Draft opinion on 'acrylamide in food'

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efsa
European Food Safety Authority

www.efsa.europa.eu

OUTLINE

- Background and terms of reference (TORs)
- Structure of the draft opinion
- Exposure assessment
  - Occurrence data submitted to EFSA
  - Food consumption data
  - Estimation of the exposure
- Hazard characterisation and identification
- Risk characterisation – draft conclusions
- Uncertainties
- Draft recommendations

BACKGROUND AND TORs

As provided by the European Commission…

- EC is monitoring acrylamide levels in food via specific monitoring recommendations. The results of the monitoring are compiled by EFSA.

- Indicative values have been established in that recommendation.

  If an indicative value is exceeded, an investigation should be carried out. The indicative values are not legal limits and do not require enforcement action if they are exceeded.

- In the near future, the Commission will assess the approach taken and decide about the need for further appropriate measures.

- Since the Statement of the CONTAM Panel in 2005 and the ESFA Scientific Colloquium on acrylamide carcinogenicity, new scientific information had become available.

In order to assess the need for further measures,
the EC asks the EFSA for a scientific opinion on the risk to human health related to the presence of acrylamide in food.

STRUCTURE OF THE DRAFT OPINION

- Sections to set the scene and provide generic (comprehensive but not exhaustive) background information on acrylamide in food to support the overall conclusions of the draft opinion:

  - **Chemistry**
  - **Legislation**
  - **Formation in food**
  - **Impact of raw material, storage and processing**
  - **Mitigation measures**
  - **Previously reported data in the literature on occurrence, exposure and risk assessments**

STRUCTURE OF THE DRAFT OPINION

- Main sections of the draft opinion: the 4 pillars of the risk assessment process

HAZARD IDENTIFICATION

EXPOSURE ASSESSMENT

Occurrence data

x

Food consumption

Relevant food groups, adults and specific groups of the population, time trends

HAZARD CHARACTERISATION

Toxicokinetics (ADME), acute/sub/chronic toxicity, human data, genotoxicity, mode/mechanism of action, dose-response for critical effect, derivation of a health based guidance value

RISK CHARACTERISATION

Relates exposure to a chemical in a given population with toxicological effects (health based guidance value/MOE), concluding with the likelihood of adverse effects

EXPOSURE ASSESSMENT

- **Occurrence data submitted to EFSA**
  - Overview of the datasets
  - Description of AA levels in main food groups
- **Food consumption data**
  - Description of food consumption data
- **Estimation of the exposure**
  - Methodology
  - Exposure estimates
  - Main food contributors
  - Specific consumption behaviours

OVERVIEW OF THE OCCURRENCE DATASETS

Two sources of occurrence data

European countries
(continuous data call)

8 240 results

Food associations
(*ad-hoc* call for data)

37 552 results

Data management and validation

- Check for consistency
- Sampling requirements
- Analytical requirements

7 448 results

35 971 results

OVERVIEW OF THE OCCURRENCE DATASETS

Two sources of occurrence data

European countries
(continuous data call)

7 448 results

Food associations
(*ad-hoc* call for data)

35 971 results

Assessment of the comparability between both datasets

- Consistency
- Complementary

ONE SINGLE DATASET

43 419 results

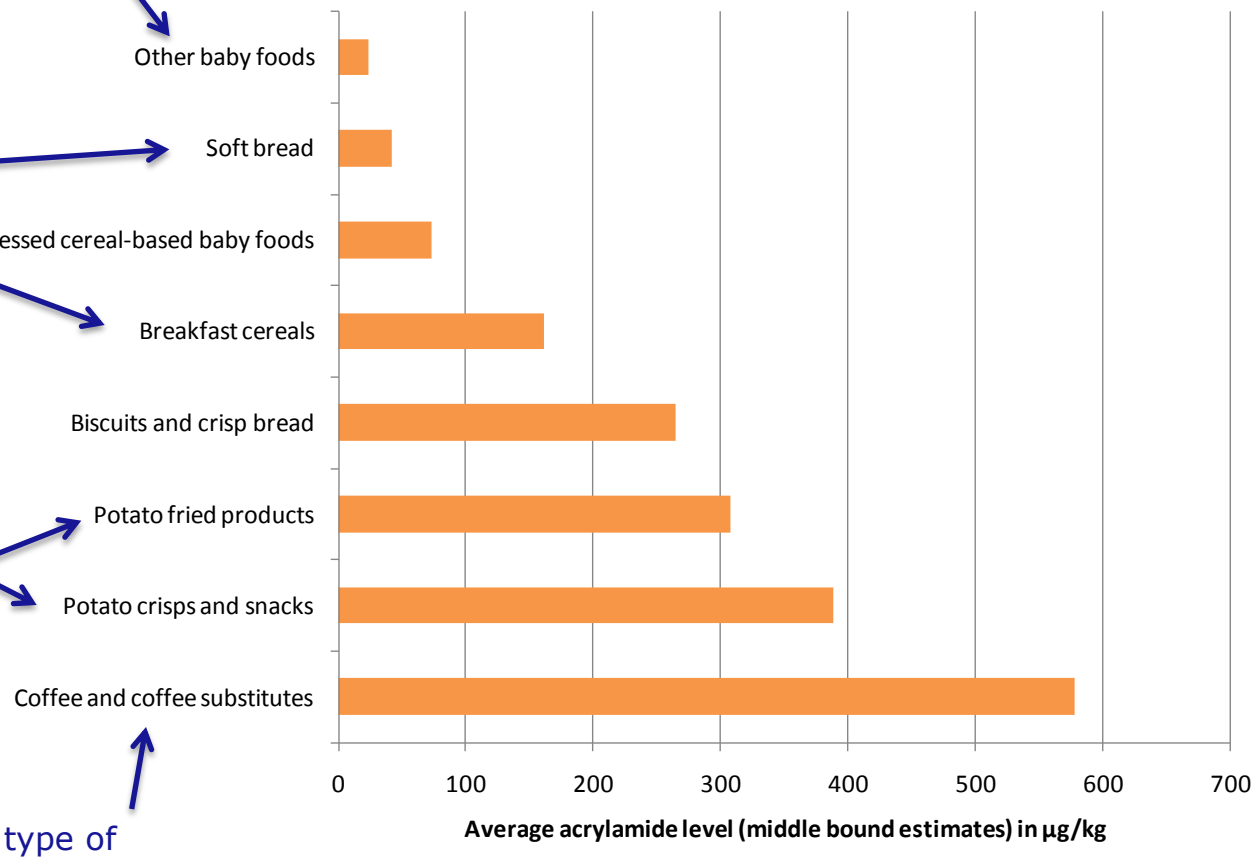
DESCRIPTION OF AA LEVELS IN MAIN FOOD GROUPS

Influence of prunes content

Influence of the type/parts of cereals used

Influence of the state of potato ingredient (fresh/dough)

Influence of the type of coffee (roasted, instant), influence of roasting degree, influence of the type of coffee substitute



FOOD CONSUMPTION DATA

Comprehensive European Food Consumption database

(2014 updated version)

In view of a chronic exposure assessment:

- 61 338 subjects from 28 surveys and 17 European countries.

- covering 7 age-groups: infants, toddlers, other children, adolescents, adults, elderly, very elderly.

- individual consumption data covering 2 to 7 days.

- collected through 24-48 hours recalls and food records.

FOOD CONSUMPTION DATA

Comprehensive European Food Consumption database

(2014 updated version)

French fries and potato fries

Mainly consumed by toddlers, other children, adolescents and adults

Highest consumption levels in adolescents and adults: 68-69* g/day on average among consumers

Potato crisps

Mainly consumed by other children and adolescents

Highest consumption levels in adolescents and adults: 20-22* g/day on average among consumers

Coffee

Mainly consumed by adults, elderly and very elderly

Highest consumption levels in elderly: 14* g dry equivalent/day on average among consumers

** Median across the population groups consuming the products*

METHODOLOGY FOR THE EXPOSURE ASSESSMENT



For 112 food groups:

mean occurrence values
(lower bound – upper bound)

