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 (RoC) as either known or reasonably anticipated to be human carcinogens. For substances removed from the RoC prior to the 1996 establishment of a formal review procedure for delisting substances from the RoC, the table below shows the reason for delisting. The table indicates the last edition of the RoC in which these substances appeared, to which reference can be made for all information available.

<table>
<thead>
<tr>
<th>Substance Name</th>
<th>CAS Number</th>
<th>Last Listing</th>
<th>Reason for Delisting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol</td>
<td>56-75-7</td>
<td>known</td>
<td>Human data considered inadequate</td>
</tr>
<tr>
<td>Aramite</td>
<td>140-57-8</td>
<td>reasonably anticipated</td>
<td>No U.S. residents exposed</td>
</tr>
<tr>
<td>N,N-Bis(2-chloroethyl)-2-naphthylamine (chlornaphazine)</td>
<td>494-03-1</td>
<td>known</td>
<td>No U.S. residents exposed</td>
</tr>
<tr>
<td>Cycasin</td>
<td>14901-08-7</td>
<td>reasonably anticipated</td>
<td>No U.S. residents exposed</td>
</tr>
<tr>
<td>Methyl iodide</td>
<td>78-88-4</td>
<td>reasonably anticipated</td>
<td>Reevaluated by IARC; evidence now considered equivocal</td>
</tr>
<tr>
<td>5-Nitro-o-anisidine</td>
<td>99-59-2</td>
<td>reasonably anticipated</td>
<td>Insufficient evidence of carcinogenicity</td>
</tr>
<tr>
<td>p-Nitrosodiphenylamine</td>
<td>156-10-5</td>
<td>reasonably anticipated</td>
<td>Insufficient evidence of carcinogenicity</td>
</tr>
<tr>
<td>Ethyl acrylate</td>
<td>140-88-5</td>
<td>reasonably anticipated</td>
<td>See following profile</td>
</tr>
<tr>
<td>Saccharin</td>
<td>81-07-2</td>
<td>reasonably anticipated</td>
<td>See following profile</td>
</tr>
</tbody>
</table>
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 carboxylesterases 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 tumor response in the various animal studies. The irritation, hyperplasia, 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 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 antici-
pated 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 con-
vincing 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 fol-
lowing consumption of diets containing sodium saccharin at concen-
trations of 3% or higher, with inconsistent findings at lower dietary
concentrations. The factors thought to contribute to tumor induc-
tion 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 con-
ditions 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% (Tisdel 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 fe-
nale rats in studies showing a positive effect in males (Arnold et al.
1980, Taylor et al. 1980). Furthermore, several initiation/promo-
tion 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 Chowniec 1977,
Cohen et al. 1979, Nakanishi et al. 1980a, West et al. 1986, Fuku-
shima 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 tumorigenesis (Fitzhugh et al. 1951, Lessel
1971, Schmähl 1973, Chowniec and Hicks 1979, Hooson et al. 1980,
Schmähl and Habs 1984).

Three mouse studies reported carcinogenicity following expo-
sure to saccharin. Two of these studies involved surgical impla-
tation of saccharin-containing cholesterol pellets into the urinary
bladders and resulted in development of malignant urothelial neo-
plasms (Allen et al. 1957, Bryan et al. 1970). In the third study, di-
etary exposure to sodium saccharin resulted in increased incidences
of malignant thyroid-gland neoplasms (Prasad and Rai 1986). Al-
though the data from studies in mice cannot be discounted, some of
these studies had methodological flaws, provided limited informa-
tion, did not show a dose-response relationship, or had unexpected
outcomes that may be species- or strain-specific, and should be ver-
ified by additional studies. The results of four studies in mice were
judged negative for tumorigenesis (Roe et al. 1970, Kroes et al. 1977,
Homerber 1978, Frederick et al. 1989), as were limited studies in
nonhuman primates (McChesney et al. 1977, Sieber and Adamson
1978, Thorgersson et al. 1994, Cohen et al. 1996) and a single ham-
ster study (Althoff et al. 1975).

Cancer Studies in Humans

Most of the relevant human epidemiology studies examined associa-
tions between urinary-bladder cancer and artificial sweeteners, rather
than saccharin per se. The time-trend data for urinary-bladder can-
cer 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 sev-
ceral case-control studies, there was no overall association between
use of artificial sweeteners and urinary-bladder cancer (reviewed by
IARC 1980, 1987b, JECA 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, Momsen et al. 1983). Taken to-
gether, 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 ex-
cluded. With regard to the general population, if sodium saccharin
is a risk factor, it is weak, and a causal relationship with cancer can-
not 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. So-
dium saccharin is essentially nonmutagenic in conventional bacterial
systems, but is weakly clastogenic or genotoxic in short-term in vi-
tro 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 predilec-
1980), an organ specificity for urinary bladder (Tisdel et al. 1974,
et al. 1985), and a dose-response when exposure to dietary concentra-
tions 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 ap-
proximately two years (Schoenig et al. 1985). The results of mecha-
nistic 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 epithe-
lium. 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
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 (Swatman 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.

**References**


