

# Agrichemical and Environmental News

A Monthly Report on Pesticides and Related Environmental Issues

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October, 2002 • Issue No. 198 • <http://aenews.wsu.edu>

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## **Acrylamide Angst: Another Annoying Distraction About Food Safety**

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Media headlines this past summer proclaimed a new concern about a contaminant in food. Swedish researchers at the University of Stockholm reported that acrylamide was present in a variety of baked and fried goods (Tareke et al. 2002). Although the name sounds like something scary that a big, bad global corporation might be foisting on us, acrylamide is actually an all-natural molecule that forms in food during the cooking process. High-carbohydrate foods seem to have the highest levels.

The irony of this story is that while we have spent countless hundreds of millions of dollars since the passage of the Food Quality

Protection Act addressing worries about pesticide residues in food, there has been a natural compound with some pretty nasty hazards right under our noses (not to mention in our stomachs if we're eating a burger and fries while reading this). At least, that is the case if high-dose rat studies are valid indicators. Which just goes to show, we know a heck of a lot more about the highly regulated chemical products synthesized one-by-one in factories than we do about the plethora of natural chemicals produced during the chemistry of cooking.

While the Europeans, acting on the input of reports from the European Commission



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(ECSCF 2002), the Swedish National Foods Agency (SNFA 2002), and the World Health Organization (WHO 2002), seem to be particularly concerned about acrylamide and beg for more studies to figure out what it all means, it's probably a good idea to take a breather and skeptically examine the hazard based on studies already in hand. After all, we humans have been exposed to this stuff ever since fire instigated our love affair with cooking.

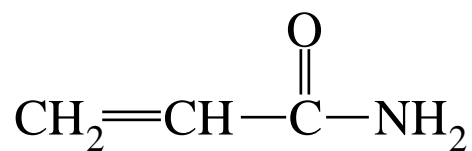
Probably the best way to understand what the fuss is about is to use the risk assessment approach. Using this strategy, I will discuss acrylamide in the context of hazard identification, dose-response relationships, exposure characterization, and risk characterization. Finally, I will compare the purported risk with the reality of what we have been observing in the human population.

## Acrylamide Acquaintance

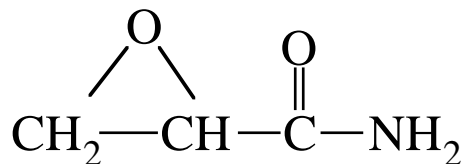
The first stop on our journey is an overview of acrylamide. Acrylamide is a small molecular weight, highly water-soluble compound composed of carbon, hydrogen, oxygen, and nitrogen (Figure 1). But don't let its simplicity fool you. It is quite reactive in air and is easily polymerized (i.e., single molecules of acrylamide are coupled together to form a larger substance with new properties). The resulting polymer, known as polyacrylamide, has a variety of important uses:

- coagulant in sewage and wastewater treatment systems and for clarifying drinking water;
- binder for strengthening paper and paperboard products;
- additive to enhance oil recovery;
- soil stabilizer in the construction of dams, foundation, tunnels, and roadways;
- separation gel in analytical biochemistry work;

- grouts for construction and repairing, including sealing sewer pipe and tunnels;
- stabilizer, foam builder, binder, film former, antistatic agent, and hair fixative in various kinds of cosmetics.



acrylamide



glycidamide

Figure 1. Chemical structures for acrylamide and an important reactive metabolite, glycidamide.

## Acrylamide Awareness

Pertinently, polyacrylamide always contains some unreacted acrylamide molecules, which are known as monomers. Thus, under the right circumstances humans can be exposed to acrylamide from a variety of sources. Indeed, concentrations of acrylamide in water are regulated by the EPA, and guidance levels have been set by the World Health Organization (WHO).

The current brouhaha about acrylamide has its origin in a serendipitous discovery associated with the use of about 1400 tons of grout to seal

a railway tunnel in porous rock underlying crop and pasture fields in rural Sweden (Reynolds 2002). Acrylamide monomers leached from the sealant and contaminated ground and surface water. Fish floated dead, cows became paralyzed, and workers reported numbness. Investigations of the worker problems led to acrylamide as an immediate suspect because of the chemical's well-known potential to cause neurotoxicity.

