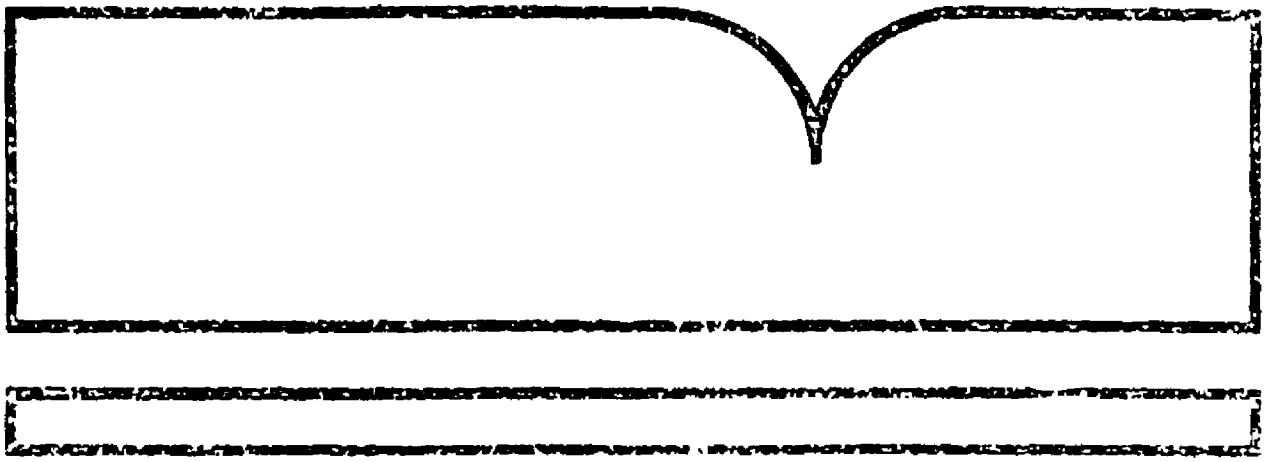
PB83-135855

Annual Report on Carcinogens (3rd)

(U.S.) National Toxicology Program
Research Triangle Park, NC

Dec 82



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MONS 222647

BIBLIOGRAPHIC INFORMATION

PB83-135855

Annual Report on Carcinogens (3rd).

Dec 82

PERFORMER: National Toxicology Program, Research Triangle Park, NC.
NTP-82-330

See also PB82-229808.

The Third Annual Report on Carcinogens, prepared by the National Toxicology Program (NTP), U.S. Public Health Service, is issued by the Secretary of the Department of Health and Human Services (DHHS), pursuant to Public Law 95-622 of November 9, 1978. This law requires the Secretary to publish an Annual Report which contains 'a list of all substances (i) which either are known to be carcinogens or which may reasonably be anticipated to be carcinogens and (ii) to which a significant number of persons residing in the United States are exposed;....' Annual Reports should also provide available information on the nature of exposures, the estimated number of persons exposed, and the extent to which the implementation of Federal regulations decreases the risk to public health from exposure to these substances.

KEYWORDS: *Carcinogens, *Toxicology, *Toxic substances.

Available from the National Technical Information Service, Springfield, Va. 22161

PRICE CODE: PC A19/MF A01

MONS 222648

PB 83 135855

Third Annual Report on

Carcinogens

December 1982

REPRODUCED BY
NATIONAL TECHNICAL
INFORMATION SERVICE
U.S. DEPARTMENT OF COMMERCE
SPRINGFIELD, VA. 22161

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service

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THIRD ANNUAL REPORT ON

CARCINOGENS

DECEMBER 1982

Pursuant to Section 301(b) (4)
of the Public Health Service Act
as Amended by Section 262, PL 95-622

Prepared by the National Toxicology Program

U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
Public Health Service

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EXECUTIVE SUMMARY

The Third Annual Report on Carcinogens, prepared by the National Toxicology Program (NTP), U.S. Public Health Service, is issued by the Secretary of the Department of Health and Human Services (DHHS), pursuant to Public Law 95-622 of November 9, 1978.* This law requires the Secretary to publish an Annual Report which contains "a list of all substances (i) which either are known to be carcinogens or which may reasonably be anticipated to be carcinogens and (ii) to which a significant number of persons residing in the United States are exposed....." Annual Reports should also provide available information on the nature of exposures, the estimated number of persons exposed, and the extent to which the implementation of Federal regulations decreases the risk to public health from exposure to these substances.

For the purpose of this Report, "known carcinogens" are defined as those substances for which the evidence from human studies indicates that there is a causal relationship between exposure to the substance and human cancer. Substances "which may reasonably be anticipated to be carcinogens" are defined as those for which there is a limited evidence of carcinogenicity in humans or sufficient evidence of carcinogenicity in experimental animals.

Substances in the above categories, for which exposure of persons residing in the United States has been demonstrated, are included in the Report. Also included are some substances which have been banned, or the use of which has been restricted, because people previously exposed are potentially at risk, or because some of these substances still remain in the environment. The Third Annual Report does not contain all known or reasonably anticipated carcinogens. Additional substances with identified carcinogenic properties will be included in the subsequent Annual Reports.

Several problems are encountered in developing the information required for the Annual Reports on Carcinogens. Estimating the number of people exposed to a substance and identifying the nature, route, and intensity of exposure are difficult tasks. It is often impossible to obtain accurate production volumes and use patterns for most chemicals. The information that is being collected by the U.S. Environmental Protection Agency under the Toxic Substances Control Act, at least that part which is public record, may assist in obtaining more accurate exposure estimates in the future. In addition, the forthcoming National Occupational Exposure Survey** will provide new information on the extent and degree of exposure for different substances and manufacturing processes.

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* Section 262, Paragraph (4).

** An update of the National Occupational Hazard Survey conducted from 1972 to 1974 by the Centers for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH).

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Perhaps the hardest task in preparing this Report is to evaluate the effectiveness of Federal regulations in decreasing the risk to public health. One reason is that virtually all Federal laws concerned with reducing risk have been enacted within the last 15 years. Thus, given the relatively long period between exposure to a carcinogen and the onset of disease, the extent to which the regulations implemented during these 15 years have reduced the risk remains unknown. Another reason is that reliable information on past exposures which could be used as a baseline for estimating future risk reduction is generally not available. Nonetheless, decreasing exposure should be considered as reducing carcinogenic risk even if the reduction cannot be quantified at present.

The Third Annual Report lists 117 agents. Included are the entries from the Second Annual Report and 28 additional substances or groups of substances. The new entries were chosen from those designated by the Agencies participating in the preparation of the Report,* from those tested within the National Toxicology Program and the National Cancer Institute Carcinogenesis Bioassay Program,** or from those evaluated by the International Agency for Research on Cancer (IARC), a part of the World Health Organization (WHO), located in Lyon, France.

Of the 117 entries, nineteen substances or groups of substances and three technological processes are listed as "known carcinogens":

4-Aminobiphenyl
Arsenic and certain arsenic compounds
Asbestos
Auramine manufacture
Benzene
Benzidine
N,N-Bis(2-chlorethyl)-2-naphthylamine (Chlornaphazine)
Bis(chloromethyl)ether and technical grade chloromethyl methyl ether
Chlorambucil
Chromium and certain chromium compounds
Coke oven emissions
Cyclophosphamide
Diethylstilbestrol
Hematite underground mining
Isopropyl alcohol manufacture (strong-acid process)
Melphalan
Mustard gas
2-Naphthylamine
Nickel refining
Soots, tars, and mineral oils
Thorium dioxide
Vinyl chloride

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* CDC/NIOSH, Consumer Product Safety Commission (CPSC), U.S. Environmental Protection Agency (EPA), Food and Drug Administration (FDA), National Institutes of Health/National Cancer Institute (NIH/NCI), National Institutes of Health/National Institute of Environmental Health Sciences (NIH/NIEHS), National Institutes of Health/National Library of Medicine (NIH/NLM), and U.S. Department of Labor/Occupational Safety and Health Administration (DOL/OSHA).

