FORUM

Risk Assessment of Acrylamide in Foods

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Daily mean intakes of acrylamide present in foods and coffee in a limited Norwegian exposure assessment study have been estimated to be 0.49 and 0.46 μg per kg body weight in males and females, respectively. Testicular mesotheliomas and mammary gland adenomas have consistently been found in 2-year drinking water rat cancer studies with acrylamide. Acrylamide also shows initiating activity in mouse skin after systemic administration. Since acrylamide is converted to the mutagenic metabolite glycidamide and forms adducts to hemoglobin in rodents and humans, the tumorigenic endpoints in rats were assumed to be an expression of acrylamide genotoxicity. Using the default linear extrapolation methods LED10 and T25, the lifetime cancer hazard after lifelong exposure to 1 μg acrylamide per kg body weight per day, scaled to humans, was calculated to be, on average, 1.3 × 10⁻³. Using this hazard level and correlating it with the exposure estimates, a lifetime cancer risk related to daily intake of acrylamide in foods for 70 years in males was calculated to be 0.6 × 10⁻³, implying that 6 out of 10,000 individuals may develop cancer due to acrylamide. For females, the risk values were slightly lower. It must be emphasized that this risk assessment is conservative. A number of processes may result in nonlinearity of the dose-response relationships for acrylamide carcinogenicity in the low-dose region, including detoxication reactions, cell cycle arrest, DNA repair, apoptosis, and immune surveillance. Thus, the true risk levels related to acrylamide intake may be considerably lower.

Key Words: acrylamide; food exposure; risk assessment; cancer; LED10, T25.

On April 24, 2002, the Swedish National Food Agency presented data that, in part, showed high concentrations of acrylamide in certain fried, baked, and deep-fried foods, and later in coffee (Swedish National Food Agency, 2002). Since acrylamide has been classified as a Group 2A carcinogen by the European Union (http://ecb.jrc.it/classification-labelling/), this finding has caused worldwide concern (WHO, 2002; European Commission, 2002). Earlier studies (Tareke et al., 2000) had documented that rats fed fried animal standard diet had generated an adduct of N-(2-carbamoylethyl)valine to the N-termini of hemoglobin, similar to the adduct formed from occupational exposures to acrylamide (Bergmark et al., 1993). Recently, it was documented that the acrylamide generated from food components during heat treatment was a result of the Maillard reaction between primarily the amino acid asparagine and reducing sugars (Mottram et al., 2002; Stadler et al., 2002).

The Norwegian Food Agency has performed a limited estimate of the intake of acrylamide from food in the Norwegian population and used this as inputs for its Scientific Committee to perform a risk assessment of acrylamide from foods, with special emphasis on cancer risk (Norwegian Food Agency, 2002). In the present communication, this risk assessment will be described and discussed.

Exposure Assessment

The Norwegian Food Agency (2002) has conducted analysis of 30 different food products plus eight brands of coffee (seven filter coffee, one instant coffee) bought on the Norwegian market. The sampling was chiefly based on results from Sweden, such that priority was given to food items (potato crisps, French fries) that were shown to have a high content of acrylamide in the Swedish analysis. The analysis was performed on pooled samples of three identical products from the same producer, but with different production dates. The analyses were carried out by the same accredited laboratory (AnalyCen, Lidköping, Sweden) that had conducted the Swedish analyses using LC-MS-MS methodology.

Data on intake in the adult population has been taken from the national food survey NORKOST 1997 (Johansson et al., 1997) based on a quantitative frequency questionnaire answered by 1291 males and 1381 females aged 16–79 years.
The mean daily intake of acrylamide was estimated to 38 \(\mu g\) per day for males and 29 \(\mu g\) for females, corresponding to daily doses of 0.49 \(\mu g/kg\) body weight in males and 0.46 \(\mu g/kg\) body weight in females (Table 1). The 97.5-percentile showed intakes that were approximately three times higher than the mean intakes.

In Table 2 the contribution of the various food items to the estimated intake of acrylamide is presented. Coffee (28%) contributed the most to the total mean intake of acrylamide, whereas potato crisps were responsible for almost 20% of the intake. From the analytical results, bread (potato cakes and dark crisp-bread excepted) contains low amounts of acrylamide. But since bread is consumed daily in relatively large amounts in Norway, this food group contributed to a considerable proportion of the acrylamide intake (21–24% of mean intake).

Food consumption data for children and adolescents were from UNGKOST 2000 (unpublished), a 4-day food intake registration in which portions were assigned according to an illustrative book with different portion sizes. The estimated intake of acrylamide in groups of children aged 9 and 13 years is shown in Table 3.

