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Opinion of the Scientific Committee on Food on new findings regarding the presence of acrylamide in food

(expressed on 3 July 2002)

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Terms of reference

The Committee is asked to assess the implications for food safety of the new information on acrylamide in foods. The Committee is also asked to advise the Commission on the scientific basis for possible measures relating to acrylamide in food. The Committee is asked to give particular attention to:

- ✓ Its earlier evaluation carried out in 1991;
- ✓ The certainties and uncertainties in the available information on the sources and presence of acrylamide in foods;
- ✓ The identification of high risk sub-groups in the population;
- ✓ The identification of gaps in knowledge, which limit the Committee's assessment.

In its deliberations the Committee is also asked to consider the results of recent evaluations of its sister committees in 1999 (SCCNFP, 1999) and 2001 (CSTEE, 2001), and by any other relevant organization (e.g. IARC, US-EPA).

Background

New findings in Sweden in April 2002 have elucidated formation of high levels of acrylamide in a variety of fried and baked common foods. Although acrylamide has been produced commercially for many years for a variety of technical uses, and its toxicological properties are well established, the finding that acrylamide can be formed unintentionally during processing of foods is new knowledge.

The SCF has evaluated acrylamide in 1991 as a monomer in food contact materials where it concluded that it is a genotoxic carcinogen. In 2001, its sister Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE, 2001) commented on an extensive risk assessment of acrylamide carried out in the framework of Council Regulation (EEC) 793/93 on the evaluation and control of the risk of "existing" substances (EC, 2000). Acrylamide has

also been examined by the Scientific Committee on Cosmetic Products and Non-Food Products (SCCNFP, 1999). Also, other international bodies such as the International Agency for Research on Cancer (IARC) have evaluated this compound. In 1994, IARC classified acrylamide as *probably carcinogenic to humans* (class 2A).

In order to gain insight into the complex issues regarding the formation of acrylamide in foods, the Committee's Working Group on Contaminants invited experts from the Swedish National Food Agency (SNFA) to participate in its meeting on the 17th of May 2002 to discuss the Swedish studies on acrylamide in food. In addition, some members of the SCF participated in their personal capacity in the FAO/WHO consultation on the health implications of acrylamide in food, held in Geneva 25-27 June 2002 (WHO, 2002).

Non-food exposures to acrylamide

Commercially produced acrylamide is used as a chemical intermediate in the production and synthesis of polyacrylamides. For the general population, non-food exposures to acrylamide are to residual monomer in polyacrylamide. The largest use of polyacrylamide is as flocculants for clarifying drinking water and for treating municipal and industrial wastewater. Other major uses are as flow control agents in oil-drilling processes and as binders and retention aids in the pulp and paper industry. Other uses of polyacrylamide are in soil stabilization. Polyacrylamides are also present in cosmetics and toiletries. Acrylamide polymerisation is used *in situ* in the formulation of grouts for construction and repairing of e.g. sewers and tunnels, and in the preparation of polyacrylamide gels used in biotechnology laboratories. Acrylamide is also a component of tobacco smoke, which indicates that it can be formed by heating of biological material (Bergmark, 1997; EC, 2000).

The major routes of exposure at the workplace appear to be dermal absorption of acrylamide monomer from solution and inhalation of dry monomer or aerosols of acrylamide solution during acrylamide and polyacrylamide manufacture, during acrylamide grouting and during laboratory preparation of polyacrylamide gels.

Non-food acrylamide exposure of the general (non-smoking) population is considered to be low, although no precise figures can be given. Exposure to low levels of residual acrylamide may occur through drinking water contaminated from the use of polyacrylamide flocculants in water treatment and from the use of polyacrylamides in cosmetics and toiletries (EC, 2000).

The Swedish studies on acrylamide formation in food

Up till now food was not recognised as contributing to the exposure of humans to acrylamide. However, a scientific group at the University of Stockholm, together with the Swedish National Food Administration (SNFA) in April 2002 released new findings that acrylamide is formed during the preparation of foods and occurs in many foodstuffs.

