

Who Knows Whether Acrylamide in Food Is Hazardous to Humans?

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In this issue of the Journal, Besaratinia and Pfeifer (1) add to the toxicologic evidence that acrylamide has the ability to induce genetic damage in mammalian cells. Acrylamide or probably glycidamide, its genotoxic metabolite, has a relatively low mutagenic potency and is likely to have a relatively small impact on the overall cancer risk of an individual. However, because rather high concentrations of acrylamide are found in frequently consumed foods, the total acrylamide burden to a population is large. If one is willing to assume that a low-dose linear relationship between acrylamide exposure and carcinogenicity exists, then the contribution of acrylamide to the total cancer incidence in a population may be important. The expectedly low carcinogenicity will, however, create difficulties in applying epidemiologic studies, and the uncertainties associated with extrapolations from experimental findings to potential risks make it difficult to communicate to the general public.

Data from cancer tests on rodents have been used to obtain a quantitative cancer risk estimate associated with acrylamide exposure (2). If this cancer risk estimate is used as the expected outcome, then the results (i.e., no statistically significant detectable effects) from epidemiologic studies among acrylamide-exposed workers (3,4) and from dietary studies (5,6) are in good agreement with the expectation. The results obtained from these studies are thus quite predictable, especially considering the low statistical power and the limited range of exposure doses. It is important to note that an epidemiologic study (or any study relying on statistics) can never prove that an exposure is harmless; it can merely provide an upper bound of a potential detrimental effect associated with an exposure.

In the case of acrylamide exposure, we have a situation in which the results from epidemiologic studies can provide us with an upper bound of its potential carcinogenic effect, which is several orders of magnitude higher than what is considered acceptable by regulatory agencies, i.e., one extra case during a lifetime among 10 000–100 000 individuals. Alternatively, we can rely on methods based on experimental findings (which, for acrylamide, must be considered as very strong) with its inherent uncertainties relating to the extrapolation from animals to humans and from high doses to low doses.

The discovery of dietary acrylamide has its origin in an incident in which Swedish workers were exposed to acrylamide at a tunnel construction site (7,8). In our experience from the assessment and communication of risks associated with this incident, we found the quantitative risk estimation based on animal tests to be useful and necessary in reducing anxiety among the workers exposed to “a probable human carcinogen” (9), despite the scientific uncertainties. The quantitative cancer risk estimation for these workers was not debated by the media, but the same risk assessment methods, when applied to the dietary intake of acrylamide, led to a considerable media and scientific debate. A comprehensive description of the scientific background and risk communication of the acrylamide “alarm” in Sweden was documented by Löfstedt (10).

In our view, the precautionary principle¹ applies in a situation like this and, given the scientific knowledge about a potential hazard, all stakeholders can apply this principle. Among food industries, the principle has already been applied and, to our knowledge, the amount of acrylamide has been reduced substantially in several products. Among the general population, an individual’s application of this principle is a matter of personal preference. It is important that communication of hazards is balanced. In the case of acrylamide, where direct epidemiologic observations seem unattainable but toxicologic evidence is quite strong, polarization between scientists (i.e., toxicologists versus epidemiologists) is in our view counterproductive and even detrimental for science. Openly admitting the pros and cons of different scientific methodologies and trying to embrace each others’ opinions is, in our view, preferable so that the public is not confused when health risks are communicated to and by the media.

In our opinion, clarification and improvement of the risk assessment of acrylamide will be obtained primarily from experimental studies. The study by Besaratinia and Pfeifer (1) shows clearly that the mutation frequency is elevated after exposure to acrylamide. Fig. 1 shows the observed dose–response curve, with doses on a linear scale (excluding the two highest doses that induced severe cytotoxicity). The leveling off of the curve, indicated by the two highest doses displayed, is in agreement with Michaelis–Menten saturation kinetics of the metabolic activation of acrylamide to glycidamide. Understanding this metabolic activation in humans, rats, and mice (and its implication for a dose–response curve) is important for improving the interspecies extrapolation of risk assessment. A fundamental problem of extrapolating risks is the shape of the dose–response curve at low doses, i.e., at concentrations relevant to human exposures. The estimated average concentration of acrylamide in the blood is approximately 6 nM (estimated from the average background level of hemoglobin adducts among nonsmokers)—a concentration that is five times lower than the lowest concentration used by Besaratinia and Pfeifer (1). Studying effects at such low exposures is very difficult even in *in vitro* studies.

