

Appendix B: Substances Delisted from the Report on Carcinogens

The agents, substances, mixtures, or exposure circumstances contained in this appendix were previously listed in the Report on Carcinogens as either *known* or *reasonably anticipated to be human carcinogens*. For substances removed from the Report on Carcinogens prior to the 1996 establishment of a formal review procedure for delisting substances from the Report on Carcinogens, the table below shows the reason for delisting. The reason for delisting is in some cases the fact that residents of the United States are not exposed to these substances because since they are no longer produced or used in the United States and in other cases that the rulings or findings as to the carcinogenic potential of the substances have been revised (e.g., as a result of new studies). The table indicates the last edition of

the Report on Carcinogens in which these substances appeared, to which reference can be made for all information available.

For each substance removed from the Report on Carcinogens as a result of a formal review for delisting (from the Eighth Edition forward), a profile is provided following the table, which summarizes the review for delisting, including the relevant information and the issues identified by the scientific review groups that led to the substance's delisting. Background documents outlining in more detail the issues considered during the reviews for delisting these substances can be obtained by contacting the National Toxicology Program at the following address: National Toxicology Program, Report on Carcinogens Center, P.O. Box 12233, MD K2-14, Research Triangle Park, NC 27709.

Substance Name	CAS Number	Last Listing	Reason for Delisting
Chloramphenicol	56-75-7	<i>known</i> First RoC (1980)	Human data considered inadequate
Aramite	140-57-8	<i>reasonably anticipated</i> Fourth RoC (1985)	No U.S. residents exposed
<i>N,N</i> -Bis(2-chloroethyl)-2-naphthylamine (chlornaphazine)	494-03-1	<i>known</i> Fourth RoC (1985)	No U.S. residents exposed
Cycasin	14901-08-7	<i>reasonably anticipated</i> Fourth RoC (1985)	No U.S. residents exposed
Methyl iodide	78-88-4	<i>reasonably anticipated</i> Fourth RoC (1985)	Reevaluated by IARC; evidence now considered equivocal
5-Nitro- <i>o</i> -anisidine	99-59-2	<i>reasonably anticipated</i> Fifth RoC (1989)	Insufficient evidence of carcinogenicity
<i>p</i> -Nitrosodiphenylamine	156-10-5	<i>reasonably anticipated</i> Fifth RoC (1989)	Insufficient evidence of carcinogenicity
Ethyl acrylate	140-88-5	<i>reasonably anticipated</i> Eighth RoC (1998)	See following profile
Saccharin	81-07-2	<i>reasonably anticipated</i> Eighth RoC (1998)	See following profile

Report on Carcinogens Review Group Actions on the Nomination of Ethyl Acrylate for Delisting from the Report on Carcinogens

Summary of data contained in the Ethyl Acrylate Background Document (December 1998)

Ethyl Acrylate

CAS No. 140-88-5

Ethyl acrylate is used in various industries as an intermediate in the production of emulsion-based polymers which are then used in paint formulations, industrial coatings, and latex products. It is also used as a synthetic flavoring substance and fragrance adjuvant in consumer products. Human exposure to ethyl acrylate occurs mostly through inhalation of ethyl acrylate vapors, but it may also result from skin contact or ingestion as a food additive or from drinking of contaminated water. The Report on Carcinogens review groups considered the data underlying the nomination to remove ethyl acrylate from the Report on Carcinogens, where it has been listed as *reasonably anticipated to be a human carcinogen* since 1989. The basis for this listing was a gavage study that resulted in dose-related benign and malignant forestomach neoplasms in rats and mice. The Basic Acrylic Monomer Manufacturers, Inc. (BAMM), submitted a nomination to remove ethyl acrylate from the Report on Carcinogens based upon the following information: (1) negative tumorigenicity results from chronic-exposure studies using routes other than gavage in corn oil, (2) research results suggesting that the forestomach carcinogenicity observed in the gavage studies was secondary to a site-specific and concentration-dependent irritating effect of ethyl acrylate, and (3) the fact that significant human exposure to ethyl acrylate monomer is unlikely in light of current manufacturing practices and patterns of usage (see Human Exposure and Cancer Studies in Humans, below).

The majority opinion of the Report on Carcinogens review groups was to recommend that ethyl acrylate be removed from the Report on Carcinogens. This opinion was based on the facts that (1) the forestomach tumors induced in animal studies were seen only when ethyl acrylate was administered by gavage at high concentrations that induced marked local irritation and cellular proliferation, (2) animal studies using other routes of administration, including inhalation, gave negative results, and (3) significant chronic human oral exposure to high concentrations of ethyl acrylate monomer is unlikely. Therefore, ethyl acrylate does not meet the criteria to be listed in the Report on Carcinogens as *reasonably anticipated to be a human carcinogen*.

Summary of Available Carcinogenicity Data and Other Relevant Information

Cancer Studies in Experimental Animals

Although mutagenic in some *in vitro* tests, ethyl acrylate is not genotoxic under *in vivo* physiological conditions, perhaps because of its rapid metabolism to acrylic acid and ethanol by carboxyesterases and detoxification through binding to non-protein sulfhydryls. Target tissue toxicity in the form of irritation was observed in the skin in a lifetime mouse skin-painting study, in the nasal olfactory mucosa in 27-month inhalation studies in rats and mice, and in the forestomach in two-year corn-oil gavage studies in rats and mice. Only body-weight reduction was observed in a two-year study of exposure via drinking water in rats. The forestomach carcinogenicity observed in the corn-oil gavage studies was the only treatment-related tumorigenic response in the various animal studies. The irritation, hyper-

plasia, and tumor responses in the forestomach were related more to target-tissue concentration of ethyl acrylate than to delivered dose in the chronic gavage study. Based upon stop-exposure studies, gavage doses of ethyl acrylate in corn oil sufficient to induce sustained mucosal hyperplasia in the forestomach must be administered for longer than six months to induce forestomach neoplasia.

Human Exposure and Cancer Studies in Humans

Prolonged consumer exposure to high levels of ethyl acrylate monomer by the oral route is unlikely. Potentially significant exposures would most likely occur in an occupational setting where the routes of exposure would be dermal or by inhalation. Ethyl acrylate has a strong acrid odor (odor threshold ~ 0.5 ppb) and is a known irritant to the skin, eyes, and mucous membranes, making it unlikely that humans would be chronically exposed to high concentrations. Data provided in the BAMM nomination on worker exposure showed occupational exposure well below the threshold limit value (TLV = 5 ppm for an eight-hour time-weighted average) and the short-term exposure limit (STEL = 15 ppm), although exposure of painters in an unventilated room has been reported to be as high as 8 ppm in the painter's breathing zone.

An epidemiology study reported on mortality from cancer of the colon and rectum in three separate cohorts of workers from two plants manufacturing and polymerizing acrylate monomers. Workers were exposed to ethyl acrylate and methyl methacrylate monomer between 1933 and 1982. Risks for both types of cancer were associated with exposure in the earliest cohort, although the rectal cancer results are imprecise because of the small number of cases involved. The greatest relative risk was found in workers with the highest level of exposure and a 20-year latency. The other two cohorts, with later dates of hire, showed no excess risk, but very few cases were available for observation. This study, by itself, can neither establish nor rule out a causal relationship of ethyl acrylate with cancer.

Action on Nomination

Ethyl acrylate will be removed from the Report on Carcinogens because the relevant data are not sufficient to meet the current criteria to list this chemical as *reasonably anticipated to be a human carcinogen*. This is based on the fact that the forestomach tumors induced in animal studies were seen only when the chemical was administered by gavage at high concentrations of ethyl acrylate that induced marked local irritation and cellular proliferation, and because significant chronic human exposure to high concentrations of ethyl acrylate monomer is unlikely.