The group at the University of Stockholm had for several years been studying the formation of haemoglobin adducts of acrylamide in humans following occupational or accidental exposure to acrylamide. Two types of haemoglobin adducts may be formed from acrylamide, one with the parent compound and one with its reactive epoxide-metabolite, glycidamide. During their studies of humans occupationally exposed to acrylamide they observed that control persons without known exposure to acrylamide had remarkably high levels of the acrylamide adduct to valine (*N*-(2-carbamoylethyl)valine (CEV)) in their haemoglobin. The average level of this adduct in haemoglobin from non-smoking control persons was reported to be about 40 (20-60) pmol/g of globin. In the general population, although not in smokers (who have levels of this adduct 2-3 times the background level), the background level of haemoglobin adducts has been estimated to correspond to a daily intake of approximately 100 μg of acrylamide per day. The fact that background levels of CEV are appreciably lower in wild animals and grazing cows prompted investigations of the human diet as a potential source (Tareke *et al.*, 2000).

Subsequent studies at the University of Stockholm in rats fed fried standard animal diet for 1 or 2 months showed a large increase (approximately 10-fold) in the level of the acrylamide-haemoglobin adduct, CEV, to between 65 and 160 pmol/g globin, compared with controls fed uncooked standard animal diet. Chemical analyses of uncooked and fried rat diets revealed that acrylamide was formed by frying of the feed at 180-200 ^{0}C to a brown colour using a Teflon pan (Tareke *et al.*, 2000). Later they also demonstrated high acrylamide levels in some foodstuffs (fried, oven-baked and deep-fried potato and cereal products) that were heated in laboratory experiments. No acrylamide was found in boiled foodstuffs. A private laboratory using a well-established GC-MS method to detect acrylamide following bromination conducted the analyses of rat diets and foodstuffs.

Levels of acrylamide in food

The findings prompted the Swedish National Food Agency (SNFA) to develop a new, high-throughput method for analysis of acrylamide in food using liquid chromatography coupled to two-stage mass spectrometry (LC-MS-MS). The method was validated according to SANCO/1850/2000. So far, more than a hundred food samples have been analyzed by the SNFA for acrylamide (www.slv.se). Subsequently, analysis of acrylamide in different foods and food products has also been done on samples collected in the United Kingdom (www.foodstandards.gov.uk), Norway (www.snt.no), Switzerland (www.bag.admin.ch) and the United States of America. The results, which verified the original Swedish observations, were compiled at the WHO Consultation (WHO 2002) and are given in table 1. By the current standard of analytical science, the findings of acrylamide in foodstuffs were considered reliable by WHO (2002). None of the methods used to measure acrylamide in foods has yet been validated by inter-laboratory collaborative trials. However, most methods fulfill the requirements of single-laboratory ("in-house") validation and accreditation.

Table 1
Acrylamide levels in different foods and food products groups from Norway, Sweden, Switzerland, the United Kingdom and the United States of America (From WHO 2002, with an additional footnote (5))

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[5]	50	50	<50 - 70	3
Chocolate powder[5]	75	75	<50 - 100	2
Coffee powder[5]	200	200	170 – 230	3
Beer	<30	<30	<30	1

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

[2] Mean and median were calculated where individual data were available; sample 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 figure relates to the dry powder. The beverage as consumed has a much lower acrylamide concentration.

No acrylamide has been detected so far in raw foodstuffs or foods cooked by boiling (potato, rice, pasta, flour and meat), with a limit of detection of 30 μg/kg. Analyses from the United Kingdom showed the presence of a very high level of acrylamide (more than 10 mg/kg) in overcooked frying chips. This demonstrates the influence of cooking temperature and duration on acrylamide formation. The highest levels of acrylamide were found in carbohydrate-rich foods. There were large variations between individual samples within the food categories analyzed. It should be emphasized that the results in most cases only refer to a single randomly selected sample of each specific product and that so far only a limited number of foods that potentially may contain acrylamide have been analysed.

Estimated dietary intakes of acrylamide

In Sweden, the SNFA estimated an average intake of acrylamide of approximately 25 micrograms per day for adults (maximum intake approximately six times higher), based on the food groups analyzed so far. The SNFA estimated that remaining food groups, not yet investigated, might account for a further 10–15 μg of acrylamide, thus arriving at an estimated total average daily intake of 35–40 μg for adults in Sweden (equivalent to approximately 0.5 μg/kg bw/day for a 70 kg adult). However, when the daily intake of acrylamide was estimated from the average acrylamide-haemoglobin adduct (CEV) background level of 40 pmol/g globin for the general population in Sweden a daily intake corresponding to approximately 100 μg per day was obtained (Granath *et al.*, 1999). Therefore, additional sources of acrylamide including intakes from foods cooked at home or sources other than foodstuffs could also contribute to the background level.

For Norway, based on the available data on levels in food, the estimated mean, median and 97.5 percentile intakes of acrylamide for men and women were (in μg/ kg bw/day): 0.36, 0.30, 1.3 and 0.33, 0.30, 1.10, respectively. For boys and girls 13 years of age the corresponding values were: 0.52, 0.30, 2.9 and 0.49, 0.28, and 2.1, respectively. Younger men aged 16 to 30 years had a higher intake than men of all ages. The main sources for all groups were potato crisps, potato chips (French fries) and fried potatoes.

At the FAO/WHO Consultation, the available data was found to only allow for 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 bw/day. Similar figures were derived when the mean intakes of acrylamide from food categories, for which analytical results were available, were compared between 10 EU Member States using results from the EPIC study (Pan-European epidemiological study on cancer, conducted by IARC). The calculated average intakes of acrylamide for adults ranged between 0.2 and 0.4 μg/kg bw/day with the Netherlands and the United Kingdom being at the higher end of the range. Within a population, it was anticipated that children would generally have exposures two to three times those of adults 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.

Toxicological properties of acrylamide

An extensive monograph on the toxicology of acrylamide has recently been prepared for the European Commission in the framework of Council Regulation 793/93 on the evaluation and control of the risks of existing substances (EC, 2000). If not otherwise stated the following toxicological information is taken from that report.

Absorption, distribution, metabolism and excretion

After oral administration, acrylamide is rapidly absorbed and widely distributed in all species that have been investigated (rats, mice, dogs, miniature pigs). An autoradiography study in mice also showed accumulation of acrylamide or its metabolites in the reproductive organs of males and rapid and extensive distribution to the developing foetus in pregnant females. In lactating rats given acrylamide the compound was also present in the milk. Binding of acrylamide or metabolites to RNA, DNA and protein (such as haemoglobin) occurs in a range of tissues. Studies in rats have shown that direct conjugation of acrylamide with glutathione is a major route of metabolism. Formation of the epoxide glycidamide, presumably via oxidation by cytochrome P450 2E1 (Sumner *et al.*, 1999), is also apparent. Evidence for glycidamide formation in humans was obtained from samples of haemoglobin taken from workers exposed to high levels of acrylamide (Bergmark *et al.*, 1993). Whereas both acrylamide and glycidamide form adducts with haemoglobin, only glycidamide forms DNA adducts in the mouse and the rat. The levels of the glycidamide-DNA adduct were similar in the different organs of rats and mice, showing that glycidamide is evenly distributed among the tissues, as is acrylamide (Segerbäck *et al.*, 1995). Excretion of the parent compound and metabolites is rapid and extensive and mostly via the urine, with smaller amounts eliminated via the faeces and exhaled CO_2.

Acute toxicity

Acrylamide is toxic at high doses by the oral route of administration. LD_{50} values are in the range of 107-203 mg/kg bw in rats.

Repeated dose toxicity

In rats, repeated oral administration of acrylamide at doses of 20 mg/kg bw/day and above produced severe lesions in the peripheral nerves with associated clinical signs of peripheral neuropathy. At these dose levels, marked toxicity was also produced at other sites, particularly atrophy of skeletal muscle, testicular atrophy, and decreased erythrocyte parameters. Peripheral nerve lesions occurred at 5 mg/kg bw/day in a 90-day study, and slight changes visualised only by electron microscopy were seen in peripheral nerve tissue at 1 mg/kg/day. No effects were seen at 0.2 mg/kg bw/day. Histopathological examination of tissues in 2-year rat carcinogenicity studies showed peripheral nerve lesions at 2 mg/kg/day, and no effects at 0.5 mg/kg bw/day.