A Swedish professor at Stockholm University, Margaret Torqvist, was consulted to investigate the worker health issues (Reynolds 2002). Professor Torqvist had been investigating biomarkers for estimating worker exposure to acrylamide. Simply stated, biomarkers are very large cellular or blood plasma molecules ("macromolecules") that can be directly measured to estimate exposure to contaminants. Typical measurements include changes in a biomarker's biological activity in the presence of contaminants or an analysis for pieces of contaminants that bind to the biomarker. Pieces of the acrylamide molecule will bind to specific amino acids such as valine and cysteine on hemoglobin molecules; hemoglobin is the oxygen-carrying protein (i.e., the macromolecule) found in the red blood cells. When hemoglobin is digested, the amino acids with bound pieces of the acrylamide molecules (known as adducts) can be detected and quantified.

Torqvist's research group noted unexposed subjects with comparatively high levels of acrylamide hemoglobin (Hb) adducts. Earlier, Torqvist's colleague from Stockholm University, Emma Bergmark, reported that laboratory personnel working with polyacrylamide gels had detectable acrylamide Hb adducts (as predicted), but so did non-lab workers (Bergmark 1997). Cigarette smoke is known to contain acrylamide, but the control group

participants were not smokers and other known sources of acrylamide exposure did not account for the magnitude of background levels of Hb adducts. Thus began the search for the source of the background acrylamide exposure. By process of elimination of known polyacrylamide sources in combination with the knowledge that heating vegetation (i.e., tobacco) caused elevated acrylamide Hb adducts, cooked food became the hypothesis to bet on.

### **Hazard Identification**

Acrylamide is very rapidly absorbed through the intestinal tract and fairly evenly distributed throughout the body organs (Dearfield et al. 1988). However, with the exception of the testes, it does not accumulate in any particular tissue. Once exposure ceases, it is rapidly lost from the body. Acrylamide is metabolized by a mechanism known as conjugation; the compound is hooked onto glutathione, a molecule composed of three amino acids. Glutathione conjugates are rapidly excreted from the body. Enzymes known as microsomal oxidases transform some of the acrylamide to the molecule glycidamide (Figure 1), which can also be conjugated to glutathione (Sumner et al. 1997). Both acrylamide and glycidamide can bind to hemoglobin and presumably other proteins in the cells (Bergmark et al. 1993).

Despite acrylamide's rapid metabolism and excretion following exposure, its high reactivity with proteins could be the reason it is hazardous to workers (Friedman et al. 1995). Because glycidamide also binds to DNA, it has been hypothesized to be the actual agent of toxicity (Segeberback et al. 1995). Acrylamide has been well studied since the 1950s as a neurotoxin owing to its extensive use for polyacrylamide production (Dearfield et al. 1988). Its neurotoxicity was manifested symptomatically in workers through nerve tissue pathologies

(axonopathies) and poor performance on neurological tests.

High doses of acrylamide can also cause adverse developmental and reproductive effects. For example, nerve degeneration and abnormal changes in intestinal enzymes have been observed in neonatal rodents (Dearfield et al. 1988). Abnormal sperm, reduced fertility, and abortions have been elevated in treated rodents.

In the early 1980s, screening studies suggested that acrylamide could initiate tumors of the skin in orally or dermally exposed mice subsequently treated with an additional chemical known to be a very potent tumor promoter. Lung tumors were also noted in acrylamide-exposed mice not subsequently treated with a tumor-promoting agent (Bull et al. 1984). These observations were surprising in light of acrylamide's failure to cause gene mutations in the usual bacteriological and mammalian cell culture studies of the time (Dearfield et al. 1988). However, when male mice were given non-lethal doses of acrylamide in drinking water and then allowed to mate with females, some fertilized eggs did not implant into the uterus, and some implanted embryos were aborted (Smith et al. 1986). This phenomenon is ascribed to dominant lethal mutations in the sperm cell chromosomes. Thus, acrylamide was hypothesized to cause chromosomal aberrations (known as clastogenicity) rather than DNA mutations (i.e., mutagenicity). On the other hand, the metabolite glycidamide can bind directly to DNA, but its mutagenic potential has been poorly studied (Segeberback 1995; Tareke et al. 2000). Regardless of the specific mechanism of interacting the genes, acrylamide has been classified as being genotoxic.

Rats given water containing acrylamide over a period of two years developed a number of different tumors. In one study (Johnson et al.

1986), tumors of the testes epithelium (a pathology known as scrotal mesothelioma) and the female mammary glands were elevated above control levels. In a later study (Friedman et al. 1995) involving a greater number of rats, only scrotal mesothelioma was definitively noted, but the significance for humans is obscure because this type of cancer is extremely rare. Nevertheless, on the basis of the Johnson et al. (1996) study and the classification of acrylamide as genotoxic (i.e., it causes mutations and/or chromosomal aberrations), the International Agency for Research on Carcinogenicity (IARC, an independent world authority for analysis of carcinogenic potential), EPA, and WHO consider acrylamide as a probable human carcinogen.

