1 Prioritised substance group: Acrylamide

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1.1 Background information

1.1.1 Hazardous properties

Acrylamide (also named 2-propenamide, acrylic amide, ethylene carboxamide, structural formula: CH_2=CH-CO-NH_2) is a low molecular weight, highly water soluble, organic compound produced for different uses in chemical industry. The concern about hazardous exposure arose in 2002 when acrylamide was discovered to be formed in certain high carbohydrate food at high temperature. From experimental animal studies, acrylamide has been shown to have neurotoxic, carcinogenic, genotoxic and mutagenic effects (category 1B, CLP classification) and also possible/suspected immunotoxic and developmental toxic (category 2 CLP classification) effects as well as adverse effects on the reproductive function in particular in males (1-4). In humans, occupational exposure to acrylamide has been shown to cause neurotoxicity in the peripheral nervous system through prolonged or repeated exposure. Other toxic effects of acrylamide in humans are still under investigation. Although epidemiological studies have not consistently observed an increasing risk of common cancers in relation to dietary acrylamide, there is a concern about its possible carcinogenic effects in humans (IARC classification 2A: probably carcinogenic to humans; SVHC: substance of very high concern). Glycidamide, its main metabolite, is considered to represent the main metabolite, from which the genotoxicity and carcinogenicity of acrylamide originate. A recent study found glycidamide mutational signature in a full one-third of approximately 1600 tumor genomes corresponding to 19 human tumor types from 14 different organs (5). Evidence from a limited number of epidemiological studies suggests that acrylamide may also negatively affect fetal growth (5, 6). It may also cause allergic reactions if in contact with the skin (7). There is no consistent evidence in humans that acrylamide may act as endocrine disruptor. A possible adverse effect of mixtures of acrylamide and other chemical compounds, particularly other carcinogens in food should be taken in consideration for the risk assessment and needs to be further investigated (8, 9).

1.1.2 Exposure characteristics

Acrylamide is manufactured and/or imported in the European Economic Area in 100 000 - 1 000 000 tonnes per year. According to REACH registration data, the substance was readily biodegradable in a screening test and is, therefore, not considered to be persistent. The substance does not bioaccumulate since it has a very low octanol-water partition coefficient. Release to the environment of acrylamide may occur from the industrial use: manufacturing of the substance, as an intermediate step in further manufacturing of another substance (use of intermediates) and for thermoplastic manufacture. Acrylamide is most commonly found in water and soil but rarely found in air. However, it is expected to be highly mobile in both water and soil. When released to land, acrylamide does not bind to soil, and move rapidly through the soil column and into ground water. It is removed from soil through enzyme-catalysed hydrolysis and it does not bioconcentrate in aquatic organisms (10).

1.1.2.1 Human related exposure sources and uses

The industrial and laboratory use of acrylamide mainly concerns the production of polyacrylamides, which are used primarily as flocculants, mainly for clarifying drinking water and treating

wastewater. Acrylamide and polyacrylamides are also used in the production of dyes, organic chemicals, permanent-press fabrics, textiles, pulp and paper products. In the oil industry, acrylamide is used as a flow control agent to enhance oil production from wells. Beyond the chemical industry use, acrylamide is used in building and construction (e.g. as grouting agent and soil stabiliser for the construction of tunnels, sewers, wells, and reservoirs), health service, and scientific research (10). Moreover, in 2002 it was observed to be generated during food processing at temperatures above 120 degrees Celsius under low moisture conditions. It is formed predominantly by food containing asparagine and reducing sugars via Maillard reaction when processed at high temperature such as frying, roasting and baking (not boiling). The main food sources of acrylamide are coffee (and solid coffee substitute), potatoes fried products (including potatoes and vegetables crisps), biscuits, cereals and other products such as roasted nuts, olives in brine, prunes and dates and baby food. Protein-based foods (such as meats) probably contain low amounts of acrylamide (11). Acrylamide is also present in tobacco smoke.

1.1.2.2 Human exposure routes

Humans are exposed through inhalation, ingestion and the dermal uptake.

Oral uptake through the ingestion of food, cigarette smoke and water is the predominant exposure route for the general population. For occupational exposure, inhalation and dermal contact at the workplace where acrylamide is used or produced is another important route of acrylamide exposure. Moreover, transplacental exposure should also be taken in consideration for the risk assessment, although more investigation is needed (6, 12, 13).