** Now part of NTP/NIEHS.

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Ninety-five substances or groups of substances are included because they "may reasonably be anticipated to be carcinogens." Nickel appears in both lists because occupational exposure associated with nickel refining is known to be carcinogenic although specific substances which may be responsible for the carcinogenesis in humans have not yet been identified; and elemental nickel and certain nickel compounds may reasonably be anticipated to be carcinogens.

For each substance or technological process, there is a summary description including a synopsis of the evidence that explains inclusion in this Report. This is followed by a collation of regulatory information received from the participating Agencies.

Among the 117 entries, two are natural substances which are not used or produced commercially: aflatoxins and cycasin. Two are food or cosmetic additives: saccharin and safrole. Safrole has been banned for most uses. The use of saccharin has been continued by Congressional mandate.

Twelve pesticides are listed: amitrole; Aramite^{R}; arsenical pesticides; 1,2-dibromo-3-chloropropane; hexachlorobenzene; Kepone^{R}; lindane and other hexachlorocyclohexane isomers; mirex; nitrofen; sulfallate; toxaphene; and 2,4,6-trichlorophenol. Most of these substances have been banned or limited in use.

There are 15 therapeutic substances: N,N-bis(2-chloroethyl)-2-naphthylamine; chlorambucil; cyclophosphamide; diethylstilbestrol; iron dextran complex; melphalan; oxymetholone; phenacetin; phenazopyridine hydrochloride; phenytoin; procarbazine; reserpine; selenium sulfide; streptozotocin; and tris(1-aziridinyl)phosphine sulfide. Two of these substances are no longer produced or used in the United States: N,N-bis-(2-chloroethyl)-2-naphthylamine and streptozotocin. Six are anticancer agents: chlorambucil, cyclophosphamide, diethylstilbestrol, melphalan, procarbazine, and tris(1-aziridinyl)phosphine sulfide.

The remaining 83 substances may be classified as various industrial chemicals and by-products (25); dyes, dye intermediates, and pigments (19); combustion products (13); solvents (6); metals and metal compounds occurring in mining, extraction, and refining processes (6); analytical and research chemicals (5); and chemicals used for miscellaneous purposes (9).

The three occupational exposures known to be carcinogenic are those associated with the manufacture of auramine, the underground mining of hematite, and the manufacture of isopropyl alcohol by the strong acid process.

Scientific knowledge and judgment play important roles in grading the available evidence of carcinogenicity as sufficient, limited, or inadequate. Similarly, in all but one category of substances, regulatory action is an interpretation by the regulators of their Congressional mandates. The sole exception is the deliberate addition of additives and colors to foods. The

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Delaney clause in the Food Additives Amendment of 1958 to the Federal Food, Drug, and Cosmetic Act requires that "no additive shall be deemed to be safe if it is found to induce cancer when ingested by man or animal, or if it is found, after tests which are appropriate for the evaluation of the safety of food additives, to induce cancer in man or animals;...."*

Requests to DHHS for conducting research, testing for carcinogenicity or providing information on the effects of standards or regulations on public health are included in the Report as received; this is required in clause (i), subparagraph (4)(D) of Section 262.

Appendix A is an index of synonyms and trade names to identify substances known under a variety of different names. Appendix B contains a glossary of frequently used terms, a list of commonly used acronyms, and some common units of measurement. Appendix C lists the substances, group of substances, and technological processes contained in the Report and tabulates the synonyms and trade names for each of them. Appendix D is a list of participating Agencies and their staff who collaborated in the preparation of the Third Annual Report, and Appendix E contains a cumulative index to the Annual Reports on Carcinogens.

Corrections or suggestions, as well as any additional information that the reader may have should be sent to the Director, National Toxicology Program, P.O. Box 12233, Research Triangle Park, North Carolina 27709. Summaries of this Report may be obtained from the Public Information Office, National Toxicology Program, B2-04, P.O. Box 12233, Research Triangle Park, North Carolina 27709. Copies of the complete report are available for a fee from the National Technical Information Service, 5285 Port Royal Road, Springfield, Virginia 22161. Request number PB 83-135855 should be indicated.

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* So far only two substances have been banned on the basis of the Delaney clause: Flectol H in 1967 and chloranil in 1969. According to the FDA, both substances were used to make adhesives for food packaging material.

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INTRODUCTION

Cancer is the second most common cause of death in the United States. One in every four Americans will suffer from cancer sometime during their lifetime; one in every five will die from cancer. In 1979, more than 400,000 Americans died of cancer.[1] In addition to the physical and emotional suffering caused by cancer, this disease may cost the Nation as much as $30 billion each year in lost production and income, medical expenses, and research resources. For these reasons, the American public is concerned about cancer and cancer hazards, especially about ways to prevent the occurrence or decrease the incidence of cancers.

Contrary to popular belief, cancer is not one but many diseases which may have different causes. Most scientists now consider that about one-third to two-thirds of all cancers are associated with the environment in which we live and work. In this context, the environment is understood as "anything that interacts with humans, including substances eaten, drunk, and smoked, natural and medical radiation, workplace exposures, drugs, aspects of sexual behavior, and substances in air, water, and soil."[2] Some cultural and behavioral patterns, apart from defined habits of smoking and alcohol consumption, may significantly influence the development of tumors in the gastrointestinal tract, breast, uterus, and prostate. These aspects of social environment, personal behavior, and habits are sometimes called "lifestyle." Although we rarely know the environmental factors and conditions which are responsible for the development of specific cancers, in some cases we are beginning to have some understanding. Most cancers that are associated with the environment should be avoidable, at least potentially.

Development of cancer also depends on "host factors." Host factors are attributes of human organisms associated with individual differences in the risk of developing a specified cancer. A host factor may be associated with reduced risk of a cancer, not only with increased risk.[3] Examples of host factors are immunological and endocrine functions, nutritional status, genetic constitution, age, and sex.[4]

As Americans have become more and more concerned about the environment and cancer, they have repeatedly asked the Federal Government to clarify what is known about cancer-causing substances. The public wants to know and should know which substances are regarded as cancer hazards in the work place and in the general environment and how well we are protected from exposure to these substances.

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Section 262 of Public Law 95-622 of November 9, 1978* reflects the requests for this information. Paragraph (4) of this section stipulates that the "Secretary shall publish an annual report which contains

"(A) a list of all substances (i) which either are known to be carcinogens or may reasonably be anticipated to be carcinogens and (ii) to which a significant number of persons residing in the United States are exposed;

"(B) information concerning the nature of such exposure and the estimated number of persons exposed to such substances;

"(C) a statement identifying (i) each substance contained in the list under subparagraph (A) for which no effluent, ambient, or exposure standard has been established by a Federal agency; and (ii) for each effluent, ambient, or exposure standard established by a Federal agency with respect to a substance contained in the list under subparagraph (A), the extent to which, on the basis of available medical, scientific, or other data, such standard, and the implementation of such standard by the agency, decreases the risk to public health from exposure to the substance; and

"(D) a description of (i) each request received during the year involved -

"(I) from a Federal agency outside the Department of Health, Education and Welfare for the Secretary, or

"(II) from an entity within the Department of Health, Education and Welfare to any other entity within the Department,

to conduct research into, or testing for, the carcinogenicity of substances to provide information described in clause (ii) of subparagraph (C), and (ii) how the Secretary and each such other entity, respectively, have responded to each request."

Annual Reports on Carcinogens are issued in response to these requirements. These reports discuss substances or technological processes which are known to be carcinogens or which may reasonably be anticipated to be carcinogens; they contain information received from Federal agencies participating in the preparation of the Reports.

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* Community Mental Health Centers Act, Amendments.