Current worries over acrylamide in food are directly related to the compound's classification as a carcinogen. Indirectly, the uncertainty over acrylamide in cooked food is related to the hypothesis that genotoxins have no threshold for cancer causation. In other words, exposure to one molecule of a genotoxin can hypothetically kick off the biochemical process leading to cancer.

### **How Much Is Too Much?**

Hazard assessment usually starts with determination of the LD<sub>50</sub>, which is defined as the dose causing death to 50% of test subjects. The acute (i.e., single) oral LD<sub>50</sub> for acrylamide in rats and mice is 107-270 mg/kg of body weight (WHO 1996). The acute dermal LD<sub>50</sub> for rats was reported to be 400 mg/kg.

Definite thresholds and no-observable adverse effects levels (NOAELs) have been observed for both neurotoxic effects and developmental/reproductive toxicity at non-lethal subchronic doses (multiple doses for periods up to 90

days). The NOAEL for peripheral nerve lesions (the most sensitive endpoint for neurotoxicity) was noted in one study as 0.2 mg/kg/day (WHO 1996) and in another study as 0.5 mg/kg (Dearfield et al. 1988). Ten weeks of exposure to drinking water with acrylamide levels equivalent to whole body doses of 0.5 mg/kg/day (for pregnant rats) and 2.0 mg/kg/day (for fetal and neonatal rats) did not cause toxicity in developmental studies (Dearfield et al. 1988). For reproductive toxicity, 0.5 mg/kg/day given to male rats for 10 weeks caused no adverse effects on reproduction (Dearfield et al. 1988). Thus, neurotoxic, developmental, and reproductive effects are considered to have dosage thresholds that are exceeded when toxicity occurs. The relationship between dose and these effects is non-linear, but remarkably, the NOAEL of 0.5 mg/kg in adult rats is similar among different types of effects (Friedman et al. 1995).

In contrast to their treatment of non-carcinogenic effects, EPA, WHO, and IARC do not consider a threshold to exist in the relationship between acrylamide levels in drinking water and tumor formation. In other words, the agencies regulate genotoxins on the basis of the hypothesis that one molecule can cause an adverse effect on a gene, thereby initiating the process of tumor formation. Yet, close examination of the actual chronic (two-year) feeding studies for almost all chemicals shows that the lowest dose of the three doses usually tested does not cause any significant increase in tumors in exposed animals compared to the unexposed (control) animals (see Figures 2 and 3). Indeed, several reviews have shown a number of chemicals actually reduce the incidence of tumors in animals at low doses (Haseman and Johnson 1996; Crump et al. 1999). And so it is with acrylamide: the study upon which governmental agencies have relied to define hazard and its relationship with dose

indicated no increase in tumors at the lowest dose tested (Johnson et al. 1986; EPA IRIS 1993). As a matter of record, a second chronic toxicity study (Friedman et al. 1995) showed that even the mid-dose did not cause any significant increase in tumors. The only significant and verifiable tumor increase was observed in the male testes at a dose of 2 mg/kg/day, and the conclusions argued for consideration of 0.5 mg/kg/day as a NOAEL for tumor formation.

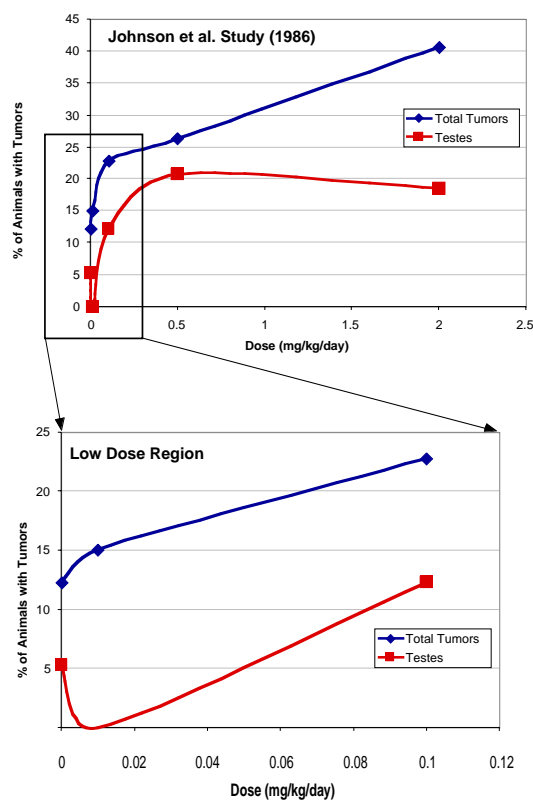


Figure 2. Dose-response relationship for total number of tumors and malignant tumors of the testes (scrotal mesothelioma) in male rats given drinking water containing acrylamide (based on Johnson et al. 1986 study as summarized in Dearfield et al. 1988). In the low dose region there are no statistically significant differences among the 0, 0.01, and 0.1 mg/kg/day treatment groups.