Report on Carcinogens Review Group Actions on the Nomination of Saccharin for Delisting from the Report on Carcinogens

Summary of data contained in the Saccharin Background Document (October 1997)

Saccharin

CAS No. 81-07-2

Saccharin and its sodium and potassium salts have been produced commercially in the United States for over 80 years. Saccharin is primarily used as a non-nutritive sweetening agent. Potential exposure to saccharin occurs through the consumption of dietetic foods and drinks and the use of some personal hygiene products. Potential exposure to saccharin also occurs in the workplace, specifically in occupations, industries, or facilities that produce and deal with saccharin

and its salts. The Report on Carcinogens review groups considered the data underlying the nomination to remove saccharin from the Report on Carcinogens where it has been listed as *reasonably anticipated to be a human carcinogen* since 1981. The basis for this listing was sufficient evidence of carcinogenicity in experimental animals. The Calorie Control Council submitted a nomination to the NTP to consider removing saccharin from the Report on Carcinogens based upon mechanistic data related to development of urinary-bladder cancers in rats (see Studies on Mechanisms of Carcinogenesis, below).

The majority opinion of the review groups was to recommend that saccharin be removed from the Report on Carcinogens. There is evidence for the carcinogenicity of saccharin in rats, but less convincing evidence in mice. Studies indicate that the observed urinary-bladder cancers in rats are related to the physiology of the rat urinary system, including urinary pH, osmolality, volume, the presence of precipitate, and urothelial damage with attendant hyperplasia following consumption of diets containing sodium saccharin at concentrations of 3% or higher, with inconsistent findings at lower dietary concentrations. The factors thought to contribute to tumor induction by sodium saccharin in rats would not be expected to occur in humans. The mouse data are inconsistent and require verification by additional studies. Results of several epidemiology studies indicate no clear association between saccharin consumption and urinary-bladder cancer. Although it is impossible to conclude with absolute certainty that it poses no threat to human health, sodium saccharin is not *reasonably anticipated to be a human carcinogen* under conditions of general usage as an artificial sweetener.

Summary of Available Carcinogenicity Data and Other Relevant Information

Cancer Studies in Experimental Animals

In four studies of up to 30 months' duration, sodium saccharin was carcinogenic in Charles River CD and Sprague-Dawley male rats, as evidenced by a dose-related increased incidence of benign or malignant urinary-bladder neoplasms at dietary concentrations greater than 1% (Tisdell *et al.* 1974, Arnold *et al.* 1980, Taylor *et al.* 1980, Schoenig *et al.* 1985). Non-statistically-significant increases in urinary-bladder cancer also were seen in saccharin-exposed female rats in studies showing a positive effect in males (Arnold *et al.* 1980, Taylor *et al.* 1980). Furthermore, several initiation/promotion studies in different rat strains showed a reduced latency and/or increased incidence of similar urinary-bladder cancers in male and female rats fed sodium saccharin after treatment with various urinary-bladder tumor initiators (e.g., Hicks and Chowanec 1977, Cohen *et al.* 1979, Nakanishi *et al.* 1980a, West *et al.* 1986, Fukushima *et al.* 1990). Several additional rat studies in which sodium saccharin was administered either in the diet or in drinking water gave negative results for tumorigenicity (Fitzhugh *et al.* 1951, Lessel 1971, Schmähl 1973, Chowanec and Hicks 1979, Hooson *et al.* 1980, Schmähl and Habs 1984).

Three mouse studies reported carcinogenicity following exposure to saccharin. Two of these studies involved surgical implantation of saccharin-containing cholesterol pellets into the urinary bladders and resulted in development of malignant urothelial neoplasms (Allen *et al.* 1957, Bryan *et al.* 1970). In the third study, dietary exposure to sodium saccharin resulted in increased incidences of malignant thyroid-gland neoplasms (Prasad and Rai 1986). Although the data from studies in mice cannot be discounted, some of these studies had methodological flaws, provided limited information, did not show a dose-response relationship, or had unexpected outcomes that may be species- or strain-specific, and should be verified by additional studies. The results of four studies in mice were

judged negative for tumorigenesis (Roe *et al.* 1970, Kroes *et al.* 1977, Homberger 1978, Frederick *et al.* 1989), as were limited studies in nonhuman primates (McChesney *et al.* 1977, Sieber and Adamson 1978, Thorgierson *et al.* 1994, Cohen *et al.* 1996) and a single hamster study (Althoff *et al.* 1975).