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Participants

Within the Department of Health and Human Services, the responsibility for preparing these annual reports has been delegated to the National Toxicology Program.* Other agencies participating in this effort are:

Centers for Disease Control/National Institute for Occupational Safety and Health (CDC/NIOSH)

Consumer Product Safety Commission (CPSC)

U.S. Environmental Protection Agency (EPA)

Food and Drug Administration (FDA)

National Institutes of Health/National Cancer Institute (NIH/NCI)

National Institutes of Health/National Institute of Environmental Health Sciences (NIH/NIEHS)

National Institutes of Health/National Library of Medicine (NIH/NLM)

U.S. Department of Labor/Occupational Safety and Health Administration (DOL/OSHA)

Four of these agencies -- CPSC, EPA, FDA, and OSHA -- are responsible for regulating hazardous substances and limiting the exposure to and use of such substances.

Identifying Carcinogens

For many years Government research agencies, industries, universities, and other research organizations have studied various substances to ascertain those which might cause cancer. Other Federal agencies have been developing information on exposure and potential hazards and making rules and regulations to control substances which have been identified as carcinogens.

The largest single national testing effort, the National Cancer Institute's Carcinogenesis Testing Program, has now become a part of NTP/NIEHS. The NCI Clearinghouse on Environmental Carcinogens, consisting of a panel of experts from governmental and non-governmental institutions, has reviewed the NCI testing results, and an analysis of results of NCI carcinogenesis bioassays of 190 chemicals has recently been published.[5] The Technical Reports Review Subcommittee of the NTP Board of Scientific Counselors, augmented by an ad hoc panel of experts in chemical carcinogenesis, has now replaced the NCI Clearinghouse as the body of non-government experts conducting peer reviews of the NTP carcinogenesis bioassay results.

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* DHHS agencies participating in NTP are NIH/NCI; NIH/NIEHS; FDA/National Center for Toxicological Research (FDA/NCTR); and CDC/NIOSH.

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Many of the substances listed in the Third Annual Report on Carcinogens have been chosen from the "IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans" published by the International Agency for Research on Cancer (IARC) in Lyon, France.* Each monograph is the product of an individual working group of experts in chemical carcinogenesis and related fields. The experts evaluate the data for each substance included in a monograph. The evaluation is based on the published information available at the time the working group meets. A joint IARC/WHO ad hoc Working Group met in October 1977 to review and revise the criteria for judging the adequacy of available data. The terms 'sufficient evidence' and 'limited evidence' of carcinogenicity used in these criteria refer only to the amount and adequacy of the available evidence and not to the potency of carcinogenic effect or the mechanisms involved. An updated version of these criteria is included in each IARC Monograph Volume. The IARC Monograph Supplement 4 contains re-evaluations by an ad hoc working group of all chemicals, industrial processes and occupational exposures for which some data on carcinogenicity in humans are available either in the first 29 volumes of monographs or in other subsequent publications.[6]

A direct comparison of the IARC evaluations[6] and the evaluation of NCI/NTP bioassay results[5] cannot be made because different criteria were used to assess the evidence; but these criteria can be related.[2] Such evaluations involve a component of personal judgment. In some cases the available evidence may be assessed differently depending on the criteria used and the composition of the group of experts.

Clause ii) in subparagraph (A)(4) of Section 262 requires "a list of all substances which are either known to be carcinogens or may reasonably be anticipated to be carcinogens." For the purpose of this report, the two categories in the law -- known to be carcinogens and reasonably anticipated to be carcinogens -- relate to the IARC criteria for the degree of evidence[6] as follows:

1. Known to be carcinogens:

   There is "sufficient evidence of carcinogenicity" from studies in humans "which indicates a causal relationship between the agent and human cancer."

2. Reasonably anticipated to be carcinogens:

   A. There is "limited evidence of carcinogenicity" from studies in humans, "which indicates that causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded." or

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* The IARC address is: 150, cours Albert-Thomas, 69372 Lyon Cedex 2. France. WHO/IARC Publications may be obtained from WHO Publications Centre USA, 49 Sheridan Avenue, Albany, New York 12210.

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B. There is "sufficient evidence of carcinogenicity" from studies in experimental animals "which indicates that there is an increased incidence of malignant tumors: (a) in multiple species or strains, or (b) in multiple experiments (preferably with different routes of administration or using different dose levels), or (c) to an unusual degree with regard to incidence, site or type of tumour, or age at onset. Additional evidence may be provided by data concerning dose response effects, as well as information on mutagenicity or chemical structure."

Most of the substances contained in this Annual Report can be identified chemically. Some carcinogens occur naturally, some are produced when materials are burned, and others are present in raw materials, or in intermediate and final products of industries. In some cases only the exposure associated with a specific technological or manufacturing process, occupation, or industry can be related to an increased incidence of cancer in humans, but the substances responsible cannot be identified. Examples of such processes are the underground mining of hematite and the strong-acid process for the manufacture of isopropyl alcohol.

Human and Animal Studies

Some understanding of the human and animal studies used for identifying carcinogens is necessary to clarify what is meant by the words "known" and "reasonably anticipated." The strongest evidence for a relationship between exposure to a suspected substance and cancer in humans comes from epidemiological studies. Although we have adequate epidemiological evidence only for a few carcinogens, we think the patterns seen in these studies show how other animal carcinogens might affect humans. Epidemiological investigations give the best information on cancer-causing agents, but such studies of groups of individuals do have shurtcomings. They may require observations over a long time because the latent period between initial exposure and cancer occurrence may be up to 20-30 years. Intentional, long-term exposures of human groups are, of course, unacceptable. As an alternative, scientists make educated predictions about the effects in humans, based on the effects observed in studies with experimental animals.

Although test animals may respond differently from humans, experience has shown that almost all known human carcinogens also cause cancer in experimental animals if adequately tested.* This finding is understandable since cancer begins in individual cells and all mammalian cells are comparable in structure and function. The basic premise of experimental carcinogenesis research is that substances that produce cancer in rodents and other experimental animals may affect human cells in the same way.

* The evidence for carcinogenicity in experimental animals of arsenic compounds is still regarded as inadequate, and the evidence for benzene is at present limited.[6]

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Relatively large doses of chemicals are used in animal studies to make up for the small number of experimental animals exposed, as compared to the size of human populations. Animal tests are costly, take years to complete, and are often difficult to interpret in terms of human carcinogenic risk. They are nevertheless, the best testing tool we have. No animal test can prove beyond doubt that a substance will or will not cause cancer in humans. Even "sufficient evidence" of carcinogenicity in experimental animals may prove not to be definitive. But if we are to prevent cancer, we cannot wait 20 to 30 years to obtain a definitive evidence of harm to human health. Therefore, substances which show "sufficient evidence" of cancer causation in experimental animals are considered as reasonably anticipated human carcinogens.

Inclusion of Substances

The Third Annual Report contains substances, groups of substances and technological processes which were listed in the Second Annual Report. Where necessary, the information has been updated. The Third Annual Report presents information on 28 additional substances. Each has been chosen either from substances tested by the NCI Carcinogenesis Testing Program or the National Toxicology Program (NTP); from designations of the participating agencies, or from substances evaluated by the IARC working groups. Other substances from the same sources will be added to the subsequent Annual Reports.

Section IIIA of the Third Annual Report lists all the substances and technological processes included. The list is divided into two sublists. One contains substances, groups of substances, or technological processes known to be carcinogens (22 entries). The other list of 95 entries includes substances or groups of substances which may reasonably be anticipated to be carcinogenic. Nickel appears in both sublists because the nickel refining process is known to be carcinogenic, whereas elemental nickel and certain nickel compounds may reasonably be anticipated to be carcinogens.

Section IIIB contains a brief description of each substance or technological process together with a summary of evidence for its carcinogenicity. References to the original papers on experimental or epidemiological studies, which can be found in the IARC Monographs or in the NCI and NTP bioassay reports, have not been included in the Third Annual Report.