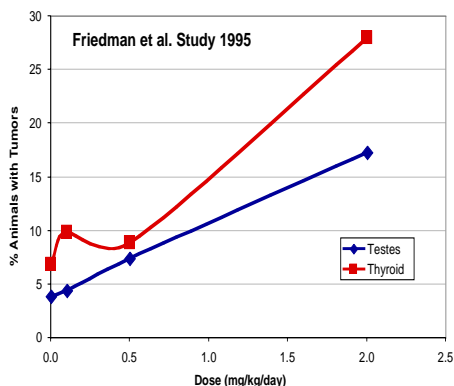


Figure 3. Dose-response relationship for testes tumors (scrotal mesothelioma) and total thyroid tumors in male rats exposed to acrylamide in drinking water (Friedman et al. 1995).

No statistically significant differences were observed among doses 0, 0.1, and 0.5 mg/kg/day. Tumor prevalence at 2.0 mg/kg/day is statistically significantly different than the prevalence in the unexposed group. This study represents a repeat of the Johnson et al. study (1986) using more numbers of rats at each dose and two control (0 mg/kg/day) groups.

## How Much Is In Food?

When Swedish researchers hypothesized that cooked food might be contributing to a “significant” background level of acrylamide exposure, they fried up some rat chow and served it to rats (Tareke 2000). They found the Hb biomarker levels in rats with this diet significantly elevated in comparison to the control rats. Chemical analysis of the fried chow revealed an average acrylamide concentration of 150 µg/kg (ppb), but none was detected in uncooked rat chow. Thus, this study started the search for acrylamide in other cooked foods.

As of October 2002, hundreds of food samples have been analyzed for acrylamide in several government, university, and private laboratories

(Table 1). Examination of all the available data sets leads to the general conclusion that fried and baked foods of all kinds have acrylamide. The highest concentrations were observed in high carbohydrate foods, including potato and wheat products, but even high protein foods like meats have easily detectable levels of acrylamide. The good news is that acrylamide hasn’t been found in beer yet.

Newspapers have been serving up alarming stories of high acrylamide levels in French fries and potato chips. However, they have completely ignored the striking variability of acrylamide levels in the high carbohydrate foods. Acrylamide concentrations in multiple samples from any one food category have been ranging from non-detectable amounts (<5 to <30 µg/kg) to concentrations of low parts per million (mg/kg) (Table 1).

Table 1. Ranges of Acrylamide Concentrations (µg/kg) Found in Restaurant or Purchased Foods As Reported in Various Studies 1/

Food Group	CSPI	SNFA	ECSCF	Tareke et al.
French Fries	250-423	300-1100	<50-3500	314-732
Potato Chips	881	330-2300	170-2287	1300-3897
Corn Chips	106-388	120-180	34-416	
Breakfast Cereals	212-247	<30-1400	<30-1346	
Biscuits/Crackers		<30-650	<30-320	37-1731
Soft Breads		<30-160	<30-162	<5-53
Bakery Products			<50-450	
Hamburger & Pork				23-45
Fish & Seafood			30-39	
Poultry or Game			39-64	
Drink Powders			<50-230	
Beer			<30	<5

1/ All reports were published in 2002; full citations are listed under References. CSPI = Center for Science in the Public Interest; SNFA = Swedish National Food Administration; ECSCF = European Commission Scientific Committee on Food (note that these data combine the SNFA data with those from Norway, Switzerland, U.K., and the U.S.); Tareke et al. 2002 (Stockholm University)

The variability of acrylamide among the food groups can be viewed best by examining the distribution of residue concentrations in individual samples of specific high carbohydrate foods (Figure 4).