In monkeys, repeated oral exposure studies using 10 mg/kg bw/day for up to 12 weeks were associated with clinical signs of peripheral neuropathy, and neuropathological effects and neurological dysfunction particularly in relation to the use of limbs. Most of the changes reversed after approximately 30 weeks without acrylamide exposure. Similar exposure levels produced marked effects on the visual system assessed by changes in functional parameters and supported by histopathological effects.

Human evidence from case reports and workplace surveys demonstrates neuropathological effects (principally peripheral neuropathy) following exposure (inhalation/dermal) to acrylamide. There is no adequate human information to establish a precise dose-response relationship. However, from studies where the adduct of acrylamide to haemoglobin (CEV) was monitored in humans the average background level was reported at 31 pmol/g globin (estimated intake of 0.8 μg/kg bw/day). The reported average adduct level was 54 pmol/g globin for laboratory workers using polyacrylamide gels (estimated intake of 1.4 μg/kg bw/day) and 116 pmol/g globin for cigarette smokers (estimated intake of 3.1 μg/kg bw/day). A NOAEL for development of peripheral neuropathy among Chinese acrylamide synthesis workers was reported at 2000 pmol/g globin, and a LOAEL for development of peripheral neuropathy in these workers at 6000 pmol/g globin (Bergmark *et al.*, 1993; Bergmark, 1997). The glycidamide adduct to haemoglobin (GAVal) could be measured in this population of Chinese workers exposed to high levels of acrylamide and was found to approach the levels of the CEV, suggesting that the *in vivo* doses of glycidamide were 30% of those of acrylamide (Bergmark *et al.*, 1993). However, improved analytical sensitivity has enabled the measurement of the GAVal levels at low acrylamide exposure levels also, and it was found that the levels of GAVal were only 3-12% of those of CEV (27-1854 pmol CEV/g globin). This was considerably lower than would have been predicted based on linear extrapolation of the GAVal levels previously found in the Chinese workers exposed to high levels of acrylamide (Pérez *et al.*, 1999).

Genotoxicity

Acrylamide does not produce gene mutations in bacterial cells, but the epoxide metabolite glycidamide does in the absence of an exogenous metabolic system. Acrylamide showed equivocal, negative or weakly positive results in mammalian gene mutation assays. It induced chromosomal aberrations, micronuclei (derived by breakage or aneuploidy), sister chromatid exchanges (SCE), polyploidy and other mitotic disturbances in mammalian cells *in vitro* in the absence of exogenous metabolic activation. Acrylamide did not induce unscheduled DNA synthesis (UDS) in rat hepatocytes, while glycidamide induced UDS in human mammary cells, with equivocal results in rat hepatocytes. Acrylamide induced somatic mutations as well as sex-linked recessive lethal mutations in *Drosophila*. In somatic cells *in vivo* acrylamide was positive in the mouse spot test, in the bone marrow chromosome aberration assay and in particular in the micronucleus assay. In a transgenic mouse model (MutaMouse) acrylamide induced a small increase in the mutation frequency. Acrylamide is clearly positive in a number of different germ cell assays (dominant lethal assays, heritable translocation and specific locus assays) indicating that it induces heritable genetic damage at the gene and chromosome level.

Glycidamide induced dominant lethal mutations, similarly to acrylamide (IARC, 1994; EC, 2000).

As already mentioned, acrylamide, and to a lesser extent glycidamide, produced adducts in rat and human haemoglobin. The only DNA adduct detected in mice and rats exposed to acrylamide was reported to be an adduct of the epoxide metabolite glycidamide with guanine. At present, data on DNA adduct formation in humans are lacking.

Cell transformation

Acrylamide induced cell transformation in four different assays with mammalian cells *in vitro*.

Carcinogenicity

Acrylamide has been tested for carcinogenicity in rats in two long-term studies (Johnsson *et al.*, 1986; Friedman *et al.*, 1995). It was concluded that the lowest effective dose observed in these studies was 1-2 mg/kg bw/day. In both studies, acrylamide produced increased incidences of benign and/or malignant tumours in the mammary gland and thyroid as well as mesotheliomas in the testes. In only one of the studies increased incidences of tumours were observed in the uterus, clitoral gland, pituitary gland, adrenal, and the oral cavity. Tumours of the brain and spinal cord were also seen in both studies, but they did not show clear dose responses and did not attain statistical significance. However, some concerns do remain, as there is a suggestion, although not convincing, of some changes at the highest dose levels and because the brain and spinal cord represent possible target tissues for acrylamide.