The largest source for the intake of acrylamide both in 9- and 13-year-old children is potato crisps, but butter biscuits and sweet biscuits are also important sources. These products contribute to approximately 55–65% of the total mean intake. It is notable that the 97.5-percentile of 13-year-old boys and girls have intakes that are about 4- to 5-fold higher than the mean intakes.

### Hazard Identification

Acrylamide is oxidized to glycidamide, a reactive epoxide, and undergoes conjugation with glutathione (Callemann et al., 1990; Sumner et al., 1992). DNA adducts from glycidamide have been reported following administration of acrylamide to rodents (Segerbäck et al., 1995). Hemoglobin adducts from direct reaction of acrylamide and from reaction with glycidamide have been detected in rodents administered acrylamide, in exposed humans, and in cigarette smokers (Bailey et al., 1986; Bergmark, 1997; Bergmark et al., 1991, 1993; Callemann et al., 1990, 1994; Fennel et al., 2003). The relationship between the acrylamide and glycidamide adducts on the N-terminal valine of hemoglobin is proportional in man and rat. Comparison of free acrylamide in plasma, valine adducts on haemoglobin, and urinary \(S-(2\text{-carboxyethyl})\)cysteine indicates that the rate of elimination of acrylamide is at least five times lower in man than in rats (Callemann, 1996).

The metabolite glycidamide is mutagenic (Adler et al., 2000; Barfknacht et al., 1988; Butterworth et al., 1992; Generoso et al., 1996; Hashimoto and Tanii, 1985). Acrylamide is neurotoxic in animals and humans (Miller and Spencer, 1985; Spencer and Schauberg, 1974a,b). Acrylamide has been shown to be carcinogenic in F344 male and female rats after administration in drinking water for up to 2 years (American Cyanamid Co., 1989; Friedman et al., 1995; Johnson et al., 1984, 1986) and in skin painting and oral administration experiments with mice (Bull et al., 1984a,b; Robinson et al., 1986).

Two long-term studies of possible carcinogenic effects of acrylamide have been conducted in rats, in that F344 male and female rats were given acrylamide in drinking water for up to 2 years. In the first study (Johnson et al., 1984, 1986) the animals received doses of acrylamide (>98% purity) corresponding to 0, 0.01, 0.5, and 2.0 mg per kg body weight per day (mg/kg bw/day) (60 rats of each sex at all doses). Maximum tolerated dose (MTD) appeared to have been reached based on reduced body weight increase and toxic effects in the high-dose group. There were temporary symptoms of a viral infection (sialodacryoadenitis virus) in some rats from day 210 of the study. All groups appeared to be affected to a similar degree.

In the second study, groups of 75–204 F344 male rats received doses of acrylamide (99.9% purity), corresponding to 0, 0.1, 0.5, and 2.0 mg/kg bw/day, and groups of 50–100 F344 female rats received doses corresponding to 0, 1.0, and 3.0 mg/kg bw/day (American Cyanamid Co., 1989; Friedman et al., 1995). Acrylamide induced statistically significant increases in the incidence of several tumor types in the experimental animals of both sexes, compared to the control animals (Table 4 [males] and Table 5 [females]).

### Table 1

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Males µg/day</th>
<th>Females µg/day</th>
<th>Males µg/kg bw/day</th>
<th>Females µg/kg bw/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>38</td>
<td>29</td>
<td>0.49</td>
<td>0.46</td>
</tr>
<tr>
<td>Median</td>
<td>29</td>
<td>24</td>
<td>0.41</td>
<td>0.42</td>
</tr>
<tr>
<td>90-percentile</td>
<td>77</td>
<td>55</td>
<td>1.01</td>
<td>0.86</td>
</tr>
<tr>
<td>97.5-percentile</td>
<td>125</td>
<td>88</td>
<td>1.62</td>
<td>1.45</td>
</tr>
</tbody>
</table>

| Table 2 |

<table>
<thead>
<tr>
<th>Food item</th>
<th>Males Mean intake 38 µg/day %</th>
<th>Females Mean intake 29 µg/day %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soft bread</td>
<td>13.0</td>
<td>11.9</td>
</tr>
<tr>
<td>Bread, other</td>
<td>7.7</td>
<td>12.2</td>
</tr>
<tr>
<td>Biscuits</td>
<td>5.0</td>
<td>5.9</td>
</tr>
<tr>
<td>Potatoes, fried</td>
<td>7.5</td>
<td>6.3</td>
</tr>
<tr>
<td>French fries</td>
<td>8.0</td>
<td>6.3</td>
</tr>
<tr>
<td>Potato crisps</td>
<td>17.6</td>
<td>17.4</td>
</tr>
<tr>
<td>Other snacks</td>
<td>5.0</td>
<td>4.6</td>
</tr>
<tr>
<td>Coffee</td>
<td>28.0</td>
<td>28.6</td>
</tr>
<tr>
<td>Other</td>
<td>8.2</td>
<td>6.8</td>
</tr>
</tbody>
</table>
Among the male rats, significant increased incidences of thyroid adenomas and testicular mesotheliomas were detected in both investigations. Adrenal pheochromocytomas were significantly increased in the high-dose group of the first study, but not in the second study. In addition, focal hyperplasia in the oral cavity was seen in the first study. An increased incidence of astrocytomas was also detected among the high-dose rats.