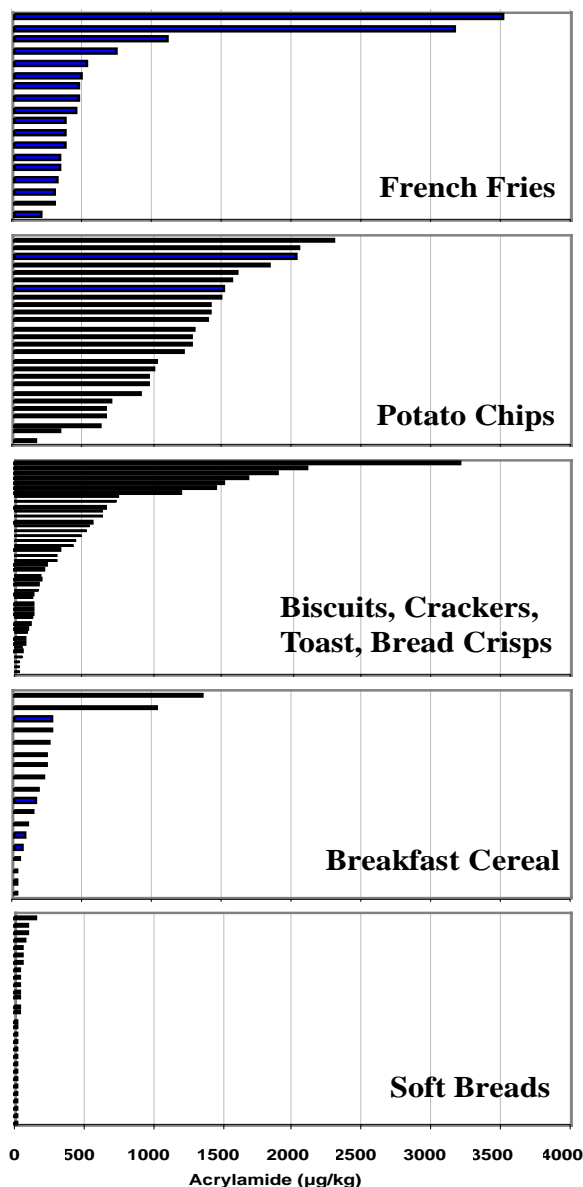


Figure 4. Distribution of acrylamide concentrations in individual samples (based on individual samples given, van Klaveren and Boon 2002).

With the exception of potato chips, the residue levels are overwhelmingly below 500 µg/kg with just a few unusually high detections. The residue levels in potato chips are more evenly distributed from the low to the high end. Thus, for most high carbohydrate foods, just examining the average residue level would tend to bias the perspective of how much acrylamide is generally in the food.

Studies are already proceeding full steam ahead to determine why cooking causes acrylamide formation, especially in high carbohydrate foods (Tareke et al. 2002). The first reports suggest that acrylamide does not form in boiled potatoes or meat (Table 2). When these same foods are fried (or, in the case of potatoes, even microwaved), detectable levels of acrylamide show up. Although the prevailing hypothesis focuses on high carbohydrate foods, fried spinach has surprisingly elevated levels of acrylamide also (Table 2).

Table 2. Acrylamide Concentration (µg/kg) in Foods Prepared under Controlled Laboratory Conditions (Tareke et al. 2002)

Food	Preparation 1/	µg/kg
Potato, boiled or raw	boiled or raw	<5
Potato, grated, microwaved	grated & microwaved	455-650
Potato, grated & fried	grated & fried	310-780
Potato, boiled, mashed, fried	boiled, mashed & fried	144-201
Beetroot	grated & fried	810-890
Spinach	grated & fried	112
Beef	boiled or raw	<5
Beef	minced & fried	15-22
Cod	boiled or raw	<5
Cod	microwaved	<5
Cod	minced & fried	<5-11

1/ Boiled preparation was for 20 min; fried was for 2.5 min per side (beef, cod, and potatoes formed into patties) at 220°C without oil; microwaved was for 3 min on each patty side at 750 Watts.

## **Exposure Assessment**

Thousands of samples will probably be analyzed for acrylamide residues over the next year. Meanwhile, with residue distributions in hand, actual whole body exposure estimates are popping up like soufflés. One of the earliest exposure estimates stemmed from the biomarker work in Swedish lab workers (Bergmark 1997). Measurements of acrylamide Hb adduct biomarkers can be used in combination with information about the metabolism and excretion rate (i.e., pharmacokinetics) of acrylamide to calculate an exposure or intake dose. Among non-smoking subjects with no laboratory exposure to polyacrylamide, the average acrylamide exposure was estimated to be 0.8 µg/kg/day. Laboratory personnel who worked with polyacrylamide gels had estimated exposures of 1.4 µg/kg/day. Smokers who didn't handle polyacrylamide were estimated to be taking up an average acrylamide dose of 3.1 µg/kg/day.