X

mean consumption
at the individual level

sum over the diet

mean exposure levels for 61 338 subjects

summary statistics at the population level

mean and 95th percentile of exposure for 82 population groups
(age group – country – survey)

Main assumptions

- **Cooking of potato products**
- **Type of coffee beverages**

EXPOSURE ESTIMATES

Baseline scenario

Age group	Mean Median [Minimum; Maximum]		P95 Median [Minimum; Maximum]	
	Lower bound	Upper bound	Lower bound	Upper bound
	µg/kg b.w. per day		µg/kg b.w. per day	
Infants	0.8 [0.5; 1.4]	0.9 [0.7; 1.7]	2.3 [1.4; 2.3]	2.5 [1.7; 2.8]
Toddlers	1.4 [1.1; 1.9]	1.5 [1.2; **1.9**]	2.6 [2.3; 3.4]	2.7 [2.4; **3.4**]
Other children	1.2 [0.9; 1.6]	1.2 [0.9; 1.6]	2.2 [1.4; 3.2]	2.3 [1.5; 3.2]
Adolescents	0.7 [0.4; 0.9]	0.7 [0.4; 0.9]	1.4 [0.9; 2.0]	1.4 [0.9; 2.0]
Adults	0.5 [0.4; 0.6]	0.5 [0.4; 0.6]	1.0 [0.7; 1.3]	1.0 [0.8; 1.4]
Elderly	0.5 [**0.3**; 0.5]	0.5 [0.4; 0.5]	0.8 [**0.6**; 1.0]	0.9 [0.7; 1.0]
Very elderly	0.5 [**0.3**; 0.5]	0.5 [0.4; 0.6]	0.9 [**0.6**; 1.0]	0.9 [0.6; 1.0]

Infants, toddlers and other children are the most exposed groups

Substantial uncertainties regarding the mode of preparation of potatoes

MAIN FOOD CONTRIBUTORS

INFANTS

- Baby foods
- Other potato/cereal/cocoa products

TODDLERS, OTHER CHILDREN, ADOLESCENTS

- Potato fried products
- Soft bread
- Biscuits
- Other potato/cereal/cocoa products

ADULTS AND ELDERLY

Additional main contributors:

- Coffee and coffee substitutes

SPECIFIC CONSUMPTION HABITS

Home-cooking habits and place of consumption

Conditions for potato frying (instruction on the packages, preference for crispy and brown French fries, current practices in restaurants) resulted in exposure levels from up to 22 % lower to up to 80 % higher than estimated in the baseline scenario

Degree of bread toasting resulted in exposure levels less than 5 % higher than estimated in the baseline scenario

Brand/products loyalty

Scenarios on brand loyalty resulted in variations of less than 5 % of the total exposure level

Scenarios on consumers' preference to certain types of coffee (roasting degree) resulted in variations of less than 15 % of the total exposure level

HAZARD IDENTIFICATION AND CHARACTERISATION

- Main conclusions on,
  - Toxicokinetics
  - Toxicity in experimental animals
  - Genotoxicity
  - Carcinogenicity
  - Mode of action
  - Epidemiological studies

TOXICOKINETICS

- AA is extensively absorbed from the gastrointestinal tract and it is rapidly distributed into the tissues.

- AA crosses the placenta and is transferred to a small extent into human milk.

- AA is metabolised to **glycidamide (GA)**, which is a reactive epoxide and is widely distributed into the tissues.

  The main enzyme involved in the AA epoxidation is CYP2E1

  Mice are more proficient in converting AA into GA than either rats or humans

TOXICOKINETICS

Biomarkers of exposure

- Both AA and GA are conjugated with glutathione (GSH), and subsequently converted to **mercapturic acids (MA)**

The MAs of AA and GA represent the major metabolites and are excreted in urine

- Covalent **adducts of AA-DNA** have been generated in chemical reactions, but have never been detected *in vivo* or *in vitro*

Covalent **GA-DNA adducts** have been detected *in vitro* and *in vivo*

- AA and GA can also react with proteins to form covalent adducts, e.g. with **haemoglobin (Hb)**

TOXICITY IN EXPERIMENTAL ANIMALS

- The major non-neoplastic findings were:

❖ **Adverse effects on the peripheral nervous system**

e.g. hind linb strenght, histopathological changes in nerves

❖ **Adverse effects on male reproductive parameters**

e.g. reduced sperm counts , effects on sperm and testis morphology

❖ **Signs of developmental toxicity**

e.g. increased incidence of skeletal variations, slightly impaired body weight gain, neurobehavioural effects

- GA studies in mice/rats revealed adverse effects similar to those reported for AA

- In rats, neurotoxicity was associated with lower AA doses and greater severity compared to GA

GENOTOXICITY

- *In vitro* genotoxicity studies indicate that AA is a weak mutagen in mammalian cells but an effective clastogen.

- GA is a strong mutagen and a clastogen. It induces mutations via a DNA adduct mechanism.

- *In vivo*, AA is clearly genotoxic in somatic and germ cells. AA exerts its mutagenicity via metabolism to GA.

- AA can also induce gene mutations by a pathway involving the generation of reactive oxygen species (ROS) and oxidative DNA damage.

CARCINOGENICITY

- AA is carcinogenic in multiple tissues of both male and female mice and rats:

Mice - Harderian gland adenomas and adenocarcinomas, mammary gland adenoacanthomas and adenocarcinomas, lung alveolar/bronchiolar adenomas, benign ovary granulosa cell tumours, skin sarcomas, stomach and forestomach squamous cell papillomas

Rats - Adenomas, fibroadenomas and fibromas of the mammary gland, thyroid gland follicular cell adenomas or carcinomas, and testes or epididymis tunica vaginalis mesotheliomas

A similar spectrum of tumours is observed when equimolar concentrations of GA were administered in drinking water to rats and mice (NTP, draft report)

Consistent with GA being the proximate carcinogenic metabolite of AA

MODE OF ACTION

- AA is an electrophilic molecule, which can react with nucleophilic target molecules. The **neurotoxic properties of AA** are considered to originate mainly from this type of reactivity.

- AA shows some reactivity towards nucleic acids. Reports on the formation of DNA adducts *in vivo* suggest that **GA is mainly, if not exclusively, responsible for the formation of DNA adducts**.

- From the available studies in the literature, evidence on hormonal and endocrine effects of AA are equivocal. Mechanistic hypotheses on local endocrine effects of AA which may explain tumour formation in certain hormone-regulated target tissues lack experimental proof.

EPIDEMIOLOGICAL STUDIES

ACRYLAMIDE EXPOSURE AND CANCER

- **Occupational exposure**

  Two cohort studies did not indicate an increased cancer risk.

- **Dietary exposure**

  34 publications based on 16 epidemiological studies on several cancer sites

  For most cancer sites, no consistent indication for an association between AA exposure and increased risk

For renal cell, endometrial and ovarian cancer a few studies have reported positive associations with AA intake, although the overall evidence is limited and inconsistent

EPIDEMIOLOGICAL STUDIES

ACRYLAMIDE EXPOSURE AND CANCER

- In most studies there was adjustment for age, sex, education and various other risk factors for the cancers considered (e.g. tobacco smoking, BMI, alcohol drinking, energy intake, hormonal/reproductive factors for female cancers)

- Possible limitations of the methodologies used to estimate AA intake,
  - FFQs not specifically designed to estimate AA intake
  - FFQ not including specific questions on cooking methods
  - Sources of AA contents of foods referring to other populations and calendar periods than those under investigation

- These limitations may have introduced some misclassifications of AA exposure. However, these are likely to be non-differential (i.e. similar in cases and non-cases) with respect to cancer outcome, and thus tend to bias the estimates towards the null

EPIDEMIOLOGICAL STUDIES

AA EXPOSURE AND REPRODUCTIVE/DEVELOPMENTAL CONSEQUENCES

- Two studies reported an inverse relation between AA exposure (measured by levels of AA and GA adducts) and birth weight and other markers of foetal growth

- Such association can be attributed to other unidentified exposures correlated with AA intake. It cannot be established whether the association between dietary AA and birth weight is causal

- The CONTAM Panel concluded that there are yet too many uncertainties to conduct a risk assessment based on these human data

EPIDEMIOLOGICAL STUDIES

AA EXPOSURE AND NEUROLOGICAL ALTERATIONS

- Studies among workers occupationally exposed to AA showed an increased risk of neurological alterations, including mostly the peripheral, but also the central nervous system.