Among the female rats, there was a significantly increased incidence of thyroid adenomas in the second study. In the first study, the incidence of thyroid adenomas and adenocarcinomas combined was significantly increased in the high-dose group. A significant positive trend was found in both studies with respect to increases of thyroid adenomas and adenocarcinomas. The incidence of fibroadenomas in the mammary gland was significantly increased in the rats of both studies. In the first study, an increased incidence of oral papillomas was found among the rats receiving the high dose. A positive trend was found for oral cavity tumors and uterine adenocarcinomas in the first study. Such tumors were not found in the second study.

There was a significant increase in tumors of the central nervous system of glial origin or in glial proliferation, an indication of initial tumor development. Astrocytomas were found in the brain and spinal cord, both in male and female rats. However, there were no clear dose-response relationships.

In a series of skin painting experiments with mice, it was found that acrylamide initiates the formation of skin tumors, both in SENCAR and Swiss-ICR mice, as well as lung adenomas in the strains SENCAR, Swiss-ICR and A/J (Bull et al., 1984a,b; Robinson et al., 1986). In an experiment with Swiss-ICR mice, the animals were given 300 mg/kg body weight acrylamide in drinking water divided in 6 doses over a 2-week period. Thereafter, the animals were painted on the skin with 0.2 ml acetone three times per week for 20 weeks. The animals were sacrificed after 52 weeks. The incidence of skin tumors was 10/40 (25%) (controls 0/40; \( p < 0.001 \)) and of lung tumors 14/36 (39%) (controls 4/36; \( p = 0.06 \)) (Bull et al., 1984b).

Sobel and coworkers (1986) have investigated mortality among 371 employees in a factory in Michigan that produced acrylamide monomer and who also worked in polymerization. In the three plants investigated, the production of acrylamide

### Table 3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Boys 9 years (n = 1299) µg/kg/day</th>
<th>Girls 9 years (n = 1658) µg/kg/day</th>
<th>Boys 13 years (n = 1711) µg/kg/day</th>
<th>Girls 13 years (n = 2068) µg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>0.36</td>
<td>0.32</td>
<td>0.52</td>
<td>0.49</td>
</tr>
<tr>
<td>Median</td>
<td>0.23</td>
<td>0.25</td>
<td>0.30</td>
<td>0.28</td>
</tr>
<tr>
<td>90-percentile</td>
<td>0.72</td>
<td>0.61</td>
<td>1.35</td>
<td>1.20</td>
</tr>
<tr>
<td>97.5-percentile</td>
<td>1.50</td>
<td>1.10</td>
<td>2.85</td>
<td>2.07</td>
</tr>
</tbody>
</table>

### Table 4

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Control (0.01)</th>
<th>0.1</th>
<th>0.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid adenomas</td>
<td>1/60</td>
<td>0/58</td>
<td>2/59</td>
<td>1/59</td>
</tr>
<tr>
<td>Trend test ( p &lt; 0.001^{**} )</td>
<td>(2%)</td>
<td>(0%)</td>
<td>(3%)</td>
<td>(2%)</td>
</tr>
<tr>
<td>Trend test ( p &lt; 0.001 )</td>
<td>3/204</td>
<td>—</td>
<td>9/203</td>
<td>5/101</td>
</tr>
<tr>
<td></td>
<td>(1%)</td>
<td>—</td>
<td>(4%)</td>
<td>(5%)</td>
</tr>
<tr>
<td>Testicular mesotheliomas</td>
<td>3/60</td>
<td>0/60</td>
<td>7/60</td>
<td>11/60</td>
</tr>
<tr>
<td>Trend test ( p &lt; 0.01 )</td>
<td>(5%)</td>
<td>(0%)</td>
<td>(12%)</td>
<td>(18%)*</td>
</tr>
<tr>
<td>Trend test ( p &lt; 0.001 )</td>
<td>8/204</td>
<td>—</td>
<td>9/204</td>
<td>8/102</td>
</tr>
<tr>
<td></td>
<td>(4%)</td>
<td>—</td>
<td>(4%)</td>
<td>(8%)</td>
</tr>
<tr>
<td>Adrenal pheochromocytomas</td>
<td>3/60</td>
<td>7/59</td>
<td>7/60</td>
<td>5/60</td>
</tr>
<tr>
<td>Trend test ( p = 0.06 )</td>
<td>(5%)</td>
<td>(12%)</td>
<td>(12%)</td>
<td>(8%)</td>
</tr>
<tr>
<td>Oral focal hyperplasia</td>
<td>0/60</td>
<td>1/60</td>
<td>1/60</td>
<td>4/60</td>
</tr>
<tr>
<td>Trend test ( p &lt; 0.01 )</td>
<td>(0%)</td>
<td>(2%)</td>
<td>(2%)</td>
<td>(7%)</td>
</tr>
</tbody>
</table>