The shape of the dose–response curve for mutagenicity is difficult to assess in the Besaratinia and Pfeifer paper (1), resulting from the choice of doses and the statistical uncertainty. Abramsson-Zetterberg (11) has convincingly demonstrated a linear dose–response relationship in the *in vivo* induction of

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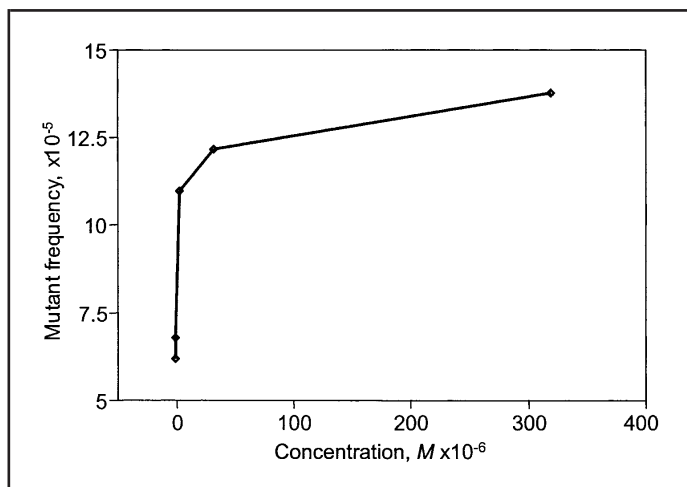


Fig. 1. Mutant frequency in Big Blue mouse embryonic fibroblasts after a 4-hour treatment of various concentrations of acrylamide.

micronuclei, a measure of genotoxicity, in mice exposed to a large range of doses, although the lowest dose used was still orders of magnitude higher than the daily intake of dietary acrylamide. Furthermore, regardless of whether glycidamide was directly administered or whether it arose as a metabolite from acrylamide administration, the induction of micronuclei per unit blood dose of glycidamide in mice was the same (12), supporting the notion that glycidamide is the predominant genotoxic agent of acrylamide exposure. However, cancer tests with acrylamide in F344 rats resulted in an excess of hormone-related tumors (13,14), suggesting that acrylamide could also have a hormone-like action. Whether glycidamide at doses comparable with those arising from acrylamide has the same potency and induces the same tumor spectra in the same rat strain would therefore be important to assess. For similar reasons, the same type of experiments with B6C3F1 mice (the strain extensively used for carcinogenicity testing by the National Toxicology Program) would also be valuable for investigating to what extent *in vivo* dosimetry could explain the difference between mice and rats.

Even if no one today can answer the question of whether dietary acrylamide is hazardous to humans, it is not inconceivable to us that acrylamide can contribute approximately 1% of the lifetime cancer risk, considering that a large fraction of all cancers has been attributed to dietary factors (15). However, because the individual's estimated cancer risk due to dietary acrylamide is quite small, there seems to be no reason to change nutritional guidelines, because the high consumption of foods such as potato chips or french fries should be avoided for other and more prominent health-related reasons, such as cardiovas-

cular disease. However, the situation for vulnerable groups, e.g., pregnant women and children, should always be carefully considered. Finally, the contrast between the high levels of "naturally" occurring acrylamide exposure and the safety limits set by regulatory agencies is challenging for our risk philosophy and how risks should be managed.

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NOTE

¹There is no consensus definition of the precautionary principle, but one oft-mentioned statement from the Wingspread conference in Racine, WI, in 1998 sums it up: "When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically."