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Acrylamide Carcinogenicity

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The induction of cancer by chemicals is a multiple-stage process. Acrylamide is carcinogenic to experimental mice and rats, causing tumors at multiple organ sites in both species when given in drinking water or by other means. In mice, acrylamide increased the incidence and multiplicity of lung tumors and skin tumors. In two bioassays in rats, acrylamide administered in drinking water consistently induced mesotheliomas of the testes, thyroid tumors, and mammary gland tumors. In addition, brain tumors appeared to be increased. In one of the rat bioassays, pituitary tumors, pheochromocytomas, uterine tumors, and pituitary tumors were noted. The conversion of acrylamide metabolically to the reactive, mutagenic, and genotoxic product, glycidamide, can occur in both rodent and humans. Glycidamide and frequently acrylamide have been positive for mutagenicity and DNA reactivity in a number of in vitro and in vivo assays. The effects of chronic exposure of glycidamide to rodents have not been reported. Epidemiologic studies of workers for possible health effects from exposures to acrylamide have not shown a consistent increase in cancer risk. Although an increase in the risk for pancreatic cancer (almost double) was seen in highly exposed workers, no exposure response relationship could be determined. The mode of action remains unclear for acrylamide-induced rodent carcinogenicity, but support for a genotoxic mechanism based on in vitro and in vivo DNA reactivity assays cannot be ruled out. In addition, the pattern of tumor formation in the rat following chronic exposure supports a genotoxic mode of action but also suggests a potential role of endocrine modification.

KEYWORDS: Acrylamide; glycidamide; genotoxicity; mutation, carcinogenicity, neuro tumors; thyroid tumors; mammary tumors; testes mesotheliomas

INTRODUCTION

The induction of cancer by chemicals (chemical carcinogenesis) is a multistage process (**Figure 1**). This process involves the formation of a mutated cell followed by the selective expansion of the initiated cell population through either increased cell proliferation or decreased apoptosis. The process is demonstrable in several animal models by distinct histological lesions. The initial step involves the generation of an initiated, mutated cell that arises from nonrepaired genomic DNA interactions with a genotoxic compound (*1, 2*). In addition, the induction of spontaneous DNA damage and resulting mutations may also occur. Thus, the first stage of the carcinogenesis process (formation of an initiated cell) may occur through chemical interaction with genomic DNA or through the acquisition of spontaneous mutations. The formation of the mutated initiated cell is threshold driven, but once the mutation occurs, it is an irreversible process (i.e., DNA cannot be repaired) unless the initiated cell is removed through apoptosis (*3*). A second stage of the process (often termed promotion) involves the selective clonal expansion of the initiated cell directly by a chemical agent or indirectly (i.e., hormonal, cytotoxicity) through activation of gene expression of cell growth regulatory genes. This process is dose dependent, threshold based, and reversible. The third stage (progression) involves the transfer from the pre-neoplastic state to the neoplastic stage and involves additional genotoxic and clastogenic events (*1, 2*).

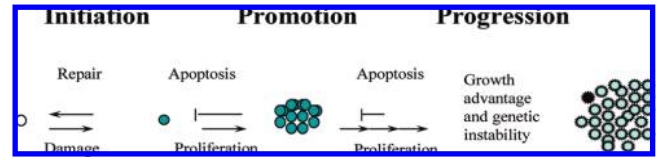

Figure 1. Multistage chemical carcinogenesis: diagram showing the multistep nature of the cancer process and formation of the initiated, mutated cell (initiation process), which undergoes selective clonal proliferation (promotion process) and subsequent acquisition of additional genetic changes to progress to the neoplastic stage (progression).

Acrylamide ($CH_2CHCONH_2$) is a low molecular weight, odorless, and colorless compound. It is readily soluble in water and can rapidly polymerize from a monomer state to a polymer form. Acrylamide is biotransformed in vivo to its epoxide, glycidamide (*4*) (**Figure 2**). Glycidamide has genotoxic proper-

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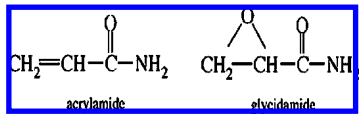

Figure 2. Structures of acrylamide and its major metabolite, glycidamide.

ties in both in vitro and in vivo test systems. In several rodent studies, acrylamide has been shown to be tumorigenic at multiple organ sites in both mice (*5, 6*) and rats (*7, 8*) when given systemically by various routes. Epidemiologic evaluations of cancer risk in workers who were exposed occupationally to acrylamide have been reported. Two cohorts of workers who were exposed to acrylamide monomer and polymerization production industries have been examined, and cancer incidence in these workers has been evaluated (*9–11*). No consistent effect of acrylamide exposure on cancer incidence in these workers has been identified.