1.1.2.3 Human Biomonitoring (HBM) data availability

Acrylamide exposure is assumend to be widespread among the general population. The most vulnerable groups for the possible adverse effect of acrylamide exposure are infants, toddlers, children and pregnant women. Of note, workers at the industrial site and manufacturing have also been shown to be highly exposed (14). Several epidemiological studies have been performed to investigate the association between occupational exposure to acrylamide and dietary acrylamide, and risk of cancer, neurological alterations and fetal growth (11). However, the exposure was mainly self-estimated (e.g. questionnaire based job history and dietary intake). Human Biomonitoring data on acrylamide are few and not been measured or published, respectively, in population representative studies up to now, in particular in Europe (5, 6, 15-20). Biomarkers of acrylamide have been identified (see Technical aspect section for details). The use of these specific and sufficiently sensitive biomarkers would represent a reliable indicator of dose instead of estimations based on self-reported data.

1.1.2.4 Health based guidance values available for HBM data

Since acrylamide and its metabolite glycidamide have been shown to generate genotoxicity and to be carcinogenic at any level, a tolerable daily intake (TDI) cannot be defined. Instead, health guidance values can be expressed as margin of exposure (MOE) and Benchmark Dose Lower Confidence Limit ($BMDL_{10}$). From animal studies, $BMDL_{10}$ values of 0.43 mg/kg body weight (b.w.) per day have been selected for peripheral neuropathy and of 0.17 mg/kg b.w. per day for neoplastic effects.

The current levels of dietary exposure to acrylamide seem not to be of concern with respect to non-neoplastic effects (MOE > 10000 or higher) The mean daily exposure of adults in Europe is estimated to be between 0.4 and 0.9 µg acrylamide/kg b.w. (EFSA, 2015). Calculating the MOE for peripheral neuropathy results in MOEs between 478 and 1075. That is well below 10,000. It is highly questionable, whether the MOE concept should be used for the risk assessment of non-neopastic effects. However, although the epidemiological association studies have not demonstrated evidence for acrylamide being carcinogenic, the MOE values indicate a concern for neoplastic effects based on animal evidence (11).

Biomonitoring equivalents (BE) - estimates of the concentrations of acrylamide and its metabolites in blood and urine - have been proposed as screening tools for interpreting HBM data for acrylamide in relation to non-cancer and cancer related effects (21). The non-cancer reference dose for acrylamide, established by the United States Environmental Protective Agency (USEPA), corresponds to a BE value for mercapturic acid of acrylamide (AAMA), a urinary biomarker of acrylamide, of 16 µg/g creatinine. The USEPA reference doses for cancer, based on an additional lifetime cancer risk of $1x10^{-4}$ and $1x10^{-6}$, correspond to 2 µg AAMA/g creatinine and 0.02 µg AAMA/g creatinine, respectively (19). For other BE values for acrylamide and for the description of how these values were estimated, please refer to Hays et al. (21).

For occupational exposure to acrylamide, the derived no- or minimum effect level (DN(M)EL), level of exposure above which a human should not be exposed, is also available: inhalation exposure, long term DMEL 70 mg/m^3 and short term (acute) 120 mg/m^3; dermal exposure, long term DMEL 100 µg/kg b.w./day and short term DNEL 3 mg/kg b.w./day.

1.1.3 Policy relevance

Regulatory measures have been taken at the EU level. Acrylamide is registered under REACH and included in the candidate list of substances of very high concern (SVHC) due to its possible carcinogenic and mutagenic effect. Based on the inclusion in the registration list Annex XVII of REACH, after 5 November 2012 acrylamide should not be placed on the market or used as a substance or constituent of mixture in a concentration equal or greater than 0.1% by weight for grouting applications. Acrylamide has also a harmonised classification under the Classification Labelling & Packaging (CLP) Regulation. The European Drinking Water Directive 98/83/EC has set a parametric value of acrylamide in water for human consumption of 0.10 µg/L. The parametric value for acrylamide refers to the residual monomer concentration in the water as calculated according to specifications of the maximum release from the corresponding polymer in contact with the water. Acrylamide is also listed in the Annex II as substance prohibited in cosmetic products. Precautions for this substance have been recommended by industries under REACH. Moreover, since 2007 acrylamide levels in food are monitored according to a EU Recommendation (further extended Commission Recommendation 2013/647/EU and 2010/307/EU). Use of acrylamide is banned in plastic material and articles intended to come in contact with food (Commission Regulation (EU) No 10/2011 of 14 January 2011). Recently, the EU established mitigation measures and benchmark levels for reducing levels of acrylamide in food (Commission Regulation (EU) 2017/2158).

1.1.4 Technical aspects

Acrylamide is extensively metabolised, mostly by conjugation with glutathione but also by epoxidation to glycidamide. Both acrylamide and glycidamide might be measured in serum. Serum concentration of acrylamide and glycidamide have both been shown to be highly correlated to acrylamide exposure but they have a short half-life. Other biomarkers include the urinary metabolites of acrylamide, mercapturic acids of acrylamide and glycidamide (AAMA and GAMA, respectively), and the hemoglobin adducts of acrylamide and glycidamide (AAVal and GAVal). Urinary metabolites are stable compounds and can be quantified with high specificity and sensitivity. They are measures of metabolic deactivation of AA and GA but are not directly related to critical target tissue doses. The hemoglobin adducts have a lifetime of about 110 days and have been shown to have high correlation with acrylamide exposure (21). Analytical methods for the determination of the aforementioned biomarkers are available and are characterised by the use of liquid- or gaschromatography (HPLC or GC, respectively) with detection by tandem mass spectrometry (MS/MS) using multiple reaction monitoring (MRM).

1.1.5 Societal concern

The societal concern is mainly related to the discovery that acrylamide is produced in processed foods rich in carbohydrates making acrylamide a widespread exposure. From the public perspective, different actions have been taking by several organisations. Chemsec, an independent organisation aiming to solicit legislators to speed-up in the decision-making process, has included acrylamide in the Sin List (Substitute it Now!) of the chemical compounds that can cause cancer, alter DNA or damage the reproductive system (CMR, class I&II). Acrylamide has also been included in the Trade Union Priority List with priority number 3, score 43. Non-governmental organisations (Safe Food Advocacy Law, and Changing Market and SumOfUs) call for mandatory EU limits of acrylamide in food after the “public scandal” related to the finding that acrylamide levels were clearly above the new benchmark level set by the European legislation in 2017, according to results from analyses of samples of potatoe crisps available on the market; in seven out of eighteen samples the acrylamide level exceeded the benchmark level.

1.2 Categorisation of Substances

Table 1-1: Substances included in the substance group, listed according to availability of toxicology and human biomarker data, in category A, B, C, D, E substances (see general introduction)

Category	Abbreviation/ Acronym	Systematic name	CAS No.	Regulation
B	AA	Acrylamide	79-06-1	REACH Regulation Annex XVII (Restriction List) REACH SVHC (candidate list) as carcinogenic (57a) and mutagenic (57b) CLP Regulation as carcinogenic, mutagenic (1B) and reprotoxic (2) IARC classifications 2A, probably carcinogenic to humans

1.3 Policy-related questions

1. What is the current exposure of the EU population to acrylamide?
2. Are the exposure levels a concern for health? Is the exposure to acrylamide associated to cancer, neurological alterations and fetal growth in humans? Is the health risk dependent on long term or intermittent exposure to low quantity of acrylamide?
3. Does the exposure to acrylamide differ significantly between countries and population groups? Are the main reasons for these differences related to different dietary habits or to other factors?
4. Are the health risks dependent on age and gender?
5. Which population groups are more at risk? Are there other sources of exposure of acrylamide that need to be discovered (e.g. smoking habits or other food sources)?
6. Is there a possible mixture of effect between acrylamide and other carcinogens (particularly dietary carcigonogens e.g.benzopyrene) ?
7. Is there an impact from the mitigation for the production in food processing and manufacturing and REACH restrictions on the distribution of acrylamide exposure? Do we need to implement other restrictions to decrease the level of exposure of acrylamide?

1.4 Research Activities to be undertaken

Table 1-2: Listing of research activities to be carried out to answer the policy questions

Policy related questions	Substance	Available knowledge	Knowledge gaps and activities needed
1) What is the current exposure of the EU population to acrylamide? (Policy makers)	Acrylamide	Malmo and Diet Cancer Cohort, Sweden blood n=142 adults (1991-1996) EPIC, FR, SE, DE, UK, IT, GR, NL, ES, DK, blood n=510 adults (1992-2000) Danish Cancer and Health cohort, blood n=377 post-menopausal women (1993-1997) Moba, Norway, blood, n= 79 women mother pregnant (1999–2008) CAPS, Sweden, blood n=377 adult men (2001-2002) Urban et al., Germany, blood, urine, n= 60 adults (2002) Fuhr et al., urine n=6, 16, 5 ; ?,men and women, men (no time measurements) Kutting et al, Germany blood, n=1033 all age and sex (2002-2004) Schettgen et al, Germany, blood n=104 (no time measurement) Boettcher et al., Germany, blood, n= 29 (no time measurement) Kellert et al., Germany, urine, n = 38 adults (no time measurement) Chevolleau et al., France, blood, n = 68 adults (no time measurement) Bjellaas et al., Norway, blood, n= 50 adults (no time measurement) NewGeneris, GR, ES, N0, UK, DK, blood, n= 1,101 mother/child (2006-2010) Heudorf et al., Germany, urine, n= 110 children (no time of measurement) Kotova et al., Sweden, blood, n= 58 adults (no time of measurement)	Lack of HBM data of the general population for most of the EU countries. Actions: ‣ to generate new data based on samples from the aligned studies. Target group: occupationally exposed and general population. Based on the high content of acrylamide in certain foods (for instance baby foods and potato chips) new data should be generated in all age groups: ‣ new born (0-6 months) ‣ children and adolescents ‣ adults (middle ages and elderly, men and women) ‣ derive EU-HBM-HBGVs for workers and for the general population based on the Biomonitoring Equivalents for non-cancer Reference Dose (RfD). (Policy makers) **Relevant WPs: WP7, WP8, WP10**

Policy related questions	Substance	Available knowledge	Knowledge gaps and activities needed
		Mojska et al., Poland, urine, n= 78 women (2012) Carlsson et al.,Sweden, blood, n=51 children (2014) Goerke et al., Germany, urine, n= 20 adults (2015) GerS V, Germany, urine, n=1,450 children (2014-2017) Bioval/Bettermilk, Spain,urine, n=666 children, 120 pregnant women (2015-2022)	
2) Are the exposure level a concern for health? Is the exposure to acrylamide associated to cancer, neurological alterations and fetal growth in humans? Is the health risk dependent on long term or intermittent exposure to low quantity of acrylamide? (Additional questions) 3) Does the exposure to acrylamide differ significantly between countries and population groups? Are the main reasons for these differences related to different dietary habits or to other factors? (Additional questions) 4) Are the health risks dependent on age and gender? (Additional question) 5) Which population groups are more at risk? Are there other sources of exposure of acrylamide that needs to be discovered (e.g. smoking habits or other food sources)? (Additional and policy maker questions)	Acrylamide	Evidence from animal studies have pointed out that acrylamide may be carcinogenic, mutagenic genotoxic, neurotoxic and have adverse effect on fetal growth. See also HBM studies listed above.	Findings from human studies are inconsistent and Human Biomonitoring is limited in Europe (5, 6, 15-20). Risk assessment is needed for both occupational settings and general population. Actions: ‣ generate new HBM data for EU populations where there is a gap that can be considered in further HBM programs.(Policy makers) ‣ include acrylamide in general population surveys at national level to assess the EU population`s exposure to acrylamide. (Policy makers) ‣ create occupational survey to assess whether workers are protected by acrylamide exposure. ‣ estimate the risk of certain endpoints (fetal growth, neurological alterations and cancer) in relation to acrylamide exposure from results of current and new epidemiological studies.(Additional) ‣ data analysis to identify current exposures levels, temporal and geographical trends and data gaps. (Additional) ‣ collection, comparison and evaluation of existing data and integration into IPCheM.(Policy makers) **Relevant WP: WP7, WP8, WP10, WP11, WP13**

Policy related questions	Substance	Available knowledge	Knowledge gaps and activities needed
6) Is there a possible mixture effect of acrylamide and other carcinogens? (Additional question)	Acrylamide		There is limited knowledge on a mixture effect of acrylamide and other carcinogens, particularly dietary carcinogens Actions: ‣ To perform investigations for better understanding of mixture effects of acrylamide and dietary carcinogens e.g benzopyrene. (Additional) **Relevant WP: WP15**
7) Is there an impact from the mitigation for the production in food processing and manufacturing and REACH restrictions on the distribution of acrylamide exposure? Do we need to implement other restrictions to decrease the level of exposure of acrylamide? (Additional questions)	Acrylamide	Restrictions, monitoring, mitigations and prohibitions have been implemented for acrylamide in chemical industry, cosmetic products and in food. This might have decreased the exposure to acrylamide. A recent EU regulation aiming to reduce the level of acrylamide in food does not seem to have been respected by the food industries.	There is lack of evidence regarding how the level of exposure of acrylamide has been affected after the adaptation of EU regulations aimed to decrease the level of exposure. Action: ‣ To evaluate whether the EU regulations had an impact on the reduction of exposure level of acrylamide and weather other restrictions should be implemented for the food industry. (Additional) **Relevant WP: WP10**

1.5 References

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