Cancer Studies in Humans

Most of the relevant human epidemiology studies examined associations between urinary-bladder cancer and artificial sweeteners, rather than saccharin *per se*. The time-trend data for urinary-bladder cancer showed no clear indication that the increased use of saccharin or artificial sweeteners commencing in the 1940s was associated with a general increase in urinary-bladder cancer when confounding factors, chiefly smoking, were controlled for. Risks of urinary-bladder cancer in diabetics, who presumably consume greater amounts of artificial sweeteners than the general population, were no greater than risks in the general population (Armstrong and Doll 1975). Based upon several case-control studies, there was no overall association between use of artificial sweeteners and urinary-bladder cancer (reviewed by IARC 1980, 1987b, JECFA 1993). However, an association between use of artificial sweeteners and urinary-bladder cancer could not be ruled out in some case-control subgroups, albeit involving small numbers (Howe *et al.* 1980, Hoover and Strasser 1980, Cartwright *et al.* 1981, Morrison *et al.* 1982, Mommsen *et al.* 1983). Taken together, the available epidemiology data show no consistent evidence that saccharin is associated with increased urinary-bladder cancer in general; however, a small increased risk in some subgroups, such as heavy users of artificial sweeteners, cannot be unequivocally excluded. With regard to the general population, if sodium saccharin is a risk factor, it is weak, and a causal relationship with cancer cannot be proven or disproven, because of a lack of exposure data and intrinsic limitations of the available epidemiology studies.

Studies on Mechanisms of Carcinogenesis

Extensive studies of the mutagenicity and genotoxicity of saccharin have shown generally negative but occasionally conflicting results. Sodium saccharin is essentially nonmutagenic in conventional bacterial systems, but is weakly clastogenic or genotoxic in short-term *in vitro* and in some *in vivo* test systems (reviewed by Ashby 1985, IARC 1987a,b, Whysner and Williams 1996). Urine from mice exposed to sodium saccharin was mutagenic in *Salmonella typhimurium* in one study (Batzinger *et al.* 1977). Saccharin does not covalently bind to DNA and does not induce unscheduled DNA synthesis in urinary-bladder urothelium.

Saccharin-induced carcinogenesis in rats showed a sex predilection for males (Tisdell *et al.* 1974, Arnold *et al.* 1980, Taylor *et al.* 1980), an organ specificity for urinary bladder (Tisdell *et al.* 1974, Arnold *et al.* 1980, Taylor *et al.* 1980, Fukushima *et al.* 1983, Schoenig *et al.* 1985), and a dose-response when exposure to dietary concentrations of 1% to 7.5% of the sodium salt of saccharin was begun early in life (beginning at birth or immediately at weaning) and continued for approximately two years (Schoenig *et al.* 1985). The results of mechanistic studies have shown that certain physiological conditions must be simultaneously or sequentially present for induction of urinary-bladder tumorigenesis. These conditions include a urinary pH greater than 6.5, increased urinary sodium concentration, increased urine volume, decreased urine osmolality, and presence of urinary crystals or precipitate, with resulting damage to the urothelium prompting a proliferative (hyperplastic) response of the urinary-bladder epithelium. All of these conditions have been studied extensively in male rats but less so in female rats or in mice. The high levels of urinary protein characteristically produced by male rats may partially explain

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the sex predilection. The high intrinsic rate of urothelial proliferation at about the time of weaning is also believed to contribute to the observed tumorigenic effects. The urinary milieu in rats, especially male rats, is sufficiently different from that in humans or other species to support the contention that these observations are specific to rats. Pharmacokinetic and metabolism data on sodium saccharin do not explain the male rat's sensitivity for induction of urinary-bladder neoplasms (Sweatman and Renwick 1979, 1980).

Action On Nomination

Saccharin will be removed from the Report on Carcinogens, because the data on cancer in rodents are not sufficient to meet the current criteria to list this chemical as *reasonably anticipated to be a human carcinogen*. This decision is based on the perception that the observed urinary-bladder tumors in rats arise by mechanisms not relevant to humans, and the lack of data in humans suggesting a carcinogenic hazard.

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