Note. Acrylamide doses in mg/kg bw/day. The upper lines represent the study by Johnson et al. (1984, 1986), and the lower lines represent the study by American Cyanamid Co. (1989) and Friedman et al. (1995).

*Significant increase in tumor incidence \( (p < 0.05) \), Fischer’s exact test; **Mantel-Haenszel trend test.
had occurred from the end of the 1950s and the beginning of the 1960s. A total of 29 deaths were observed up to 1982 (38.0 expected). There were 11 cancer deaths, compared to 7.9 expected. The increased number of cancer cases was due to cancer of the digestive tract and the respiratory organ in a subgroup that had previous exposure to organic dyes. Among the employees who had no exposure to organic dyes, four deaths were observed compared to 6.5 expected.

Collins and coworkers (1989) investigated causes of death in four factories, three in the United States and one in the Netherlands, in order to assess possible cancer risks after exposure to acrylamide. The investigation included 8,854 males employed in the factories between 1925 and 1976, and exposure to acrylamide was defined as cumulative exposure /$H_{11022}$0.001 mg/m$^3$-years. A total of 2,293 males were identified as being exposed. Information on smoking habits was available from approximately 1/3 of the group. Among the exposed workers, a significantly reduced mortality from all causes was found (Standardised Mortality Ratio [SMR] = 81), but a weak indication of increased cancer incidence was revealed for pancreatic cancer (eight cases; SMR = 203 (95% CI = 87–400) as well as for Hodgkin’s disease (five cases; SMR = 129 (95% CI = 42–300). No increased trend was found in cancer deaths when higher-exposed workers were compared to lower-exposed workers.

Marsh and coworkers (1999) have presented an update for the period 1984–1994 of the same cohort of Collins and coworkers (1989). For the period 1925–1994 the following results were found: tumors of the brain and central nervous system, SMR = 65 (95% CI = 36–109); thyroid tumors, SMR = 211 (95% CI = 44–612); tumors in the testes and other sexual organs, SMR = 110 (95% CI = 99–122). As presented in the article, mean occupational duration was 1.7 years, and mean acrylamide exposure was 0.1 mg/m$^3$. The authors conclude that there is little evidence for a causal relationship between exposure to acrylamide and cancer mortality.

Recently, Mucci et al. (2003) reanalyzed a population-based Swedish case-control study encompassing cases with cancer of the large bowel ($n = 591$), bladder ($n = 263$) and kidney ($n = 133$) and 538 healthy controls. They assessed dietary acrylamide by linking extensive food frequency data with the acrylamide levels reported by the Swedish National Food Agency (2002). There was a consistent lack of an excess risk, or any convincing trend of cancer of the bowel, bladder, or kidney in high consumers of 14 different food items with a high or moderate acrylamide content.

### Hazard Characterization

The no-observed-adverse-effect level (NOAEL) of acrylamide neurotoxicity for the most sensitive effect (microscopic nerve changes) in rats was 0.5 mg/kg body weight/day (Spen-
cer and Schaumberg, 1974a). In reproductive toxicity studies with rats, reduction in the number of sperm and decreased

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Control</th>
<th>0.01</th>
<th>0.1</th>
<th>0.5</th>
<th>2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid adenomas</td>
<td>0/58</td>
<td>0/59</td>
<td>1/59</td>
<td>1/58</td>
<td>3/60</td>
</tr>
<tr>
<td>Trend test $p = 0.01$**</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(2%)</td>
<td>(2%)</td>
<td>(5%)</td>
</tr>
<tr>
<td>Thyroid adenomas</td>
<td>0/100</td>
<td>—</td>
<td>—</td>
<td>7/100</td>
<td>16/100</td>
</tr>
<tr>
<td>Trend test $p &lt; 0.001$</td>
<td>(0%)</td>
<td>—</td>
<td>—</td>
<td>7%*</td>
<td>(16%)*</td>
</tr>
<tr>
<td>Thyroid adenocarcinomas</td>
<td>1/58</td>
<td>0/59</td>
<td>0/59</td>
<td>0/58</td>
<td>3/60</td>
</tr>
<tr>
<td>Trend test $p &lt; 0.01$</td>
<td>(2%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(0%)</td>
<td>(5%)</td>
</tr>
<tr>
<td>Thyroid adenocarcinomas</td>
<td>2/100</td>
<td>—</td>
<td>—</td>
<td>3/100</td>
<td>7/100</td>
</tr>
<tr>
<td>Trend test $p = 0.03$</td>
<td>(2%)</td>
<td>—</td>
<td>—</td>
<td>(3%)</td>
<td>(7%)</td>
</tr>
<tr>
<td>Mammary gland fibroadenomas</td>
<td>10/60</td>
<td>11/60</td>
<td>9/60</td>
<td>19/58</td>
<td>23/61</td>
</tr>
<tr>
<td>Trend test $p &lt; 0.001$</td>
<td>(17%)</td>
<td>(18%)</td>
<td>(15%)</td>
<td>(33%)*</td>
<td>(38%)*</td>
</tr>
<tr>
<td>Mammary gland adenocarcinomas</td>
<td>0.96</td>
<td>—</td>
<td>—</td>
<td>20/94</td>
<td>26/95</td>
</tr>
<tr>
<td>Trend test $p &lt; 0.001$</td>
<td>(9%)</td>
<td>—</td>
<td>—</td>
<td>(21%)*</td>
<td>(27%)*</td>
</tr>
<tr>
<td>Mammary gland adenocarcinomas</td>
<td>2/60</td>
<td>1/60</td>
<td>1/60</td>
<td>2/58</td>
<td>6/61</td>
</tr>
<tr>
<td>Trend test $p &lt; 0.01$</td>
<td>(3%)</td>
<td>(2%)</td>
<td>(2%)</td>
<td>(3%)</td>
<td>(10%)</td>
</tr>
<tr>
<td>Mammary gland adenocarcinomas</td>
<td>2.96</td>
<td>—</td>
<td>—</td>
<td>2/94</td>
<td>4/95</td>
</tr>
<tr>
<td>Trend test $p = 0.17$</td>
<td>(2%)</td>
<td>—</td>
<td>—</td>
<td>(2%)</td>
<td>(4%)</td>
</tr>
<tr>
<td>Uterine adenocarcinomas</td>
<td>1/60</td>
<td>2/60</td>
<td>1/60</td>
<td>0/59</td>
<td>5/60</td>
</tr>
<tr>
<td>Trend test $p &lt; 0.01$</td>
<td>(2%)</td>
<td>(3%)</td>
<td>(2%)</td>
<td>(0%)</td>
<td>(8%)</td>
</tr>
<tr>
<td>Oral cavity papillomas</td>
<td>0/60</td>
<td>3/60</td>
<td>2/60</td>
<td>1/60</td>
<td>7/61</td>
</tr>
<tr>
<td>Trend test $p &lt; 0.01$</td>
<td>(0%)</td>
<td>(5%)</td>
<td>(3%)</td>
<td>(2%)</td>
<td>(11%)*</td>
</tr>
</tbody>
</table>

*Note. Acrylamide doses in mg/kg bw/day. The upper lines represent the study by Johnson et al. (1984, 1986) and the lower lines represent the study by American Cyanamid Co. (1989) and Friedman et al. (1995).

*Significant increase in tumor incidence ($p < 0.05$), Fischer’s exact test; **Mantel-Haenszel trend test.
fertility has resulted, plus an increase in premature embryonic deaths (Tyl et al., 2000). The NOAEL for reduced fertility was 5 mg/kg body weight/day and for premature embryonic death 2 mg/kg body weight/day.

For genotoxic carcinogens for which the most plausible mode of carcinogenic action is a consequence of genotoxic events, the prudent position has been to assume nonthreshold dose-response relationships. The basic default is to assume linearity if that is suggested by the mode of action analysis or if the mode of action is not understood (U.S. EPA, 1996, 1999; EU Technical Guidance Document, 2003). The U.S. Food and Drug Administration has also advocated the use of a “linear-at-low-dose, no threshold model” (Lorentzen, 1984). The U.S. Environmental Protection Agency (1996) has proposed to use the parameter LED10 as the point of departure for quantitative hazard characterisation of nonthreshold carcinogens. The LED10 is the lower 95% confidence limit for the dose giving the animals an increased tumor incidence of 10%, calculated with the multistage model. In the European Union, the tumor dose indicator T25 (Dybing et al., 1997; Sanner et al., 2001) has also been used as a basis for quantitative hazard characterization of carcinogens. The T25 is the dose that increases the tumor incidence by 25% under standard conditions.