A substance not listed in this Annual Report may still be a known carcinogen or a reasonably anticipated carcinogen. More substances than those included may potentially present a carcinogenic risk to persons living in the United States. These substances will be incorporated into subsequent Annual Reports as resources permit. Some chemicals will be introduced as a result of testing performed by industry in response to EPA's requests under the Toxic Substances Control Act. The National Toxicology Program will also play a role in providing new information for these reports as further test results become available.

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Ionizing radiation, ultraviolet radiation (including sunlight), tobacco, alcoholic beverages, and some viruses are known or suspected to be carcinogens. They have not been included in this Report because ionizing radiation is discussed thoroughly in a General Accounting Office report,[7] and a recent Surgeon General's report[8] reviews the overwhelming relationship between tobacco and cancer. Several publications issued by the National Cancer Institute[9] explain the relationship of alcoholic beverages, ultraviolet radiation, and viruses to cancer.

Estimating Exposure

According to clause (ii) of subparagraph (4)(A), this Report is required to include those substances "to which a significant number of people residing in the United States are exposed." Substances to which only a few people are exposed are not included for the most part. Yet some substances which have been banned or restricted in use are contained in the Report (e.g., safrole, arsenical pesticides, mirex) either because people who were previously exposed remain potentially at risk, or because these substances are still present in the environment.

Subparagraph (4)(B) requires that the Annual Reports provide "information concerning the nature of such exposure and the estimated number of persons exposed to such substances." The determination of the number of people exposed and the route, intensity, and duration of such exposure for each substance remains a formidable task. This Report attempts to respond to these questions, and wherever adequate answers could be obtained, they are included in Section IIIB. Exposure to carcinogens can occur anywhere. Some carcinogens have always been present in the environment, and their amount varies, depending on geographical location and other environmental conditions. Every year human activities may add more carcinogens to the ambient air, water, food, soil, and occupational environment. Although scientists attempt to estimate the amount of carcinogens present in and added to the environment, there is no reliable way to predict who is exposed to what carcinogen and when exposure occurs. Also, since human populations are always exposed to many chemicals at the same time, this may modify the effects of a specific exposure either by multiplying (synergism) or reducing its action (antagonism).

If exposure is linked to a specific habit such as smoking, a specific use such as medical diagnosis or treatment, or a restricted environment such as the work place, our ability to estimate exposure improves, and in some cases the size of population segments involved can be estimated. Production and use data may also help estimate exposure, but this information may not be publicly available for many substances, and where it is, it may be out-dated or even contradictory.

The National Occupational Hazard Survey (NOHS), conducted by CDC/NIOSH from 1972 to 1974, gave information on the number of workers exposed and on some broader aspects of occupational exposure. The forthcoming National Occupational Exposure Survey (a repeat of NOHS) should yield valuable information with respect to more recent exposures. Subsequent Annual Reports on Carcinogens will explore this and other available data bases, and their strengths and limitations.

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Regulatory Status

Subparagraph (4)(C) of Section 262 also requires "a statement identifying (i) each substance contained in the list under subparagraph (A) for which no effluent, ambient, or exposure standard has been established by a Federal agency;...." The Third Annual Report responds to this requirement by appending to the description of each substance in Section 1118 a summary of Federal regulations as submitted by the participating agencies. Some of these standards and regulations have been enacted for reasons other than the carcinogenicity of the substance, for instance, to prevent other adverse health effects or to improve the environmental quality or food quality. Solid or liquid wastes or wastes discharged into the air may contain carcinogens, yet these may be regulated as toxic substances or hazardous pollutants and not specifically as carcinogens. But if these regulations reduce exposure to carcinogens, then the carcinogenic risk posed by such substances will also decrease.

Estimating Risk Reduction

Clause (ii) in subparagraph (4)(C) requires a statement identifying "for each effluent, ambient, or exposure standard established by a Federal agency with respect to a substance contained in the list under subparagraph (A), the extent to which, on the basis of available medical, scientific, or other data, such standard, and the implementation of such standard by the agency, decrease the risk to public health from exposure to the substance;...." This requires quantified information on the amount of protection from cancer the public receives from established Federal standards.

Estimating the amount of health protection is perhaps the most difficult task in preparing the Annual Reports. One reason is that most Federal laws concerned with reducing carcinogenic risk have been enacted within the last 15 years. Given the long period between the initial exposure to a carcinogen and the onset of disease, it is still too early to evaluate how much Federal standards and other regulations have decreased the risk to public health. Another reason is that information on past exposure levels, which could serve as a baseline for estimating future risk reduction, often is not available or accurate.

The risk -- the likelihood of developing cancer -- depends on the intensity, route, and duration of exposure to a carcinogen. Individuals may respond differently to similar exposures, depending on host factors such as age, sex, nutritional status, overall health and inherited characteristics. Only in a few instances, where studies of long-term human exposures and cancer incidence in restricted environments are available, can risk be estimated with confidence.

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The regulation of asbestos in the work place provides a good example. In 1969, under the Walsh-Healy Act which then regulated only the firms with Government contracts, the standard for permissible exposure was 12 fibers of asbestos per cubic centimeter (cc) of air. Under the Occupational Safety and Health Act, this standard was reduced to 5 fibers/cc in 1972 and to 2 fibers/cc in 1976. On April 17, 1980, a joint NIOSH-OSHA Working Group recommended the elimination of all non-essential uses of asbestos and the implementation of a public health program to reduce human exposures. The high risk to workers exposed prior to 1969 is well known. The actual data on exposure levels in the '40s, '50s, and '60s are fragmentary, although exposure levels were undoubtedly unacceptably high by today's standards. Mesothelioma (primarily an asbestos-induced cancer) and lung and other cancers, the incidence of which is increased by exposure to asbestos, generally take 20-40 years or more to develop and become apparent. For these reasons, we will not know until early in the next century to what extent the series of exposure reductions in the '70s have reduced the cancer risk to those persons exposed to asbestos.

One possible way to provide quantitative estimates of risk reduction might be to assume that the carcinogenic risk is directly proportional to exposure. This approach also supposes that data on past and present exposure levels are available, or that conditions in all work places are in compliance with regulations. However, information supporting these assumptions is only rarely obtainable. Nevertheless, it is reasonable and prudent to accept that the reduction of exposure, for any reason, particularly to substances shown to be carcinogenic in experimental animals, will decrease the incidence of cancer. This is the basis of current regulatory policies which aimed to lower human exposure to cancer-causing substances and thereby improve public health. For a more detailed discussion of the issues involved, see the previously cited report to Congress on the assessment of technologies for determining cancer risks from the environment.[2]

Requests for Research, Testing, and Information

The last requirement of subparagraph (4)(D) is

> "a description of (i) each request received during the year involved -
>
> "(I) from a Federal Agency outside the Department of Health, Education and Welfare for the Secretary, or
>
> "(II) from an entity within the Department of Health, Education, and Welfare to any other entity within the Department, to conduct research into, or testing for, the carcinogenicity of substances or to provide information described in clause (ii) of subparagraph (C), and (ii) how the Secretary and each other entity, respectively, have responded to each such request."

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Section IV of the Report provides a list of such requests as received from the participating agencies. The inclusion of a substance in this table does not imply that it is a known or reasonably anticipated carcinogen.

Appendixes

Appendix A is an index of synonyms and trade names of substances included in the Third Annual Report. Appendix B contains a glossary of frequently used terms, acronyms and units of measurement. Appendix C lists in alphabetical order the substances, groups of substances, and technological processes included, and the synonyms and trade names for each of them. Appendix D is a list of participating agencies and their staff members who collaborated in preparing the Third Annual Report. Appendix E is a cumulative index to the Annual Reports on carcinogens.

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1. National Center for Health Statistics. Advance Report of Final Mortality Statistics, 1979, Monthly Vital Statistics. Report, 31, No. 6, Supplement, September 30, 1982.

2. Office of Technology Assessment, Congress of the United States. Assessment of Technologies for Determining Cancer Risks from the Environment. U.S. Government Printing Office, Washington, D.C., 1981, pp. 3, 65-109.

3. Cole, P. Epidemiological Clues to Host Factors in Human Carcinogenesis. In: H. Bartsch and B. Armstrong, eds. Host Factors in Human Carcinogenesis. IARC Scientific Publications, No. 39. Lyon, France: International Agency for Research on Cancer, 1982, p. 3.

4. Bartsch, H., and B. Armstrong, eds. Host Factors in Human Carcinogenesis. IARC Scientific Publications, No. 39. Lyon, France: International Agency for Research on Cancer, 1982, p. xi.

5. Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis, eds. Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

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7. Comptroller General, U.S. General Accounting Office. Problems of Assessing Cancer Risk of Low Level Ionizing Radiation Exposure. Report to the Congress of the United States. EMD-81-1, Washington, D.C., 1981.

8. Office of Smoking and Health. The Health Consequences of Smoking: Cancer, a Report of the Surgeon General. Rockville, Maryland: U.S. Department of Health and Human Services, Public Health Service, 1982.

9. See, for example, Shimkin, M.B. Science and Cancer. NIH Publications No. 80-568, Third Revision. National Cancer Institute, National Institutes of Health. Bethesda, Maryland: U.S. Department of Health and Human Services, 1980.

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III. SUBSTANCES LISTED

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* An alphabetized list of substances, their synonyms, and their trade names appears in Appendix A. The synonyms and trade names for each substance included are listed in Appendix C.

** For the purpose of this Report, "known carcinogens" are defined as those substances for which the evidence from human studies indicates that there is a causal relationship between exposure to the substance and human cancer. Substances "which may reasonably be anticipated to be carcinogens" are defined as those for which there is a limited evidence of carcinogenicity in humans or sufficient evidence of carcinogenicity in experimental animals.

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B. Individual Substances

2-ACETYLAMINOFLUORENE

Incorporation of this compound into the feed caused increased incidences of malignant tumors in a variety of organs in the rat.[1] Long-term studies in which mice were given 2-acetylaminofluorene (AAF) in the diet showed increased incidences of liver and urinary bladder cancers.[2]

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[1]Wilson, R.H., F. DeEds, and A.J. Cox. The Toxicity and Carcinogenic Activity of 2-Acetylaminofluorene. Cancer Research. Vol. 1, 1941, pp. 595-608.

[2]Staffa, J.A., and M.A. Mehlman (eds.). Innovations in Cancer Risk Assessment (ED_{01} study): Proceedings of a Symposium. Journal of Environmental Pathology and Toxicology. Vol. 3, 1980, pp. 1-246.

AAF was intended for use as a pesticide, but this chemical was never marketed because it was found to be carcinogenic in experimental animals.

AAF is used as a positive control by biochemists and technicians engaged in the study of liver enzymes and of the carcinogenicity and mutagenicity of aromatic amines. These research persons may be exposed to AAF.

AAF is distributed by several companies that deal in specialty chemicals. EPA reported one producer in one region (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record). Information obtained from the distributors indicates that AAF is imported from Europe. A typical chemical distributor keeps approximately 10 lb of AAF in stock. The chemical is usually sold in 1-, 5-, or 25-g quantities. Based on this information, it is estimated that the total U.S. usage is less than 20 lb per year.

Human exposure to AAF may occur through inhalation and skin absorption. The occupations at greatest risk to AAF exposure are organic chemists, chemical stockroom workers, and biomedical researchers. Although neither NIOSH nor OSHA has estimated the number of U.S. workers exposed to AAF, perhaps fewer than 1000 workers in 200 laboratories may come in contact with this animal carcinogen.

Because AAF is an animal carcinogen, on February 11, 1974, OSHA promulgated a standard for this chemical designating protective clothing, hygiene procedures for workers, and special engineering requirements for the manufacture or processing of AAF.

MONS 222672

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known use in consumer products. (CPSC)		
RCRA, 3001 3004: Listed as a hazardous constituent of waste. Wastes known to contain this chemical are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80. The Carcinogen Assessment Group at EPA has included this chemical on its list of carcinogens. As a result of this listing, this chemical is regulated under the Resource Conservation and Recovery Act's hazardous waste disposal rule. The Office of Planning and Management is developing a chapter in EPA's Occupational Safety Manual stipulating handling procedures for chemicals posing chronic health hazards, including carcinogenicity to users. This chemical is included. (EPA)		40 CFR 261.33 (EPA)
Protective clothing, respirator, hygiene, training, and medical surveillance requirements for workers; exhaust fan requirements; open-vessel operations prohibited; contamination control requirements, sign requirements for regulated areas; labeling requirements for containers. (OSHA)	Regulatory History: 5/10/73: Emergency Temporary Standards--protective clothing and hygiene requirements for workers, open-vessel operations restricted, engineering requirements. 2/11/76: Final Standard--current regulations effective. (OSHA)	29 CFR 1910.1014 (OSHA)

MONS 222673

ACRYLONITRILE

There is sufficient evidence for the carcinogenicity of acrylonitrile (AN) in experimental animals; the evidence of carcinogenicity in humans is limited.[1] Acrylonitrile was carcinogenic in rats where administered by gavage and in drinking water, or by inhalation.[1,2]

An epidemiological study of workers potentially exposed to acrylonitrile and observed for 20 years or more showed an increased incidence of cancers of the lung, large intestine and prostate. The mortality from lung cancer was also increased. Another similar study of persons occupationally exposed to acrylonitrile and followed for 10 years or more also indicated an increased incidence of cancers of the stomach, colon, brain and respiratory tract.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 19. Lyon, France: IARC, 1979, pp. 73-133.

AN is a reactive chemical that is commercially important because it polymerizes readily. It is a volatile liquid, soluble in water and in most common organic solvents.

AN is used extensively in manufacturing of synthetic fibers, resins, plastics, elastomers, and rubber for a variety of consumer goods such as textiles, dinnerware, food containers, toys, luggage, automotive parts, small appliances, and telephones. In 1976, about 48 percent of the AN was used to produce acrylic and modacrylic fibers; 21 percent to produce acrylonitrile-butadiene-styrene (ABS) and styrene-acrylonitrile (SAN) resins; 19 percent to produce nitrile elastomers and latexes such as butadiene acrylonitrile copolymers; and 12 percent to produce adiponitrile, an intermediate used in nylon production.

AN has been produced in the United States since 1940. NIOSH has reported that approximately 1.5 billion lb of AN are now manufactured annually.

Exposure to AN can occur during manufacture and production. The compound is volatile, and exposure occurs primarily through vapor inhalation and skin absorption. OSHA estimated that approximately 276,000 persons are potentially exposed to AN. These persons work as acrylic resin makers; organic chemical synthesizers; pesticide workers; rubber, synthetic fiber, and textile makers.

MONS 222674

According to the Consumer Product Safety Commission in 1980, direct consumer exposure to AN through consumer product use is low, because there is little migration of the monomer from such products. The levels of AN in consumer products are estimated to be less than 1 ppm in acrylic and modacrylic fibers, 30-50 ppm in ABS copolymers, 15 ppm in SAN copolymers, and 0-750 ppm in nitrile rubber and latex goods. The presence of AN, even as a trace contaminant, may be cause for concern; however, data describing the actual levels of residual in finished products and the potential for consumer exposure and uptake are currently lacking. The extent of exposure to AN of the general population through air emissions from production, manufacture, bulk storage, and waste disposal has not been determined. However, a 1977 report cited that total AN air emissions are 2.2 percent of total production.

During 1978, EPA declared AN a hazardous substance based on the reported acute toxic effects. As a result, EPA promulgated hazardous spill regulations in 1979 under the Clean Water Act, establishing reportable quantities of 100 lb for AN. The EPA Carcinogen Assessment Group included AN on its list of carcinogens. Because AN is an animal carcinogen, EPA proposed in 1980 to reduce the reportable quantity of AN to 10 lb. Under the Resource Conservation and Recovery Act, EPA regulates waste products, off-specification batches, and spill residues in excess of 2200 lb AN.

FDA and OSHA have also regulated AN. During 1977, FDA banned the use of AN copolymers for beverage containers and proposed to limit AN migration from other food-contact materials to 50 ppb. During 1979, FDA was asked to review the ban, and this has been a continuing effort. In 1983, the FDA intends to review all AN regulations and bring them into alignment with current carcinogenicity data. This review will include an advisory opinion and subsequently a proposal for use of a new type of container that limits AN migration. In addition, OSHA enacted regulations in 1978 to reduce worker exposure to AN by establishing a standard of 2 ppm (4.5 mg/m^3) as a time-weighted average. This standard requires personal protective equipment, training, medical surveillance, signs and labeling, and engineering controls.

MONS 222675

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No regulatory plans at present (CPSC)		
CWA, 311 Hazardous spill regulation establishing reportable quantity (100 lb, 45.4 kg) and imposing reporting requirements. Promulgated 6/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipment of the chemicals and should result in reduction of accidental exposures.	40 CFR 117.3, 117.33
Proposal to reduce reportable quantity to 10 lb (4.54 kg), proposed 7/9/80.	Based on carcinogenicity.	45 FR 133, p. 46094
FIFRA, 3: Classified for restricted use, 2/9/78.	Accident history of acute effects. (EPA)	40 CFR 162.31
FIFRA, 6: Voluntary cancellation of product registration by three producers, 6/19/76, and two subsequent dates in 1978.		43 FR 16310 (first notice)
RCRA, 3001-3004. Subject waste products, off-specification betches, and spill residues in excess of 1000 kg to handling and *reporting/recordkeeping* requirements. Also designates acrylonitrile as a hazardous constituent of waste and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
CAA: Exposure assessment completed 8/79. Technology assessment in progress.		DADPS, personal communication, 10/80 (EPA)
See Carcinogen Assessment Group statement for 2-acetylaminofluorene. (EPA)		
Bureau of Foods, FD&CA.	To eliminate or minimize exposure to acrylonitrile monomer through migration into food. (FDA)	
June 1976 Regulation published interim listing of acrylonitrile copolymers		
September 1976 Report received showing positive results in teratology studies.		
January 1977: Interim report on 2-year rat feeding study showed a strong tumorigenic response.		
March 1977: Stay of beverage bottle regulations published. Additionally, a proposal to limit acrylonitrile migration from food-contact articles other than beverage bottles to 50 ppb was published.		
March 1977: U.S. Court of Appeals set aside the FDA stay of the beverage container regulations and held a public hearing.		
June 1977 Public hearing on acrylonitrile.		

(Continued)

MONS 222676

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
August 1977: Administrative law judge upheld FDA position on acrylonitrile beverage containers. November 1977: Appeal of Commissioner's decision. November 1979: The court upheld the revocation of the acrylonitrile bottle regulations and remanded to FDA the issue of new bottles with lower residual acrylonitrile monomer levels as well as the issue of the safety of all other acrylonitrile copolymers. As a part of the opinion, the court also upheld the Commissioner's right to decide that certain levels of substances were too trivial to be considered under the food additive provisions of the FD&CA. FDA Bureau of Medical Devices, FD&CA: No regulation of medical device uses. Amount of migrati,n is not known. (FDA)		
PEL: 2 ppm 8-hr TWA; 10 ppm 15-min TWA ceiling. No skin or eye contact with liquid acrylonitrile. Additional Regulations: Protective clothing, hygiene, training, and medical surveillance requirements for workers; respirator requirements where engineering and work practice controls not sufficient or feasible; monitoring requirements; housekeeping and waste disposal requirements; sign requirements for regulated areas; labeling requirements for containers. (OSHA)	Regulatory History 1952: Meiss-Healy, 20 ppm maximum allowable concentration. August 27, 1971: OSHA Takeover Standard--skin, 20 ppm 45 mg/m^3 8-hr TWA. January 17, 1978: Emergency Temporary Standards--2 ppm 8-hr TWA; 10 ppm 15-min TWA ceiling; no skin or eye contact. November 2, 1978: Final Standard--current level effective. (OSHA)	29 CFR 1910.1045 (OSHA)

MONS 222677

AFLATOXINS

There is sufficient evidence for the carcinogenicity of aflatoxins in experimental animals. The evidence of carcinogenicity in humans is limited.[1] Aflatoxins were carcinogenic in mice, rats, fish, ducks, marmosets, tree shrews, and monkeys by several routes of administration (including oral), producing mainly cancers of the liver, colon, and kidney.[2]

Epidemiological studies have shown a positive correlation between the average dietary concentrations of aflatoxins and the incidence of primary liver cancer. No studies have been carried out that could link an increased risk of liver cancer to actual aflatoxin intake in individuals.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 10. Lyon, France: IARC, 1976, pp. 51-72.

Aflatoxins are a group of toxic metabolites produced by certain types of fungi. They are intensely fluorescent in ultraviolet light and slightly soluble in water.

Aflatoxins are not commercially manufactured; they are naturally occurring contaminants that are formed by fungi on food during conditions of high temperature and high humidity.

Human exposure to aflatoxins occurs through ingestion of contaminated food. Grains, peanuts, tree nuts, and cottonseed meal are among the more common foods on which these fungi grow. Meat, eggs, milk, and other edible products from animals that consume aflatoxin-contaminated feed are additional sources of potential exposure. Americans consume an estimated 0.15 to 0.50 μg of aflatoxins daily.

Under the Resource Conservation and Recovery Act, 3001-3004, EPA regulates aflatoxins as a hazardous constituent of waste. In addition, the EPA Carcinogen Assessment Group considered aflatoxins to be carcinogenic. The FDA has established enforcement levels of 0.5 ppb in milk and 20 ppb for other food products.

MONS 222678

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004: Listed as a hazardous constituent of waste. Wastes known to contain any aflatoxin are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80. Because aflatoxins are naturally occurring contaminants, EPA has a limited regulatory authority over these substances. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11 (EPA)
Aflatoxins were found to be unavoidable contaminants in foods. Enforcement action levels of 20 ppb (total B_1, B_2, G_1, G_2) for all products and 0.5 ppb aflatoxin M_1 in milk are in effect. (FDA)	Holds human exposure to lowest practicable level. (FDA)	Compliance Policy Manual Guide Numbers 7106.10, 7112.02, 7112.07, 7112.02, 7112.07, 7112.08, 7120.26, 7126.33 (FDA)

MONS 222679

2-AMINOANTHRAQUINONE

Technical grade 2-aminoanthraquinone (impurities unspecified), administered in the feed, was carcinogenic in male Fischer 344 rats, causing a combination of hepatocellular carcinomas and neoplastic nodules of the liver. The compound was also carcinogenic in B6C3F1 mice, causing hepatocellular carcinomas in both sexes and malignant hematopoietic lymphomas in females.[1] An IARC working group considered that the evidence for the carcinogenicity in experimental animals of the material tested was limited.[2] In view of another evaluation of NCI bioassay results, the evidence can be considered as sufficient.[3]

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[1]National Cancer Institute. Bioassay of 2-Aminoanthraquinone for Possible Carcinogenicity. Technical Report Series No. 144. DHEW Publication No. (NIH) 78-1399. Bethesda, Maryland, 1978.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 27. Lyon, France: IARC, 1982, pp. 191-98.

[3]Griesmer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees or Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis, eds. Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

2-Aminoanthraquinone (AAQ), an aromatic amine, is insoluble in water and soluble in alcohol.

AAQ is used as an intermediate in the industrial synthesis of anthraquinone dyes. It is the precursor of five dyes and one pigment, including Colour Index Vat Blues 4, 6, 12, and 24; Vat Yellow 1; and Pigment Blue 22.

