals or in humans, and hence further study is required.

The question was raised as to why acrylamide was singled out as a suspect agent and not some of the other Maillard reaction products that can be expected to be formed. A complete overview of the Maillard reactions should be considered in order to put acrylamide into perspective. In this respect, it must be noted that throughout history foodstuffs have been prepared in ways that are now known to cause the formation of acrylamide. Outwardly one could reason that if acrylamide were very harmful, the harmful effects of the consumption of fried and baked foods might have been observed long ago. However, only detailed epidemiological studies can reveal the actual additional cancer cases due to acrylamide in food. In addition, the question can be raised whether during evolution humans may have adapted to the type of products that is formed during the processing of food.
Epidemiology and Exposure

Observations in humans are potentially the best way to confirm the relevance of findings from animal experiments. More epidemiological studies in this field are desperately needed to evaluate the potential hazard in humans with regard to normal and high intakes of acrylamide (-rich foods) and to put this risk into perspective. Until now, only a retrospective case-control study on this issue has been reported. That case-control study only focussed on colorectal, bladder and kidney cancer. Other cancer sites that seem to be at least as relevant from earlier acrylamide work in animal studies (e.g., breast, brain, mesothelioma, oral cavity, pancreas) were not included. The estimation of acrylamide intake was still incomplete. Importantly, the retrospective nature of a case-control study makes it vulnerable to several types of bias. This can be avoided in a prospective cohort study. Several cohort studies in the field of nutrition and cancer are ongoing, generating substantial follow-up information that can be used for the purpose of evaluation of human health hazards due to acrylamide.

Whilst it is possible to reach an accurate estimate of the average intake of acrylamide, the distribution and the ranges of exposure are problematical. It will be necessary to re-examine large, ongoing studies to study the relationship between dietary intake of acrylamide or consumption of foods rich in acrylamide and risk of various cancers and other diseases. In this endeavour, one must recognize the influence of confounding variables, such as fat intake, which have known links to cancer in man and to appropriate control for these factors in the analyses. Moreover, subgroups that consume disproportionate amounts of foods that contain large amounts of acrylamide or have a large intake via high levels of consumption of dietary staples with relatively ‘low’ acrylamide levels must be identified.

In contrast to industrial food processing, of which the products can be examined directly, there is only indirect information on the presence of acrylamide in home-cooked food, or in food from restaurants and the catering (food service) sector. This information was obtained by preparing food according to the instructions on the label. Further understanding of these sectors is essential to estimate their contribution to the overall daily dietary intake. To properly assess the total intake of acrylamide it is necessary to model scenarios and to determine the impact of changes within food production, including home cooking and the food service sector.

Formation

The formation of acrylamide during the range of different commercial and domestic production and preparation processes, in the chain from agricultural supply to domestic cooking, was reviewed for a number of food groups. Current knowledge was summarised with the aid of the scheme presented in appendix 1. This demonstrates that whereas some information is available on the reducing sugars and free asparagine content of the raw agricultural commodities (particularly potatoes and cereals) and how these constituents and the processing conditions impact the formation of acrylamide, much less is known about the effects of final preparation in food service and domestic situations. Laboratory research is currently focussed on aspects of agricultural and industrial processing, and much less research is being conducted on aspects of the domestic and food service sectors.

The issue arises as to whether or not it is possible to advise the public on avoiding or reducing the formation of acrylamide, based on the limited information presently available. Two aspects must be considered. The first is that in general the formation of acrylamide cannot be considered in isolation. For example, if lowering the frying temperature of French fries lowers the acrylamide content, but raises the fat content, the overall health problem may
have become worse. Secondly, the temperature setting on home fryers, ovens and toasters is often at variance with the actual temperature. Simple, practical advice on optimal preparation temperatures can therefore not currently be provided.

**Practical possibilities for action**

The second series of parallel sessions was based on the earlier reviews and centred on the question of what action to take at this time and who should take it.

**Research**

The following priorities were suggested:

In the area of toxicology, deficiencies were identified in the present research programmes with regard to:

- Long term studies on the effect of acrylamide intake from food
- Extrapolation from animals to humans
- Metabolism of acrylamide and glycidamide (e.g. metabolic profiles, protein adducts)
- A focus on all the Maillard reaction products and not just on acrylamide
- Clarification of the link between genotoxicity, DNA adducts and tumour formation
- Information on hormonal and early developmental effects
- Neurotoxic effects at low exposure levels
- Bioavailability of acrylamide from food.

The participants were aware that research is already being conducted in the last of these areas, but considered it a key area, which needs to be addressed vigorously.

Similarly, five main areas of concern were identified with regard to epidemiology and exposure:

- How large is the potential risk of cancer in humans associated with increased acrylamide intake?
- What type of cancers in humans are associated with acrylamide?
- Are other chronic diseases associated with increased intake of acrylamide?
- Are there groups of consumers with high acrylamide intake or who are more vulnerable to the effects of acrylamide?
- The exposure from domestic cooking and catering needs to be taken into account in intake estimates.

The participants concluded that almost no studies in this area are conducted, but this type of research is essential to estimate the risk humans and in risk assessment.

Pertaining to the formation of acrylamide, three issues were prioritised:

- Research on the effects of domestic cooking.
- Development and harmonisation of analytical methodology.
- Formation of a forum/task force of researchers on acrylamide formation.

The EC’s Joint Research Centre (JRC) will be hosting an analytical workshop in Belgium on 28-29 April 2003. This workshop, which seeks to recommend suitable analytical methods and method performance criteria for acrylamide analysis in food, was welcomed by all
participants as very valuable in the advancement of acrylamide research. It was hoped that results obtained on a wide variety of foodstuffs would become comparable.

**Information exchange**

The development of an information exchange mechanism was deemed essential by all in attendance at the workshop. Such a forum would facilitate rapid sharing of knowledge and experience between all researchers investigating acrylamide in food, thereby preventing unnecessary duplication of effort and allowing the rapid identification of gaps and overlooked topics. Industry partners within the CIAA have already created such a group and would welcome expansion to include other stakeholders in the research field. It was felt that being able to pool knowledge with official labs and research institutes would provide benefits for all.

The North American Joint Institute for Food Safety and Applied Nutrition (JIFSAN) already has a website with possibilities for discussions, the Acrylamide Infonet Forum, in development. This forum is completely open to the public. Some attendees felt uncomfortable about participating in such a public forum where individual results might not be placed in their proper perspective. The EC database of research and the developing JIFSAN/WHO database provide information on research being conducted. Combining all the requirements voiced during the brainstorm sessions, a consensus was reached that an effective forum would need to consist of:

- A mechanism, open to the public, that contains a summary of results
- Conferencing (i.e. face-to-face meetings) of researchers from all active interest groups.
- Another platform for those working in the area, that can contain research data and serve for discussions.
- Subgroups within the latter for specialized topics.
- Electronic discussion groups for research and technical aspects.

Except for the first two, these should only be accessible by password, while adding new data or discussion items should only be possible through the intervention of a moderator. This implies the need for a webmaster. It is evident that there is much to be gained by cooperating closely with JIFSAN, but the exact structure of this cooperation is still to be determined. In order to progress the science, face-to-face discussions between researchers will be an essential part of the process, especially to maximise the synergies from the research activity; and this should be an integral part of the proposed information exchange network.

Various practical difficulties are anticipated in the development of an information exchange forum. It is clearly understood that, with respect to food safety, data and knowledge would be freely shared across and between industry and government, but that proprietary information relating to product development and quality issues would not generally be shared. The CIAA/JRC database anonymises product specific information prior to submission to the open database. This procedure could be adopted more generally. Even when no competitive aspects are involved, it might still be appropriate to limit access as technical reports can be misinterpreted by laymen, potentially leading to undesirable confusion and unnecessary concern.

It is essential to create mutual trust between industry and regulators where this does not yet exist and to encourage sharing of information and knowledge. Lastly, an issue specific to academic researchers is that prestigious publications often insist that data are not published
in any way, including electronically, before the publication date of the journal. Joint action by the EFSA and the FDA to convince the editors of major journals to provide some exemption from this practice for publications on food safety, is highly desirable as publication in such journals is imperative for many researchers.

**Demarcation of responsibilities between industry, national authorities and the EFSA**

The responsibilities of the EFSA are defined in the EU General Food Law, giving it a primary responsibility for risk assessment and safeguarding public health in general. National authorities can be responsible for both risk assessment and law enforcement. Risk assessment can include the responsibility to commission research. Based on the risk assessment, a risk management plan, including the setting of safety standards for compounds such as acrylamide, can be devised. In addition, regulators have a role in risk communication. Risk communication is the primary instrument to influence home cooking, in the case of acrylamide potentially a major risk determinant.

Industry has the primary responsibility to produce safe food products. The responsibility to manage risks inherent to production processes and to adapt the latter to new insights and new standards derived from these, is intrinsic to this overall responsibility for producing safe food.

Cooperation between industry and regulators can be envisaged when analytical methodology needs to be developed and an overview of the presence of the compound in question needs to be completed. Information exchange between industry, regulators and researchers from other settings, is by its very nature of fundamental interest to all parties involved.

**Recommended actions**

The following actions are proposed, based upon the considerations above:
1. Formulate a research plan to fill the gaps in current knowledge and coordinate the implementation of individual projects.
2. Promote the harmonisation of methodology both for measuring acrylamide precisely, and for rapid screening.
3. Identify any groups of consumers most at risk.
4. Devise and execute a communications strategy to create awareness of acrylamide formation in domestic and catering (food service) settings.
5. Further development of databases for research and analytical results on acrylamide conducted within the EU and beyond, in cooperation with JIFSAN and building upon the JRC initiative.
6. Create a mechanism for information exchange and discussion, possibly connected to the aforementioned database.

Almost all these actions are joint responsibilities of EFSA, national authorities, industry and academic researchers. To facilitate the implementation of the plans, it may be appropriate to select for each of the action points one institution that will be asked to take the lead. For the action points 1, 3, and 5, it seems appropriate that the EFSA or the European commission would take the lead role. For point 2, industry could take primary responsibility for the development of analytical methodology, with the EU (JRC) leading in relation to
harmonisation of methodology. In respect of establishing a mechanism for the exchange and discussion of research information, data and ideas (point 6), it would appear appropriate for EFSA, the national authorities and JIFSAN to take the lead jointly, while the national authorities, in consultation with each other and other stakeholders, can devise the communications strategy (4).

For further information please contact
Dr. B.H. ter Kuile
+31 (0) 70 378 5981
b.m.ter.kuile@vwa.nl
Table 1: Review of current research activity on formation to identify areas with lack of data, areas where co-ordination is important, and areas where absence of methods impair the research effort.

<table>
<thead>
<tr>
<th>Commodity</th>
<th>Agricultural</th>
<th>Laboratory trials</th>
<th>Processing</th>
<th>Food Service (Catering)</th>
<th>Domestic cooking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potatoes</td>
<td>• The chips (French fries) industry has a lot of information on sugar contents in relation to storage conditions (temperature), because sugars are responsible for browning.</td>
<td>• Preliminary work shows that control of reducing sugars has a greater effect on reducing acrylamide, and is therefore a limiting factor.</td>
<td>• Essential to link to product quality: reduced acrylamide in the product may not be related to quality / sensory attributes of the product.</td>
<td>• Sugar production during storage is dependent on variety. What varieties are used in food service?</td>
<td>• What varieties are used in domestic cooking?</td>
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<tr>
<td></td>
<td>• Lack of information on Asparagine and other amino acids content of cultivars.</td>
<td>• Asparagine also plays an important role, but control of acrylamide can probably be better exercised through reducing the availability of the carbonyl-source.</td>
<td>• Impact of additives?</td>
<td>• How can acrylamide formation be controlled?</td>
<td>• Are recommendations on storage and cooking needed for consumers?</td>
</tr>
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<td></td>
<td>• In the selection of cultivars showing “lower” acrylamide levels in processed products, there is a lack of information on the impact of seasonal variation, agronomical aspects (fertilisation, etc).</td>
<td>• Decoupling wanted Maillard from acrylamide formation (kinetic studies).</td>
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\[1\text{ greater variability compared with food service}\]
<table>
<thead>
<tr>
<th>Cereals (bread, biscuits, breakfast cereals)</th>
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<tbody>
<tr>
<td>• In a cereal mix, wheat has the main effect on acrylamide formation.</td>
<td>• Bread: no impact of glucose oxidase.</td>
<td>• Spices and additives have influence on acrylamide formation.</td>
<td>• Investigate domestic practices.</td>
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<tr>
<td>• Currently no link between free Asparagine and acrylamide in cereal products.</td>
<td>• Fast and easy method for acrylamide analysis is needed to advance research.</td>
<td>• Some baking powders may reduce acrylamide formation.</td>
<td>• Advice to consumers (avoid over-baking: follow advice on label).</td>
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<tr>
<td>• Need to establish free amino acid profiles (e.g. wheat, rye, oats, rice) and variability.</td>
<td>• Lack of information on the impact of seasonal variation, agronomical aspects, etc</td>
<td>• Information is needed on variation in ingredients, type of preparation, baking, fermentation.</td>
<td></td>
</tr>
<tr>
<td>• Spices and additives have influence on acrylamide formation.</td>
<td></td>
<td>• Lack of information on impact of cooking process and type of cereal/biscuit.</td>
<td></td>
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<tr>
<td>Coffee</td>
<td>Coffee</td>
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<tr>
<td>• Knowledge on free Asparagine content is being generated.</td>
<td>• Could other mechanisms of formation be favoured in coffee, e.g. pathways involving free radicals?</td>
<td>• Not many options open to mitigation measures. Preliminary work shows that higher roasting temperatures lead to a relatively lower concentration of acrylamide (elimination?).</td>
<td></td>
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<tr>
<td>• There are analytical constraints in determination of acrylamide.</td>
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<tr>
<td>Cocoa</td>
<td>Cocoa</td>
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<tr>
<td>• Determination of free amino acid profiles in progress.</td>
<td>• Method of analysis problematical, between-laboratory variability high. This inhibits further work.</td>
<td>• Need for information on formation during the different processing stages.</td>
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</table>
### Nuts
- Raw almonds contain free Asparagine at appreciable levels.
- Almonds: is acrylamide formation during roasting linked to Asparagine?

### Vegetables
- Lack of information on composition.
- A wide range of vegetables may be affected.
- Investigate influence of different cooking methods (baking, battering, grilling, microwave).

### Composite foods
- Some are high in Asparagine; low in acrylamide (e.g. onions).
- Investigate influence of different cooking methods (baking, battering, grilling, microwave).

### Meat and fish – including battered and breaded products
- Investigate apparent inhibitory mechanism, including in battered and breaded products.
- Low in acrylamide (binding through constituents/reaction with inherent nucleophiles ?).