The use of biomarkers and pharmacokinetics are probably the best way to estimate human exposure. However, too few humans can be feasibly studied to garner population-wide estimates of exposure. For a broader view of exposure, therefore, food residues can be multiplied by the amount of food people typically eat. This type of exposure calculation is exactly what EPA uses for estimating dietary risk of pesticide exposure. Depending on who is doing the calculating, estimated average daily dietary exposures to adults have been ranging from 0.2 µg/kg to 0.8 µg/kg (ECSF 2002). The Swedish National Food Administration (SNFA 2002a) estimated an exposure from all sources as 100 µg/day; thus, for an adult of 70 kg (the standard "toxicological" weight), the daily whole body dose would be 1.4 µg/kg.

## **Betting on Acrylamide Exposure**

The above exposure estimates give an average daily exposure. To conduct a risk assessment for an entire population, it is also desirable to know the distribution of exposures. In other words, some foods have low amounts of acrylamide while others have high amounts. This variation is true even for similar food products, like chips and fries. Also, some people eat a lot of certain foods one day and very little the next. Furthermore, adults eat different amounts of snack foods than do kids. Thus, to gain insight into a population-wide exposure to acrylamide, toxicologists can run a probabilistic estimation of dietary intake.

A probabilistic assessment of dietary exposure would randomly select one food sample and an associated residue from the available database of residues (see Figure 4 for a distribution of acrylamide residues by food category). This residue would then be multiplied one at a time by the amount of that food eaten by one individual recorded in a food consumption database (for further explanation of the use of probabilistic analysis see Felsot 2002). The probabilistic analysis employs a computer modeling technique called Monte Carlo analysis. This little calculation game is like playing cards, where the toxicologist randomly selects a card from the acrylamide residue deck and pairs it with a randomly selected card from the food consumption database deck.

Probabilistic dietary exposure was recently assessed for people living in Netherlands (Klaveren and Boon 2002). The residue data were taken from the developing acrylamide residue databases in the United Kingdom, Sweden, and Norway. The result of the analysis is actually a distribution of exposure values. For long-term exposure (i.e., daily lifetime exposure), the average of the distribution is



relevant; it was estimated to be 0.8  $\mu\text{g}/\text{kg}/\text{day}$  for adults and 1.83  $\mu\text{g}/\text{kg}/\text{day}$  for young children. High-end exposures are estimated from the upper five percent of exposures; the 95<sup>th</sup> percentile of exposure was estimated at 3.1  $\mu\text{g}/\text{kg}/\text{day}$  and 6.4  $\mu\text{g}/\text{kg}/\text{day}$  for adults and children, respectively. In other words, 95% of the adult population may be exposed to acrylamide at a dose of 3.1  $\mu\text{g}/\text{kg}/\text{day}$  or less. Pertinently, these comparatively high exposure levels only represent a short-term (one to a few days) exposure, not a daily lifetime exposure.

### **Risk Characterization: MOEs vs. Models**

To characterize the risk or probability of adverse non-carcinogenic effects from acrylamide exposure, agencies typically examine the ratio of the NOAEL to the exposure level. The magnitude of this ratio, known as the Margin of Exposure (MOE), should be within agency risk guidelines to conclude a “reasonable certainty of no harm.” For example, if the NOAEL for the most sensitive neurotoxic effect caused by acrylamide is 0.2 mg/kg/day (i.e., 200  $\mu\text{g}/\text{kg}/\text{day}$ ), and the short-term exposure at the 95<sup>th</sup> percentile is 3.1  $\mu\text{g}/\text{kg}/\text{day}$ , then the MOE is 65. In other words, 65 times less acrylamide is consumed at the high end of exposure than is associated with a complete absence of the most subtle neurotoxic effect in rodents. Based on the upper end estimate of average daily intake of 0.8  $\mu\text{g}/\text{kg}/\text{day}$ , the MOE is 250.

By the way, both rodents and humans are believed to be susceptible to neurotoxic effects from acrylamide exposure, and furthermore, the rate of uptake from the intestine and subsequent distribution and metabolism seems similar (Dearfield et al. 1988). Thus, rodents may be reasonable sentinels for humans with regard to non-carcinogenic effects. Indeed, based on current knowledge of dietary exposure levels, regulatory agencies worldwide are not

concerned that acrylamide residues in food will cause adverse neurological, developmental, or reproductive effects.