Production in 1971 was 200,000 lb for AAQ and its salts. Imports in 1974 were 375,000 lb. EPA reported five producers and importers of AAQ between 1975 and 1977 (Toxic Substances Control Act, Chemical Substance Inventory, Initial Inventory, 1979, public record). Production of AAQ was not reported to the U.S. International Trade Commission in 1979-1980. Data from NCI indicated that imports through principal U.S. customs districts in 1980 were only 250 lb. The 1982 Directory of Chemical Producers indicates that only one U.S. company now produces AAQ and its salt. Recent production figures for AAQ are considered proprietary and are not available.

MONS 222680

Human exposure to AAQ is principally through inhalation and skin contact. Because AAQ is used on a commercial scale solely by the dye industry, the potential for exposure to the compound is greatest for workers at dye manufacturing facilities. However, no additional data are available on the number of facilities using AAQ.

The National Occupational Hazard Survey in 1974 made no estimate of the potential occupational exposure to AAQ (NIOSH). However, the Consumer Product Safety Commission staff believes that trace amounts of unreacted AAQ may possibly be present in some dyes based on this chemical and in the final consumer product. Exposure even to trace amounts may be a cause for concern. This concern is based on experience with other dyes derived from aromatic amines. Data are not available on the actual levels of impurities in the final product, the potential for consume exposure, and the uptake.

2-Aminoanthraquinone

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
Because of its low production volume, 2 aminoanthraquinone is of low regulatory priority to EPA. It may be considered as the dyes and pigments industry is studied. (EPA)		

MONS 222681

4-AMINOBIPHENYL

There is sufficient evidence for the carcinogenicity of 4-aminobiphenyl both in humans and in experimental animals.[1] 4-Aminobiphenyl is carcinogenic in mice, rats, rabbits and dogs after oral administration, producing principally cancer of the urinary bladder.[2]

Epidemiological studies, which are confined to one series of workers occupationally exposed to commercial 4-aminobiphenyl, show a high incidence of bladder cancer.[1-3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 1. Lyon, France: IARC, 1979, p. 22.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 1. Lyon, France: IARC, 1972, pp. 74-79.
[3]Melamed, M.R. Diagnostic Cytology of Urinary Tract Carcinoma. European Journal of Cancer. Vol. 8, 1972, pp. 287-92.

4-Aminobiphenyl is an aromatic amine that is slightly soluble in water. Although formerly used as a rubber antioxidant, this compound has no current commercial use in the United States. Nor is there evidence of any current commercial production. For 1975-77, EPA reported only one producer in one region, according to the Toxic Substances Control Act (TSCA), Chemical Substances Inventory, 1979, public record.

4-Aminobiphenyl has been used as a research chemical and as a reagent for the detection of sulfates. The compound also occurs as a contaminant in 2-aminobiphenyl.

2-Aminobiphenyl, a chemical closely related to 4-aminobiphenyl, is used in the manufacture of dyes. According to OSHA, approximately 130 workers are potentially exposed to 4-aminobiphenyl during the production of 2-aminobiphenyl.

EPA regulates 4-aminobiphenyl under the Resource Conservation and Recovery Act as a hazardous constituent of waste and under TSCA. The EPA Carcinogen Assessment Group lists 4-aminobiphenyl as a carcinogen. In February 1974, OSHA issued a final standard requiring use of exhaust fans, protective clothing, and respirators; prohibiting operation in open vessels; and requiring control of plant contamination.

MONS 222682

In 1980, the Consumer Product Safety Commission preliminarily determined that 4-aminobiphenyl was not present in consumer products under its jurisdiction. The Commission subsequently requested (45 FR 61344) public comment to verify the accuracy of their information, and no comments were received. Pending the receipt of new information, the Commission plans no action on 4-aminobiphenyl.

4-Aminobiphenyl

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products. (CPSC)		
RCRA, 3001-3004: Listed as a hazardous constituent of waste. Wastes known to contain 4-aminobiphenyl are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/88. Also applies to diphenylamine.		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Protective clothing, respirators, hygiene, training, and medical surveillance requirements for workers; exhaust fan requirements; open-vessel operations prohibited, containment control requirements; sign requirements for regulated areas, labeling requirements for containers. (OSHA)	Regulatory History: 5/10/78: Emergency temporary Standards--protective clothing and hygiene requirements for workers, open-vessel operations restricted, engineering requirements. 2/11/74: Final Standard--current regulations effective. (OSHA)	29 CFR 1910.1011 (OSHA)

MONS 222683

1-AMINO-2-METHYLANTHRAQUINONE

Technical-grade 1-amino-2-methylanthraquinone (impurities unspecified), administered in the feed, was carcinogenic in Fischer 344 rats, inducing hepatocellular carcinomas in rats of both sexes, and kidney tumors (such as tubular-cell adenomas and adenocarcinomas) in males. The compound was carcinogenic in female B6C3F1 mice, producing an increased combined incidence of hepatocellular carcinomas and neoplastic nodules.[1] An IARC working group considered that the evidence for the carcinogenicity in experimental animals of the material tested was limited,[2] but in view of another evaluation of NCI bioassay results, the evidence can be considered as sufficient.[3]

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[1]National Cancer Institute. Bioassay of 1-Amino-2-methylanthraquinone for Possible Carcinogenicity. Technical Report Series No. 111. DHEW Publication No. (NIH) 78-1366. Washington, D.C., 1978.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 27. Lyon, France: IARC, 1982, pp. 199-204.

[3]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis, eds. Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

1-Amino-2-methylanthraquinone is an aromatic amine that is insoluble in water and soluble in ethanol, acetone, and benzene.

1-Amino-2-methylanthraquinone is used almost exclusively as a dye intermediate for the production of a variety of anthraquinone dyes. The Society of Dyers and Colourists in 1971 reported that it can be used as a dye for a variety of synthetic fibers, especially acetates, as well as wool, sheepskins, furs, and surface dyeing of thermoplastics. None of the dyes that can be prepared from it are presently produced in commercial quantities.

1-Amino-2-methylanthraquinone had been produced commercially in the United States since 1948, but production was last reported by one company in 1970. Imports through the principal U.S. customs districts were only 260 lb when last reported in 1972. A recent study by the Consumer Product Safety Commission (CPSC) staff indicated that 1-amino-2-methylanthraquinone was no longer either regularly produced in commercial quantities or imported. However, in their inventory of chemicals in commerce (1979, public record), EPA reported two importers in one region. The amount of the imports was not reported.

MONS 222684

According to NCI, no evidence was available to indicate that 1-amino-2-methylanthraquinone was either produced commercially or imported in the United States. Domestic production was not reported to the U.S. International Trade Commission for 1979-1980.

Human exposure to 1-amino-2-methylanthraquinone is principally through inhalation of vapors. The potential for exposure is greatest among workers engaged in the dyeing of textiles. The National Occupational Hazard Survey of 1974 contains no information on 1-amino-2-methylanthraquinone, but does estimate that 6400 workers may have been exposed to anthraquinone dyes. 1-Amino-2-methylanthraquinone is not presently used in consumer products according to the CPSC.

EPA has proposed regulation of 1-amino-2-methylanthraquinone under the Toxic Substances Control Act, 8(a), reporting rule, which would provide detailed production and marketing data.

1-Amino-2-methylanthraquinone

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
No current action. (CPSC)		
TSCA, 8(a) -- Reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with the risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13[illegible] (EPA)

MONS 222685

AMITROLE

There is sufficient evidence of the carcinogenicity of amitrole in experimental animals; the evidence of carcinogenicity in humans is considered inadequate.[1]

Amitrole was carcinogenic in several strains of mice and rats, producing thyroid and liver tumors following administration in drinking water, diet, or by stomach tube, or subcutaneous injection.