In screening bioassays, acrylamide, given either orally or intraperitoneally, increased both the incidence and multiplicity of lung tumours in strain A mice. Acrylamide also initiated a dose-related increase in the incidence of squamous-cell papillomas and carcinomas of the skin of mice after oral, intraperitoneal and topical administration, followed by topical treatment with 12-*O*-tetradecanoylphorbol 13-acetate.

The potential carcinogenicity of acrylamide has not been thoroughly investigated in humans. Two cohort mortality studies have been conducted among workers exposed to acrylamide. The first study involved workers exposed to acrylamide at 3 factories in the United States of America and at one factory in the Netherlands. There were 2293 persons in the "acrylamide-exposed" group (those exposed to >0.001 mg/m^3-years) and 8094 people in the group of "unexposed" workers (exposed to <0.001 mg/m^3-years). Overall, this study did not reveal any significant increases in mortality from any given cause, including site-specific cancer, amongst the workers potentially exposed to acrylamide at these plants. However, among the "acrylamide-exposed" workers, there was a slight, but not statistically significant increase, in cancer of the pancreas (SMR=2.03; 95% confidence intervals, CI =0.87-4.00). There was no trend with increasing exposure. It was stated that this study would have been able to detect a 25% increase in total cancer, 50% increase in respiratory cancers, and a 3-fold increase in cancer of the brain and central nervous system with a power of 80% (EC, 2000).

The second study showed no significant excess of cancer as well. However, the study only involved 371 workers and the exposure and latency periods were of short duration.

Reproductive and developmental toxicity

Impaired fertility has been demonstrated in male rats exposed to 15 mg/kg bw/day or more for 5 days. The impaired fertility may have been associated with effects on sperm count and sperm motility parameters. In other rat studies effects on fertility were less clear, with impaired copulatory ability possibly arising as a secondary result of neurotoxic effects. However, studies did indicate marked reductions in sperm count, which also suggests that male fertility could be impaired. In mice impaired fertility was also observed in one study with marked effects on sperm parameters. As with the rat studies, it was unclear whether or not impaired fertility was secondary to neurotoxicity. No effects on fertility in rats were observed in a 2-generation reproduction study in which males and females of each generation received 5 mg/kg/day for 10-11 weeks. No clear effects on fertility were seen in a continuous breeding study in mice exposed to about 9 mg/kg bw/day acrylamide for up to 27 weeks.

Acrylamide was not teratogenic to rats or mice after oral treatment of dams with doses up to the toxic level. Studies in rats and mice have demonstrated some minor signs of developmental toxicity (increased incidence of skeletal variations and slightly impaired bodyweight gain) at exposure levels that were associated with maternal toxicity during the major period of organogenesis (about 15 mg/kg/day or more for rats and about 45 mg/kg/day for mice). Such effects are considered likely to be secondary to maternal toxicity and are therefore of limited toxicological significance.

Risk estimates presented by the Swedish and Norwegian authorities

The SNFA has presented results of several quantitative risk assessments. These assessments were based on the results of long-term studies in rats administered acrylamide in the drinking water, where increased incidences of tumours were seen in several organs. The outcomes of these risk assessments were somewhat different since they were based on different mathematical models. By assuming an intake of 1 µg acrylamide/kg body weight/day the lifetime risk for cancer has been calculated to be 4.5 per 1000 by the U.S. EPA in 1993 (EPA Integrated Risk Information System (IRIS) at www.epa.gov/iris), 0.7 per 1000 by WHO (WHO, 1996) and 10 per 1000 by the research group at Stockholm University (Granath *et al.,* 1999).

The Norwegian authorities performed a linear extrapolation using the tumour incidence indicator T25 including a scaling factor per kg body weight $W^{0.25}$ in the extrapolation from rats to humans (Sanner *et al.*, 2001; Dybing *et al.*, 1997). The LED10, which is the 95% lower confidence interval of the dose causing an increase of 10 % in the tumour incidence of the animals, as proposed by US EPA was also used as a starting point for a linear extrapolation. Also in this case was the same scaling factor used in the extrapolations from rats to humans.

The induction of breast fibroadenoma in female rats in the study of Johnson *et al.* (1986) was used. The calculated life time risks for humans were 1.0 and 1.6 per 1000 assuming an intake of 1 μg acrylamide/kg bw/day and using the two extrapolation methods, respectively.

Discussion and conclusions

Analyses conducted on samples collected in the United Kingdom, Norway, Switzerland and the United States of America have verified the original Swedish observation that acrylamide is formed primarily in carbohydrate-rich food prepared or cooked at high temperatures (see Table 1). So far, the highest levels have been found in potato chips (French fries), potato crisps and other fried, deep-fried or oven-baked potato products, together with some crisp bread, biscuits, crackers and breakfast cereals. The presence of a very high level of acrylamide (more than 10 mg/kg) in overcooked frying chips demonstrates the influence of cooking temperature and duration on acrylamide formation. No acrylamide formation was detected in raw and boiled foodstuffs.

Considerable variations in acrylamide levels have been observed within each food group analysed so far. This suggests that it may be possible to reduce the levels by changing the methods of production and preparation.

The finding of acrylamide formation in various processed foods does not represent a new risk, in the sense that it is not due to an introduction of a new carcinogenic chemical in the food chain or the application of a new food technology. Rather the finding is new knowledge about a so far unnoticed, but existing risk. The findings are important in that they may serve to bring about an improvement in food safety in the future, if appropriate measures can be taken to lower the concentrations of acrylamide in foods.

The mechanism of formation of acrylamide following heat treatments is not known at present. As has been already stated, the available results suggest that acrylamide is formed primarily in carbohydrate-rich foods at high temperatures and it is likely that elucidation of the mechanisms behind this formation may lead to changes in food processing and cooking procedures that will decrease the formation of acrylamide.

Estimates of the dietary intake of acrylamide by adults were available from Sweden (approximately 0.5 μg acrylamide/kg bw/day) and Norway (median and 97.5 percentile: 0.3 and 1.3 μg acrylamide/kg bw/day). Based on the analytical data and dietary data from different countries WHO considered an order-of-magnitude estimate of the average long-term dietary intakes of acrylamide in developed countries to be 0.3 to 0.8 μg/kg bw/day.

In all of the above mentioned cases the estimated dietary intake of acrylamide by children, adolescents and younger men were considered to be significantly higher than for adults in general. It is likely that the consumption of snacks by children and young adults is higher than that of the rest of the population. Children also have a lower average body weight than adults and a higher average food intake per kg body weight than adults. Thus on a body weight basis

the exposure to various substances could be larger for children compared to adults. This was particularly evident from estimates made on the intake of acrylamide in children and adolescents in Norway.

There may be considerable differences between the European countries, due to the differences in food consumption patterns and cooking traditions. The estimated mean intakes of acrylamide from food categories, for which analytical results were available, were compared between 10 EU Member States and it appeared that some countries had higher intakes than others. However, more precise estimates for the European countries have to await further analysis of the formation and presence of acrylamide in foods. Therefore, it should be stressed that analytical data so far are only available for a limited number of foods that may potentially contain acrylamide.

The above estimated daily intake of acrylamide via food is about 5 orders of magnitude lower than the acute toxic dose in experimental animals and acute toxicity (e.g. seizures) is, therefore, not expected to occur.

Repeated oral administration of acrylamide to experimental animals produces peripheral neuropathy. Peripheral neuropathy has also been reported in humans following occupational exposures. Histopathological examination of tissues in 2-year rat studies showed peripheral nerve lesions at 2 mg/kg/day, and a no adverse effect level (NOAEL) at 0.5 mg/kg bw/day.

Acrylamide is considered to be both genotoxic *in vivo* and carcinogenic in experimental animals. It is positive not only in genotoxicity studies in somatic cells, but also in a number of different germ cell assays, indicating that it may produce heritable genetic damage in humans. The genetic effects of acrylamide can be explained by at least two types of mechanisms. The first type involves acrylamide-protein binding. Cross-linking of the chromosomes or chromosome-associated proteins (e.g. protamines) may be responsible for the induction of structural and numerical chromosome aberrations. This is a threshold-based event. The second type of mechanism involves DNA binding. Glycidamide adducts are responsible for this activity and they may be involved in the induction of both gene mutations and structural chromosome aberrations. This is a non-threshold-based event.

In long-term rat studies, acrylamide produced increased incidences of benign and/or malignant tumours in a number of tissues, such as the mammary glands and thyroid, as well as mesothelioma in the testes. This pattern of tumour induction at different sites is consistent with a genotoxic mode of action. Although humans are able to form the reactive metabolite glycidamide from acrylamide, there is as yet no evidence of carcinogenicity in humans from the limited data available. The International Agency for Research on Cancer (IARC) in 1994 classified acrylamide as *probably carcinogenic to humans* (class 2A).

The Committee evaluated acrylamide in 1991 as a monomer in food contact materials where it concluded that it is a genotoxic carcinogen. An adequate database and all the essential studies in relation to the evaluation of the oral short- and long-term toxicity of acrylamide, including its genotoxicity and carcinogenicity, were already available at that time and considered by the

Committee, and no new information has appeared that would change the opinion given in 1991. Therefore, this evaluation is still valid. The same conclusion was reached by CSTEE in its Opinion on the Risk Assessment Report of Acrylamide carried out in the framework of Council Regulation (EEC) 793/93 on the evaluation and control of the risks of existing substances.

For substances that are both genotoxic and carcinogenic the Committee uses a weight-of-evidence assessment of all the available scientific data in describing the hazard. However, characterisation of the risk has been more difficult and the Committee has generally recommended that exposures should be as low as reasonably achievable (ALARA). ALARA was found to be the appropriate recommendation for genotoxic carcinogens because such substances are considered to be without a threshold in their action on DNA.

The Committee has never used mathematical modelling, often described as quantitative risk assessment, to extrapolate from animal data in order to estimate risks to humans at low exposures to genotoxic carcinogens in food. Such estimates are made by assuming that humans will respond in the same way as rodents and then modelling the missing part of the dose-response curve below the lowest data point in a rodent bioassay, i.e. extrapolating down to zero from much higher doses. At the present time, the Committee does not recommend the use of mathematical modelling for chemicals because 1) it is rarely known, for a particular substance, whether a given model actually reflects the underlying biological processes, 2) there is no agreement between regulatory bodies as to which model should be used, and 3) the numerical estimate of risk obtained is critically dependent on which model is used. This can result in estimates of risk for the same substance varying by several orders of magnitude, depending on the model selected.

Therefore, the Committee is of the opinion that it is not possible at present to determine the actual risk from exposure to acrylamide in food.

Recommendations

The Committee recommends that levels of acrylamide in food should be as low as reasonably achievable. However, given the current lack of detailed knowledge about a number of aspects in relation to acrylamide and food safety, the Committee at this stage can only offer general advice on the scientific issues relevant to risk management.

Considerable variations in acrylamide levels have been observed within each food group analysed so far. This suggests that it may be possible to reduce the levels by changing the methods of production and preparation.

The Committee is of the opinion that several principles can be already applied in order to minimise human dietary exposure to acrylamide. To this end the Committee endorsed the interim advice given by the FAO/WHO Consultation (WHO, 2002):

- *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.*

The Committee noted that the high levels of acrylamide so far found formed by heat processing of food calls for urgent research into measures to lower this formation and for research to understand the implications for human health. Initiatives should therefore be taken nationally and internationally to commence multidisciplinary research related to:

- Measures to reduce the levels in food, both in households and industry
- The mechanisms of formation of acrylamide in food
- Levels in food and extended dietary exposure assessments, covering also national variations
- Bioavailability of acrylamide in food
- Elucidation of the mode of action as a carcinogen
- Investigation of the relationship between dietary intake of acrylamide and formation of glycidamide-DNA adducts
- Analysis of dietary acrylamide intake, exposure biomarkers and disease endpoints in existing European and worldwide epidemiological cohorts.
- Epidemiological studies on cancer in populations of known high exposure, such as occupationally exposed workers.

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