CRITICAL EFFECTS

- From all data available, the CONTAM Panel identified four possible critical endpoints for AA toxicity:

  - ✓ neurotoxicity,
  - ✓ effects on male reproduction
  - ✓ developmental toxicity
  - ✓ carcinogenicity

- The data from human studies were not adequate for dose-response assessment.

- The CONTAM Panel performed **benchmark dose (BMD) analyses** on data from experimental animals induced by AA:

  - ✓ **neurotoxicity**
  - ✓ **tumour incidences**

HAZARD IDENTIFICATION AND CHARACTERISATION

- **Reference point for non-neoplastic effects**

0.43 mg/kg b.w. per day

Lowest $BMDL_{10}$ from the data on incidences of peripheral nerve (sciatic) axonal degeneration in male F344 rats exposed to AA in drinking water for 2 years

Using this $BMDL_{10}$ for neurotoxicity as the reference point is conservative when considering other possible non-neoplastic effects.

- **Reference point for neoplastic effects**

0.17 mg/kg b.w. per day

Lowest $BMDL_{10}$ from data on incidences of Harderian gland adenomas and adenocarcinomas in male $B6C3F_1$ mice exposed to AA for 2 years.

Although the Harderian gland is an organ absent in humans, it was considered a conservative endpoint for assessment of the risk for neoplastic effects of AA in humans.

RISK CHARACTERISATION

AA and its metabolite GA are positive in a variety of genotoxicity tests

Concern with respect to genotoxicity

Not appropriate to establish a tolerable daily intake (TDI)

MARGIN OF EXPOSURE (MOE) approach

RISK CHARACTERISATION – DRAFT CONCLUSIONS

▪ Non-neoplastic effects (neurotoxicity)

— Taking into account differences between species and within the human population, the MOEs across surveys and age groups are not of concern.
— The MOEs for the 95th percentile UB exposure estimates for toddlers and other children are close to the value that might be of concern for neurotoxicity.

▪ Neoplastic effects

— The MOEs are all lower than the value of 10 000.
— Although the available human studies have not demonstrated AA to be a human carcinogen, the MOEs across surveys and age groups indicate a concern with respect to neoplastic effects.

▪ The CONTAM Panel noted that AA is a **germ cell mutagen** and that there are at present no established procedures for risk assessment using this endpoint.

UNCERTAINTIES

SOURCES OF UNCERTAINTY

- Lack of representativeness for certain food commodities
- Heterogeneity of the data (mode of food preparation)
- Limited number of samples available in some food groups
- Lack of information on the way potato/coffee are prepared

- Use of the Harderian gland as the target tissue
- Relatively wide variation in the outcomes of the BMD modelling
- Lack of support from the occupational studies for the major critical effects, except for neurotoxicity
- Inconsistency in the human studies of associations between AA dietary exposure and cancer

The impact of the uncertainties on the risk assessment is moderate.

DRAFT RECOMMENDATIONS

– The reporting of AA occurrence data should be improved regarding the mode of food preparation before analysis.

– Duplicate diet studies are recommended in order to improve exposure assessment (provide a more accurate indication of AA levels in food as prepared and consumed at home).

– Data on urinary metabolites levels from individuals participating in the duplicate diet studies should be generated for the purpose of validation of the biomarkers.

– Further epidemiological studies are required to confirm or refute the inverse relation between dietary AA intake and birth weight and other markers of foetal growth observed in two studies.

– Improved approaches for the detection and risk assessment of germ cell mutagens should be developed, and applied to AA and GA.

ACKNOWLEDGEMENTS

- Members of the **WG AA in Food**
- Members of the **CONTAM Panel**

- **EFSA staff** (DATA and BIOCONTAM Units)

- **Member States - European countries**
- **Stakeholders**

(occurrence/consumption data)