Regulatory concern over carcinogenic effects of acrylamide is a different story. The policy basis for the MOE approach is the hypothesis that non-carcinogenic effects have clear thresholds below which health effects are nil. When it comes to genotoxicity and carcinogenicity potential, however, the regulatory agencies switch their game and invoke the hypothesis that a single exposure (i.e., one molecule) can lead to cancer. In this case, officials do not rely on an empirically derived NOAEL (i.e., a dose directly observed in experimentation). Rather, they pull out the old linear dose-response computer models and extrapolate the curve down to low doses that were never tested. The result of this mathematical exercise is the derivation of a slope for the linearized dose-response curve that represents the tumor rate, or the number of tumors per milligram of dose per kilogram of body weight per day (tumors/mg/kg/day). Based on this extrapolation of high dose data to low dose virtual exposures, EPA had estimated a slope factor of 4.5/mg/kg/day (EPA IRIS 1993).

Using the slope factor of 4.5 and an assumed exposure of 1  $\mu\text{g}/\text{kg}/\text{day}$  (i.e., 0.001 mg/kg/day), EPA has calculated a lifetime risk of 4.5 excess cancers per 1000 population (EPA IRIS 1991). Using different models but the same exposure factor, other calculations of risk for cancer offer probabilities of 0.7 per 1000 and 10 per 1000 (ECSCF 2002). The results of these calculations should not be interpreted to mean that 10 people will actually get cancer from short-term exposures to acrylamide. Rather, these risks represent the probability that x number of people in a population of 1000 will develop cancer if exposed to acrylamide over a lifetime. Such a probability should be weighed

against the current estimated lifetime risk for cancer of 330 per 1000 (SNFA 2002b).

If the prevailing regulatory hypothesis had been that a threshold actually does exist for tumor development in rodents, then a NOAEL approach could have been used for estimating the lifetime cancer risk from exposure to acrylamide. In this case, the MOE could have been calculated from the Friedman et al. 1995 study for the statistically significant tumors (NOAEL = 0.5 mg/kg/day) and a dietary intake of 0.001 mg/kg/day. The resulting MOE would be 500. This value could be interpreted as saying that the current dietary intake levels of acrylamide are 500-fold lower than the dose associated with no significant tumor development in rats exposed daily for two years.

### **Is the No-Threshold Hypothesis Relevant?**

The wisdom of the no-threshold hypothesis for carcinogenicity has been increasingly criticized over the last decade (e.g., Ames and Gold 1993; Ames et al. 1993; Cohen and Elwein 1992; Clayson 1998; Goodman 2001). Critics urge EPA to examine the mechanisms of toxicity, not just count the tumors, before making a blanket decision on whether a compound is a probable carcinogen. Nevertheless, WHO and the European Union have treated acrylamide as a very dangerous, high-potency carcinogen by accepting lock, stock, and barrel the hypothesis of no threshold for putative genotoxins. Yet, a closer examination of acrylamide's hazards with regard to chronic toxicity suggests a compound that might actually be working through hormonal actions, rather than directly on the gene (EC 2001). This hypothesis stems from observations that reproductive tissues (e.g., sperm, testes, mammary glands) seem to be particularly vulnerable to high-dose effects of acrylamide.

Acrylamide itself does not readily bind to DNA; however, one of its metabolites (glycidamide) does when injected into the body cavity of rats at high doses (50 mg/kg) (Segerback et al. 1995). Glycidamide adduct levels associated with background acrylamide exposures have been too low to accurately measure (Bergmark 1997). Glycidamide Hb adducts, however, have been measured in highly exposed acrylamide industry workers in China, especially when neurological pathologies were noted (Bergmark et al. 1993).

Bear in mind several operational principles regarding biomarker adducts. First, DNA adducts are generally repaired as long as the cell is healthy (Ames et al. 1993). Secondly, compounds forming Hb adducts can bind to a lot of different proteins, including the proteins surrounding the DNA in the chromosomes (Friedman et al. 1995). The fact that acrylamide exposure at high doses causes chromosome aberrations (as opposed to gene mutations) suggests that deformations in the proteins put strains on the DNA strands, resulting in breakage (Friedman et al. 1995). If this hypothesis is correct, then acrylamide tumorigenic effects, which are only seen at unreasonably high doses in rats and mice, occur in such a way that repeated interactions or hits are required. In other words, acrylamide's biochemical interactions fit a profile that favors invoking the threshold paradigm.. Finally, glycidamide resulting from high dose administration of acrylamide may bind with DNA of different rodent tissues, but failure to find accumulation of adducts in the testes tissue suggests that the tumors noted in this site (Johnson et al. 1986; Friedman et al. 1995) may not be due to a genotoxic effect (Segerback 1995). In other words, a threshold may exist for tumor formation.