Acrylamide is rapidly absorbed and appears to be distributed throughout the body. Acrylamide is oxidized in rodents and humans to glycidamide through CYP2E1 (*12*). Evidence for glycidamide formation in humans has been shown indirectly in the hemoglobin of acrylamide workers exposed to relatively high levels of acrylamide (*13*). Both acrylamide and glycidamide appear to be equally distributed among the organs in rodents. The conversion of acrylamide to glycidamide has been shown to be saturated at higher doses in rats. Both compounds are detoxified by glutathione conjugation, and glycidamide is also detoxified by hydrolysis. Excretion of acrylamide and metabolites is rapid and occurs mostly via the urine where *N*-acetyl-*S*-(2-carbamoylethyl)cysteine is found from the degradation of the glutathione conjugate. The metabolic conversion of acrylamide to glycidamide, a very reactive epoxide metabolite, occurs via CYP450 2EI. Glycidamide can react with genomic DNA as well as interact with protein via a Michael reaction to a nucleophile. Acrylamide reacts rapidly with SH groups in proteins. The in vitro reaction with DNA in contrast is relatively slow and has not been shown to occur in vivo. Acrylamide is highly water soluble, but is equally well soluble in some organic solvents including methanol and ethanol.

An important reaction of acrylamide is with protein and the formation of hemoglobin adducts (Hb). Adducts are formed at the site of SH groups and on the amino groups of the N-terminal amino acids. Hb adduct formation was linear in a dose response manner when the epoxide metabolite glycidamide or acrylamide was administered to experimental animals (*14*).

Acrylamide adduct formation with DNA has also been reported. The carcinogenic and mutagenic significance of acrylamide adducts is not known. The only adduct detected in mice and rats has been a glycidamide−guanine adduct (*15*). A higher level of DNA adduct formation has been found in mice compared to rats correlating with the greater metabolic conversion of acrylamide to glycidamide in mice compared to rats. The guanine−acrylamide DNA adduct appears to be detectable in multiple tissues following exposure to acrylamide. DNA adduct formation after acrylamide exposure in humans is lacking.

The genotoxicity of acrylamide and glycidamide has been studied extensively. Acrylamide did not induce gene mutations in *Salmonella typhimurium* (Ames test). In contrast, glycidamide induces gene mutations in *S. typhimurium* strains TA15 35 and TA100 with and without metabolic activation (S9 mix) (*16, 17*). The failure of acrylamide to produce a positive mutation may be related to the lack of CYP2E1 in the liver S-9. Acrylamide failed to produce an increase in unscheduled DNA synthesis

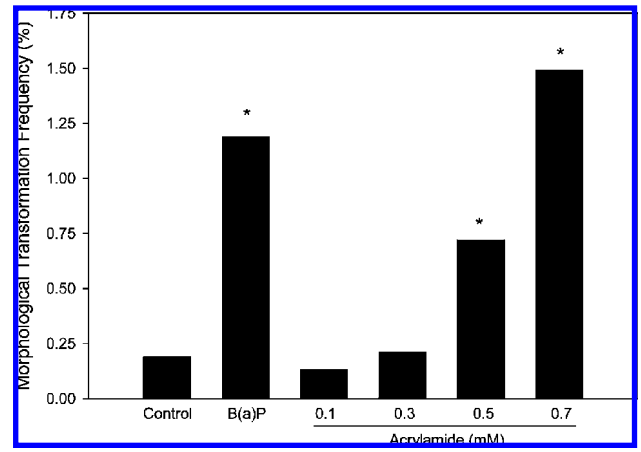

Figure 3. SHE cell transformation assay following acrylamide exposure. Acrylamide induced an increase in cell transformation after 7 days of continual exposure at the two highest doses.

(UDS) in rat hepatocytes. Similarly, in an in vivo−in vitro unscheduled DNA synthesis (UDS) assay, acrylamide failed to increase UDS in the liver of rats receiving single or repeated (five times) intraperitoneal (ip) injections of 0, 30, or 100 mg/kg bw of acrylamide (*18*). In contrast, glycidamide induced UDS in human mammary cells and rat hepatocytes. Glycidamide also induced UDS in mouse spermatids in vivo (*19*).

Acrylamide has produced a positive increase in SHE, NIH/3T3, and C3H/10T1/2 cellular transformation assays with and without metabolic activation (*20, 21*). Acrylamide at concentrations of 0.5 mM and greater induced an increase in morphological transformation (*21*) (**Figure 3**). Coexposure of acrylamide and 1-aminobenzotriazole (an inhibitor of CYP450) produced SHE cell transformation similar to that seen with acrylamide only (*21*). This and other works suggests that metabolism is not required for cell transformation by acrylamide. However, depletion of glutathione in the SHE cell assay enhanced the transformation rate by acrylamide, whereas supplementation with glutathione inhibited the SHE transformation by acrylamide (*21*) (**Figure 4**).

In in vivo genotoxicity studies, acrylamide produced a dose-dependent increase in the mouse micronuclei assay at doses of 0.18, 0.35, and 0.70 mmol/kg of body weight (bw). The dose response relationship was linear at the concentrations studied (*22*). In contrast, in rats, acrylamide doses of 0.7 and 1.4 mmol/kg of bw did not produce an increase in micronuclei. This may be related to the greater metabolism of acrylamide to glycidamide in the mouse. Acrylamide failed to produce a significant increase in mutations in the transgenic MutaMouse, although an increase in mutations was seen, albeit not significantly (*23, 24*). Acrylamide has also consistently produced dominant lethal mutations in rodents after all forms of administration (ip, gavage, dermal, and drinking water) (*25, 25*). In addition, acrylamide (**Figure 5**) produced an increase in DNA damage, measured by the Comet assay in the target tissues (thyroid and adrenal) for tumorigenesis following treatment of F344 rats with acrylamide.

CARCINOGENICITY OF ACRYLAMIDE IN MICE

In studies employing the strain A mouse (A/J) lung tumor bioassay (a strain very susceptible to lung adenomas), acrylamide was examined at doses of 0 (control), 6.25, 12.5, or 25.0 mg/kg of bw acrylamide by oral gavage three times per week for 8 weeks (purity > 99%). Acrylamide resulted in an increase in lung adenoma multiplicity and incidence in mice sampled

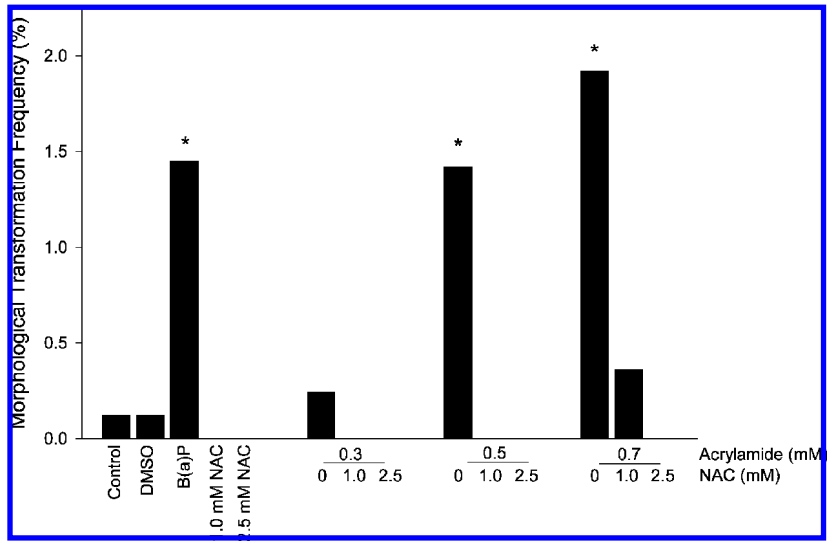

Figure 4. Effect of supplementation of glutathione on acrylamide cell transformation. SHE cell transformation by acrylamide is prevented by co-incubation with the glutathione donor (*N*-acetylcysteine) in a dose-dependent manner.

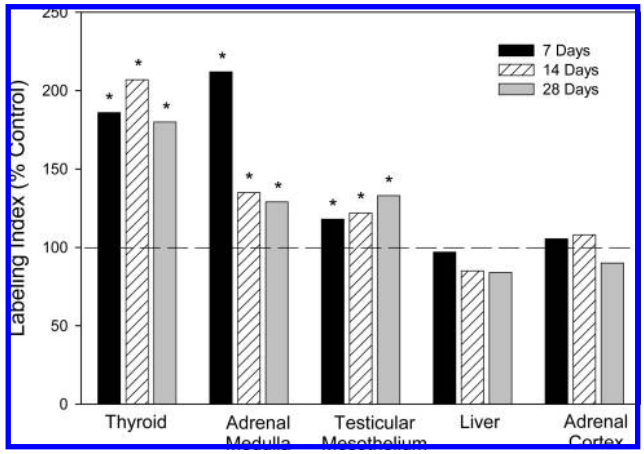

Figure 5. DNA synthesis (labeling index) in F344 rat tissues following acrylamide exposure in drinking water (15 mg/kg/day) for 7, 14, and 28 days. Acrylamide increased DNA synthesis in those tissues that displayed tumors in chronically treated rats. In contrast, nontarget tissues (liver and adrenal cortex) showed no increase in DNA labeling index. Rats received an osmotic minipump containing BRDU for 6 days prior to sacrifice. Labeling index was determined by immunohistochemistry.

after 7 months of treatment. The increase was dose dependent (*5*). Similarly, in a companion study, the male A/J mice received acrylamide (in distilled water) via ip injection three times per week for 8 weeks at doses of 0, 1, 3, 10, 30, or 60 mg/kg of bw. The highest dose (60 mg/kg of bw; ip) produced peripheral neuropathy and decreased survival. Lung adenomas showed a significant increase in incidence in males in a dose-dependent manner (vehicle controls, 2/16; 1 mg, 8/16; 3 mg, 6/16; 10 mg, 10/17; and 20 mg, 14/15). In females a dose-dependent increase in lung tumor incidence was also seen (vehicle controls, 1/15; 1 mg, 6/17; 3 mg, 9/17; 10 mg, 11/14; and 30 mg, 14/15). The mean number of lung adenomas per mouse was also increased with increased acrylamide treatment in both males and females (in males, 0.06; vehicle controls, 0.75; 1 mg, 0.69; 3 mg, 0.88; 10 mg, 1.87; 30 mg) (in females, 0.13; vehicle controls, 0.35; 1 mg, 0.88; 3 mg, 1.57; 10 mg, 2.53; 30 mg) (*5*). SENCAR mice were treated with 12.5, 25.0, or 50.0 mg/kg of bw of acrylamide by gavage or via skin painting in an initiation−promotion protocol. Following treatment with acrylamide (three times per week for 2 weeks) (initiation) mice received treatment with 12-*O*-tetradecanoylphorbol-13-acetate (TPA) (promotion) for 20 weeks. Treatment with both acrylamide and TPA resulted in an increase in skin papillomas and squamous cell carcinomas in a dose-dependent manner (*24, 28*). ICR-Swiss mice were also treated with acrylamide and TPA in an initiation−promotion protocol. ICR-Swiss mice received acrylamide by gavage followed by administration of TPA. Acrylamide with or without TPA produced a significant increase in alveolar adenomas and carcinomas (*6*).

CARCINOGENICITY OF ACRYLAMIDE IN RATS

Fischer 344 rats, 5−6 weeks of age (90 male and 90 female rats) received 0, 0.01, 0.1, 0.5, or 2 mg/kg of bw of acrylamide per day in drinking water for 104 weeks. Survival at the end of the study was reduced in both males and females at the 2 mg/kg of bw dose. Tumors induced by acrylamide included significant increases in thyroid gland tumors and testicular mesotheliomas in males and mammary gland, glial and brain, thyroid, oral cavity, uterus, and clitoral gland in female rats (*7*). Tumor incidence was dose dependent at doses above 0.5, whereas doses of 0.01 and 0.1 mg/kg of bw failed to increase tumor incidence in both females and males.

In a second study, male and female Fischer 344 rats were treated with acrylamide in drinking water for 104 weeks. Acrylamide doses included in females 0, 1.0, or 3.0 mg/kg of bw/day and in males 0, 0.1, 0.5, and 2.0 mg/kg of bw/day. Similar to the previous study, an increase in thyroid follicular-cell tumors was seen in both males and females, testicular mesotheliomas in males, and mammary tumors in females. The tumors previously reported, the glial, brain, thyroid, oral cavity, uterus, and clitoral gland tumors in female rats, were not reported in this study (*8*). These target tissues are also the site of DNA damage (**Figure 4**) and increase in cell proliferation following exposure to acrylamide (**Figure 6**) (*29*).

OCCUPATIONAL EPIDEMIOLOGIC STUDIES IN HUMANS

Two industrial epidemiologic studies have been performed (*9, 23*). Sobel and co-workers reported on the mortality of 371 acrylamide worker employees who had possibly been exposed to acrylamide from 1955 to 1979 during monomer and polymerization operations in Michigan (*9*). Individual exposure levels were not measured, but environmental amounts of

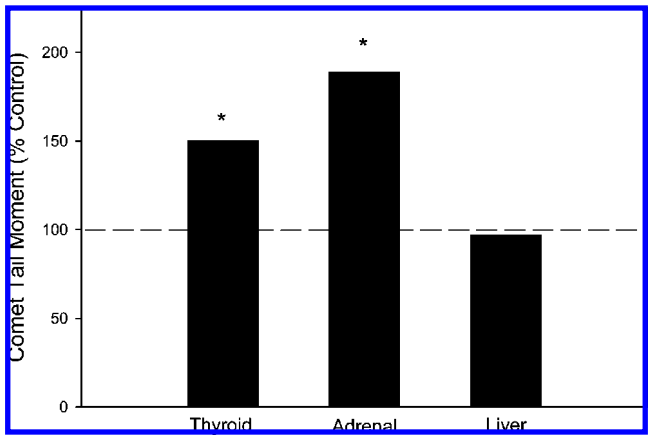

Figure 6. Comet assay in acrylamide-treated F344 rats. Examination of DNA damage using single-cell gel electrophoresis (the Comet assay) showed an increase in DNA damage in selected target tissues (adrenal and thyroid) that showed an increase in tumors following chronic exposure to acrylamide, but not in a nontarget tissue (liver). F344 male rats were treated with 15 mg/kg/day acrylamide in drinking water for 14 days.

acrylamide were measured during the manufacturing period and showed a reduction with time. For example, from 1955 to 1957 the 8 h TWA ranged from 0.1 to 1.0 mg/m^3, and from 1957 to 1979, the TWA was 0.1−0.6 mg/m^3. Acrylamide workers were identified from workers at the plant 1955−1979. All subjects were white, with 365 of the 371 males. Only 19% had started work before 1960. Mortality was examined from initial exposure until the end of 1982. Standardized mortality ratios (SMRs) were estimated from mortality rates for U.S. white males. In the workers, 29 deaths were seen of the 38 that were expected for the U.S. white males. Death from cancers was slightly greater than expected, but was not statistically significant. No linkage of cancer type to worker exposure was found.

Another larger cohort study examined mortality in four plants, one in The Netherlands and three in the United States (*10*). A total of 8854 men with potential exposure to acrylamide, employed from 1925 to 1976, were examined with most (95%) from the U.S. plants. Acrylamide exposure estimates were determined from ambient air monitoring beginning from 1977. Estimated SMRs for expected deaths were calculated from national death rates and adjusted for age and race. From the exposed workers, a decrease in mortality compared to the expected rates was observed (healthy worker). Of cancers, a slight increase in pancreatic cancer and Hodgkin's disease was noted. No trend in cancer mortality was seen. In an 11-year followup (*11*), 1115 additional deaths and nearly 60000 person-years were added to the original study (*10*). For the 1925−1994 timeline, overall mortality risks were found for cancer of the brain and other areas of the central nervous system, thyroid, testis, and lung cancer. However, the findings were not statistically associated with exposure to acrylamide. A significant (20.2-fold) increased risk of pancreatic cancer among workers exposed to acrylamide greater than 0.30 mg/m^3/year was seen (a total of nine individuals). However, no consistent dose response relationship to acrylamide exposure was found. Thus, the findings of the followup seem to confirm the initial cohort study on the lack of a causal relationship between acrylamide exposure and cancer mortality.

More recently, studies by Hogervorst et al. (*29*) and Olesen et al. (*30*) have reported a linkage between dietary intake of acrylamide and endocrine tumors in women (endometrial, ovarian, and breast). In the Hogervorst study, women in The Netherlands cohort were analyzed for endometrial, ovarian, and breast cancer incidence in concert with reported food uptake diaries (*29*). The authors concluded that a linkage between acrylamide in food and the induction of cancer was apparent. In an examination of blood from 374 postmenopausal women with breast cancer, Olesen et al. showed a positive association between acrylamide hemoglobin adduct levels and breast cancer incidence (*30*). Both of these studies suggest a linkage between cancer and dietary acrylamide uptake.

MODE OF ACTION

The mode of action remains unclear for acrylamide-induced rodent carcinogenicity, but support for a genotoxic mode based on in vitro and in vivo DNA reactivity assays cannot be ruled out. In addition, the pattern of tumor formation in the rat following chronic exposure supports a genotoxic mode of action, but also suggests a potential role of endocrine modification (*31*). However, no studies noting a modification of endocrine activity or sensitivity in acrylamide-treated rodents has been provided. Furthermore, tumors of endocrine glands and hormone-dependent tissues in rodents are frequently produced by genotoxic, DNA reactive carcinogens. In addition, many established neurocarcinogens in rodents are DNA reactive (*32*).

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