In Table 6 are given LED10 and T25 values for the two most sensitive tumor endpoints in the Johnson et al. (1986) and Friedman et al. (1995) studies, namely testicular mesotheliomas and mammary gland adenomas, respectively.

The differences in the estimated tumorigenic dose indicators are small. Mostly, the LED10 and the T25 values were somewhat lower for mammary gland adenomas compared to testicular mesotheliomas. Therefore, mammary gland adenomas in the Johnson et al. (1986) study were chosen as the most sensitive outcome for the further calculations. Assuming that the tumor responses caused by acrylamide reflect a genotoxic mechanism, the LED10 and T25 values were converted to values corresponding to the low-hazard level of $10^{-5}$ (World Health Organization, 1996) by default linear extrapolation by dividing with 10,000 and 25,000, respectively. These figures were then scaled to the human situation using the scaling factor $W_{0.75}^{human} = (weight_{animal}/weight_{human})^{0.75} = (70/0.25)^{0.25} = 4.1$ for rat to human conversion (U.S. EPA, 1996). The outcomes of these calculations are presented in Table 7.

The two calculations resulted in a lifetime hazard level that was 1.6 times higher with the T25 compared to the LED10 method. For the risk characterization step, a mean value of $1.3 \times 10^{-3}$ was used to represent the hazard corresponding to a lifelong exposure to $1 \mu g$ acrylamide per kg body weight per day.

### Risk Characterization

When the intake doses presented in Table 1 are correlated to the hazard estimates given in Table 7 [risk = (lifetime hazard after lifelong exposure to $1 \mu g$ acrylamide per kg body weight per day) × dose], a lifetime cancer risk related to daily intake of acrylamide in foods for 70 years becomes, on average, $0.6 \times 10^{-3}$ (corresponding to 6 cancer cases per 10,000 individuals) (Table 8). For the 10% and 2.5% males with the highest intake, lifetime cancer risks were estimated to 13 and 21 cancer cases

### Table 6

<table>
<thead>
<tr>
<th>Experiment</th>
<th>LED10 Males (testicular mesotheliomas)</th>
<th>LED10 Females (mammary gland adenomas)</th>
<th>T25 Males (testicular mesotheliomas)</th>
<th>T25 Females (mammary gland adenomas)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johnson et al., 1986</td>
<td>0.66</td>
<td>0.40</td>
<td>0.89</td>
<td>0.64</td>
</tr>
<tr>
<td>Friedman et al., 1995</td>
<td>0.84</td>
<td>0.86</td>
<td>3.7</td>
<td>1.9</td>
</tr>
</tbody>
</table>

**Note.** All estimates are in mg/kg bw/day.

### Table 7

<table>
<thead>
<tr>
<th>Model</th>
<th>Lifetime exposure dose which represents a cancer hazard of $10^{-5}$</th>
<th>Lifetime hazard after lifelong exposure to $1 \mu g$ acrylamide per kg body weight per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>LED10 = 0.40 mg/kg bw/d</td>
<td></td>
<td>0.0098 μg/kgbw/day (1.0 \times 10^{-5})</td>
</tr>
<tr>
<td>LED10(^{-5}) = 0.040 μg/kg bw/d</td>
<td></td>
<td>0.0062 μg/kgbw/day (1.6 \times 10^{-3})</td>
</tr>
<tr>
<td>HLED10(^{-5}) is estimated by dividing by 4.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T25 = 0.64 mg/kg bw/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T10(^{-5}) = 0.0256 μg/kg bw/d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HT10(^{-5}) is estimated by dividing by 4.1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
per 10,000 individuals, respectively. For females, the lifetime cancer risks were somewhat lower than for males.

Assessment of potential risks for neurotoxic and reproductive toxic effects assumes that such effects have a dose threshold, where the NOAEL is used as a surrogate for the dose threshold. Since the NOAEL for the most sensitive effect (neurotoxicity) was 0.5 mg/kg bw/day (or 500 µg/kg bw/day) and the exposure dose for males 16–30 year olds was 0.49 µg/kg bw/day (Table 1), the margin of safety for these individuals becomes approximately 1,000 (500/0.49). For the 97.5-percentile of 13-year-old boys with an estimated intake of 2.85 µg/kg bw/day, the margin of safety becomes 175.

### Uncertainties in the Risk Assessment

There is considerable uncertainty related to the analytic results of acrylamide in the reported food products; this is especially the case for the lowest acrylamide levels, as in bread. The analyses of the Norwegian foods included in the calculation are restricted to 30 different products, and an only very limited pool of three samples. However, the results give clear indications and present a basis to assume that the mean values used in the calculation are of a correct order of magnitude. Both the Swedish and the Norwegian analytical data showed that there are large differences between the different brands of the same food item (e.g., potato crisps).

A basic premise for the present risk assessment is that the tumor responses are a reflection of a genotoxic mechanism of action. Since acrylamide produced tumors in endocrine-sensitive organs (testis and mammary gland), this could point to an endocrine, nongenotoxic mechanism. On the other hand, the acrylamide metabolite glycidamide is clearly mutagenic (Adler et al., 2000; Barfknecht et al., 1988; Butterworth et al., 1992; Generoso et al., 1996; Hashimoto and Tanii, 1985) and acrylamide showed carcinogenic initiating activity in mouse skin after systemic administration (Bull et al., 1984b). Given that there is no strong evidence to support an endocrine mechanism of action in the tumor responses, it seems prudent to assume that the responses are related to the genotoxic actions of acrylamide. This was also the reason for IARC (1994) to upgrade the classification of acrylamide from Group 2B to Group 2A.

The present risk assessment has used a linear extrapolation from the points of departure (LED10 and T25), to describe the hazard at low levels of exposure. Such a default extrapolation can also be questioned, since cellular protective mechanisms may be operative at low doses, including detoxication processes, cell cycle arrest, DNA repair, apoptosis and the control of neoplastically transformed cells by the immune system. Thus, a linear extrapolation may overestimate the actual risk for the exposure levels related to acrylamide in food. In support of a linear extrapolation, Abramsson-Zetterberg (2003) has demonstrated a linear dose-response relationship for acrylamide in inducing micronucleated erythrocytes in mice exposed to acrylamide in single doses of 1 to 30 mg/kg body weight intraperitoneally.

There are several examples in the literature of genotoxic carcinogens that show a linear dose-response relationship in the low dose range, such as for liver tumors in rats induced by aflatoxin B1 (Wogan et al., 1974) or N,N-diethylnitrosamine (Peto et al., 1991), and liver tumors in mice induced by 2-acetylaminofluorene (Littlefield et al., 1979). On the other hand, in a review of carcinogenesis data for 315 chemicals from the NCI-NTP bioassay programs, the tumor site data were more often consistent with a quadratic response than with a linear response, suggesting that the default use of linear extrapolations will often overestimate the risk (Hoel and Portier, 1994). In fact, genotoxic carcinogens were found to differ from linearity more often than nongenotoxic compounds. On the other hand, because of the small number of doses tested experimentally, i.e., usually only two or three, almost all data sets fit equally well various mathematical functions, and it is generally not possible to define dose-response curves on the basis of mathematical modeling.

It is further assumed that acrylamide shows 100% bioavailability from the gastrointestinal tract; this is supported by animal experiments (Miller et al., 1982). However, it is possible that there are matrix effects when the reactive acrylamide is generated from the various food products; this may reduce the bioavailability and, thus, the risk estimates. On the other hand, it may be envisioned that the present risk values are an underestimation, since the tissue dose of glycidamide may be higher in humans compared to rats (Calleman et al., 1996).

It may be questioned whether the epidemiological studies should have identified an increased cancer risk in relation to acrylamide exposure, should this risk be a reflection of a genotoxic response with a relative risk of 1.006. The study by Marsh et al. (1999) is the only workplace study that can be used for quantitative considerations. However, it can be calculated that, using the present risk estimates, the exposure levels should have been about 5 to 10 times higher in the Marsh et al. (1999) study, in order to observe a significant increase in any of the tumor types recorded. A possible reason for the difference in response between the test animals and the occupational effects was the length of exposure; the test animals were exposed to acrylamide over a longer period of time than the occupational cases. Additionally, the test animals were exposed to acrylamide in a single dose while the occupational cases were exposed to acrylamide over a longer period of time; this may have resulted in a different response to the exposure.
cohorts is that the animals were dosed at a much younger age. In
the study of Mucci et al. (2003) acrylamide intake through
the diet was estimated to approximately 0.4 μg per kg body
weight and day for a person weighing 70 kg. Using the present
risk characterization it is unlikely that the difference in expo-
sure between their groups with the lowest and highest exposure
levels would represent a lifetime cancer risk of more than
0.5 × 10−3. The Mucci et al. (2003) study is much too small to
significantly detect such a low increase in risk, given that this
risk level is true.

Were the tumor responses revealed in the drinking water
studies with rats a reflection of a nongenotoxic mechanism
with a threshold response, the NOAEL for testicular me-
sotheliomas and mammary gland fibroadenomas would be 0.1
mg/kg bw/day, although there was a non-significant increase in
testicular mesotheliomas at this dose in one of the two exper-
iments. Relating this NOAEL to the mean exposure of acryl-
amide from food, the corresponding margins of exposure
would be 204 and 217 in males and females, respectively.

The attempts to quantify cancer risks at low doses of acryl-
amide in food should be seen as an aid to the regulatory
agencies in their assignment of priorities and choice of actions.
Alternatively, instead of attempting to quantify the risk, the
regulators may apply the ALARA principle (As-Low-As-Rea-
sonably-Achievable) for a genotoxic carcinogen, aiming at
reducing the acrylamide exposures as much as possible. This
approach does not run the chance of over-interpreting the
hazard characterization data and leaves it to the risk manager to
decide the level of reduction that may be technologically and
financially practicable. A disadvantage of using the ALARA
principle is that it does not give a quantitative dimension on
which to prioritize the problem.

Even if there are considerable uncertainties in the exposure
assessment of acrylamide in food, the safety margins with
respect to neurotoxic effects of acrylamide are judged to be
large enough to conclude that the risks appear to be very low.
This also holds true for the 97.5-percentile of 13-year-old boys
who have the highest estimated acrylamide intake. Since the
NOAELs for reproductive toxicity are higher than that for
neurotoxicity, any risk for reproductive toxic effects related to
consumption of acrylamide in food should be extremely low.

Conclusion

In a limited exposure assessment of acrylamide in food
conducted in Norway, mean intakes were estimated to 38 and
29 μg acrylamide per day in males and females, respectively,
corresponding to intake doses of 0.49 and 0.46 μg per kg body
weight and day. The 97.5-percentiles of adults had intakes that
were approximately 3-fold higher than the mean intakes.

In 2-year drinking water cancer studies with acrylamide
(Friedman et al., 1995; Johnson et al., 1986), testicular me-
sotheliomas and mammary gland adenomas were consistently
found. Since acrylamide is converted to a mutagenic metabo-
lite (Adler et al., 2000; Barfknecht et al., 1988; Butterworth
et al., 1992; Generoso et al., 1996; Hashimoto and Tanii, 1985)
and shows initiating activity in mouse skin after systemic
administration (Bull et al., 1984b), it is assumed that the tumor
responses seen after acrylamide administration are a reflection
of its genotoxic potential. Using the conservative default linear
extrapolation methods LED10 (U.S. EPA, 1996) and T25
(Dybing et al., 1997; Sanner et al., 2001) for genotoxic car-
cinogens, the lifetime cancer hazard after lifelong exposure to
1 μg acrylamide per kg body weight per day scaled to humans
was on average calculated to be 1.3 × 10−3. Using this hazard
level and correlating it with the exposure estimates, a lifetime
cancer risk related to daily intake of acrylamide in foods for 70
years in males was calculated to 0.6 × 10−3, corresponding to
6 cancer cases per 10,000 individuals. For the 10% and 2.5%
males with the highest intakes, lifetime cancer risks were
estimated to 13 and 21 cancer cases per 10,000 individuals. For
females, the risk values were slightly lower.

It must be emphasized that the risk assessment presented
here is highly conservative, so that the true risk levels may be
lower. Firstly, the exposure estimates are based on a limited
number of measurements of a limited number of products and
samples. Also, the exposures are estimated from food intake
questionnaires, which may overestimate the exposure. Sec-
donely, the assessment does not take into account the possibility
that bioavailability of acrylamide from the gastrointestinal tract
may be reduced due to food matrix effects. Thirdly, it is
assumed that the tumor responses seen in rats are an expression
of the genotoxic activity of acrylamide. Given that the critical
carcinogenic responses occur in endocrine-sensitive organs,
they could also reflect a nongenotoxic mechanism. And finally,
the risk assessment presented here assumes that there is a direct
linear relationship between tumor responses seen in the rat
experiments and responses at the calculated exposure levels, an
assumption that may be questioned. Thus, the calculated risk
numbers are presumably very conservative but do give an
indication of the magnitude of a risk for cancer related to
acrylamide in foods.

Available epidemiological studies have not been sensitive
enough to detect any possible cancer risk based on the calcu-
lated risk levels from the experimental data, given that these
levels are a true reflection of the actual risk.

Any risk of neurotoxic or reproductive toxic effects associ-
ated with acrylamide in foods is judged to be very small.

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