Another reason for being skeptical of the no-threshold hypothesis for acrylamide comes from a careful examination of the chronic toxicity study (Johnson et al. 1986) relied upon for the risk assessment. Graphical examination of the results of the most significant tumors in the two-year drinking-water study shows a few percentage points' difference between tumor prevalence in the control group and the group given up to 0.1 mg/kg/day (Figure 2). None of the observed differences are statistically significant (Dearfield et al. 1988). Buried in the Johnson et al. (1986) report are other extenuating circumstances that have raised questions about its utility for risk assessment (Friedman et al. 1995). For example, at the highest doses, significant numbers of rats died and many of the remainder showed evidence of nerve pathologies, raising the issue that cellular toxicity rather than genotoxicity was operational. Also, some of the subject rats were reported to have a viral infection, again raising concerns over stressors that could enhance the toxicity of acrylamide.

More importantly for purposes of risk characterization, the experiments in the Johnson et al. study were repeated by Friedman et al. (1995), and the conclusions were somewhat different. The Friedman et al. study strongly argued that a clear NOAEL of 0.5 mg/kg/day existed for the only significant tumor observed, scrotal mesothelioma (Figure 3). Thyroid tumors, which had been used by the NSFA to estimate cancer risk were not significant in the updated study. Furthermore, all of the genotoxicity studies that have measured clastogenicity of acrylamide or dominant lethal effects also show clear threshold effects (i.e., the lowest tested doses generally show no adverse effect; e.g., Smith et al. 1986). In short, the regulatory agencies have been basing their risk assessment partly on a chronic toxicity study that has been

superceded with a better designed study. Regulators continue to ignore the repeated result of no effect associated with the lowest dose tested.

### **Reality Checks**

Risk communication about the discovery of acrylamide in cooked foods has ranged from commendable to awful. The United Kingdom (UK) Food Standards Agency has communicated well using a question-and-answer format to inform consumers about what we know and don't know, and to communicate a rational approach for eating a balanced diet (UK FSA 2002). On the other hand, WHO officials expressed alarming themes with quoted sound bites such as, "After reviewing all the available data, we have concluded that the new findings constitute a serious problem" (WHO/FAO 2002). "We know we get a lot of cancers from food, some of it might come, or it is very likely that it does come, from acrylamide" (ABC NewsOnline 2002). "...[G]iven that we know acrylamides are cancer-causing in animals and probably in humans, it is intolerable that they are in foods at the levels found and we have to find a remedy" (Kaufman 2002).

### **FOLKS, IT'S TIME FOR A REALITY CHECK.**

In addition to the points made in the above discussions about the relevancy of the no-threshold hypothesis, other observations give pause to pushing the panic button. Occupational epidemiological studies with workers, the most highly exposed human population, are useful as sentinels for excess cancer risk in the population. At least three different studies of acrylamide factory workers have been published that concluded no excess mortality from any disease, including cancer (Marsh et al. 1999). If acrylamide was as potent a carcinogen as the regulators (and WHO

officials) believe, then over 8500 workers exposed between 1925-1994 should tell us something, especially with regard to cancers of the testes and thyroid gland. Yet, no associations between exposure and cancer mortality at any organ site were found (Marsh et al. 1999).

Considering that cooked foods have been a staple of our diets since the advent of fire, our exposure to acrylamide is both ancient and unavoidable. Concern has been greatest over the inordinately high levels of acrylamide in cooked, high-carbohydrate foods, but that type of exposure has been with us since the cultivation of the first grains. By clinging to the hypothesis that there is no threshold for acrylamide's tumorigenic effects, we have painted ourselves into a proverbial risk corner. If there is truly no threshold, then regulatory officials need to explain why many types of cancers in addition to lung cancer are either falling or have stabilized in incidence rate at a time when we are supposedly eating a lot more of these high-carbohydrate, cooked foods (Wingo et al. 1998; Wingo et al. 1999). Is it worth worrying about naturally occurring substances that test out as rodent carcinogens? Consider the conclusions of the National Research Council report, "Carcinogens and Anticarcinogens in the Human Diet" (NRC 1996), which pointed out that natural products and synthetic chemicals in the diet are "present at levels below which any significant adverse biologic effect is likely, and so low that they are unlikely to pose an appreciable cancer risk."

One theme propounded by everyone is the need to eat a well-balanced diet with plenty of fruits and vegetables. If this advice is faithfully followed, then why would anyone want to back off potatoes, no matter how they are cooked? This vegetable, whether fried, baked, or boiled, can provide up to 40% of the recommended

daily dose of cancer-fighting ascorbic acid (Vitamin C) (NRC 1996; OECD 2002).

Here's my risk communication message: next time that you drive up to your neighborhood fast food joint, have it your way. Just remember to order a mixed salad with those super-size fries!

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