Railroad workers who were exposed to amitrole and other herbicides showed a slight excess of cancer when all sites were considered together. Because the workers were exposed to several different herbicides, no conclusions could be made regarding the carcinogenicity of amitrole alone.[1,2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 7. Lyon, France; IARC, 1974, pp. 31-43.

Amitrole, a herbicide also known as aminotriazole, is soluble in water and very soluble in ethanol. Amitrole is formulated into soluble powders, liquids, and aerosols.

The major use for amitrole in the United States has been as a herbicide, but this use is now limited to noncrop applications.

Amitrole was first patented for use in the United States in 1954. Current domestic production is limited to approximately 4000 lb/yr. No reports are available on current imports, but 893,000 lb were imported in the first 9 months of 1973.

The potential for exposure to amitrole exists in its manufacture and application as a herbicide. According to NIOSH, an estimated 83 persons have been exposed to amitrole during its production, but no data are available on the number of people who may be exposed during its application or on the exposure levels in the general population.

After application, amitrole will persist in soil for several weeks and in water for more than 200 days.

MONS 222686

The use of amitrole on croplands was canceled in 1971, and EPA's Office of Pesticide Programs does not permit any residues on any food or feed crop. Under the Resource Conservation and Recovery Act, EPA also regulates the use and production of amitrole. In addition, EPA is reviewing amitrole under the Federal Insecticide, Fungicide, and Rodenticide Act to determine if further regulation may be warranted.

Amitrole

REGULATIONS		
Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Promulgated 5/19/80. Also lists amitrole as a hazardous constituent of waste subject to some requirements. FIFRA, 6: Under review to determine if additional regulation may be warranted. This study was triggered by the finding of carcinogenicity. No target for completion. Canceled for use on croplands, July 1971. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)

MONS 222687

o-ANISIDINE AND o-ANISIDINE HYDROCHLORIDE

There is sufficient evidence for the carcinogenicity of o-anisidine in experimental animals.[1,2] o-Anisidine hydrochloride, given in the diet, was carcinogenic in Fischer 344 rats and B6C3F1 mice, inducing transitional-cell carcinomas or papillomas of the bladder in animals of both sexes and transitional-cell carcinomas of the pelvis and the kidney, and follicular-cell tumors of the thyroid in male rats.[3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 27. Lyon, France: IARC, 1982, pp. 63-77.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[3]National Cancer Institute. Bioassay of o-Anisidine Hydrochloride for Possible Carcinogenicity. Technical Report Series No. 89. DHEW Publication No. (NIH) 78-1339. Bethesda, Maryland, 1978.

o-Anisidine, a derivative of aniline, is volatile with steam; practically insoluble in water; and miscible with alcohol, ether, acetone, and benzene.

o-Anisidine hydrochloride, reported to be used in the manufacture of dyes, is a possible ingredient in permanent oxidation hair dyes. Chloro, nitro, alkyl, and aryl derivates of o-anisidine are also used in the synthesis of azo dyes. Consumer Product Safety Commission (CPSC) staff members were unable to find any suppliers for this dye intermediate. However, the Chemical Buyer's Directory and the 1982 Chemical Week Buyer's Guide list 12 suppliers for o-anisidine.

Production of o-anisidine hydrochloride was not reported to the U.S. International Trade Commission (USITC) in 1980, although production was reported in 1979 by one producer, indicating an annual production greater than 5000 lb. Imports of o-anisidine and its meta and para isomers for 1979 were reported to the USITC as 3.2 million lb. Imports of o-anisidine through principal U.S. customs districts in 1980 were 2.4 million lb (NCI). No data are available on the importation of o-anisidine hydrochloride.

o-Anisidine hydrochloride was not reported in the Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record.

MONS 222688

If o-anisidine is used in the manufacture of dyes, the CPSC staff stated that residual traces of o-anisidine may possibly be present in some of these dyes and in the final consumer product. Exposure even to trace amounts may be a cause for concern. This concern is based on experience with other dyes derived from aromatic amines. No data are available on the actual levels of o-anisidine in the final product. The National Occupational Hazard Survey in 1974 made no estimate of potential worker exposure to o-anisidine hydrochloride (NIOSH); however, it estimated that approximately 1800 workers were potentially at risk of exposure to anisidine derivatives.

OSHA adopted a permissible exposure level of 0.5 mg/m^3 time-weighted average, and noted a potential for skin absorption.

o-Anisidine and o-Anisidine hydrochloride

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
No current action. (CPSC)		
Because of small production volumes, o-anisidine and o-anisidine hydrochloride are of low regulatory priority to EPA. They may be considered as the dyes and pigments industry is studied. (EPA)		
PEL: 0.5 mg/m^3 TWA (anisidine o,p-isomers). Potential for skin absorption noted. [Standard adopted for toxic effects other than cancer.] (OSHA)	Regulatory History: 1968: Walsh-Healy, 0.5 mg/m^3 TWA. 8/27/71: OSHA "carcinogen standard"--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 222689

ARAMITE^R

There is sufficient evidence for the carcinogenicity of Aramite^R in experimental animals.[1] Aramite^R was carcinogenic to several strains of rats and to the dog when administered in the diet. It produced liver tumors in the rat and carcinomas of the gall bladder and biliary ducts in the dog.[2]

Aramite^R was tested in several strains of mice by dietary administration and produced a significant increase of hepatomas in males of one strain.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 5. Lyon, France: IARC, 1974, pp. 39-46.

Aramite^R is the proprietary name for an organic aromatic compound that is insoluble in water but miscible with most organic solvents.

Aramite^R was previously registered for use as a pesticide on 39 crops, 20 of which were fruits and nuts, but in 1970, its use was restricted to postharvest application on fruit trees (EPA).

The single producer of Aramite^R ceased production in 1975, prior to the 1977 voluntary cancellations of registrations by all distributors. Aramite^R is probably not available in the United States. Although actual production volumes are not known, this pesticide was not widely used. For example, only 20,000 lb were used on fruit and nuts grown in California in 1971. By 1977, only 135 lb of the formulated product were available on the U.S. market, according to EPA.

No data are available on the number of workers who were actually or potentially exposed to Aramite^R during its manufacture and formulation. Nor are estimates available on direct consumer exposure to the pesticide through consumption of contaminated fruit and nut crops. Regulatory action has now eliminated the potential for exposure of the general public.

EPA regulates Aramite^R under the Federal Insecticide, Fungicide, and Rodenticide Act and the Resource Conservation and Recovery Act. The significant regulatory action was a voluntary cancellation of the active ingredient registration by the sole producer in 1975. One formulator holding remaining stockpiles was permitted to sell them through December 1977.

MONS 222690

Arsenic[a]

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
FIFRA, 6: Voluntary cancellations of registrations by all producers. 6/12/77.	One formulator was permitted to distribute 135 lb of finished product prior to 12/31/77. No longer available. (EPA)	42 FR, p. 18905
RCRA, 3001-3004: Designated Arsenic[a] as a hazardous constituent of waste, and subjects wastes known to contain it to handling and report/recordkeeping requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.33 (EPA)

MONS 222691

ARSENIC AND CERTAIN ARSENIC COMPOUNDS

Information on the carcinogenicity of arsenic compounds in experimental animals is considered inadequate for evaluation.[1] There is sufficient evidence that skin cancer in humans is causally associated with exposure to inorganic arsenic compounds in drugs, drinking water, and the occupational environment. The risk of lung cancer was increased 4 to 12 times in certain smelter workers who inhaled high levels of arsenic trioxide. However, the influence of other constituents of the working environment cannot be excluded in these studies. Case reports have suggested an association between exposure to arsenic compounds and blood dyscrasias and liver tumors.[1,2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 23. Lyon, France: 1980, pp. 39-141.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: 1982.

Arsenic is an element that is used as many compounds including arsenic trioxide, arsenic pentoxide, sodium arsenate, and sodium arsenite, all of these forms are soluble in water. Arsenic trioxide, referred to as white arsenic, is the source for 97 percent of all arsenic products. Pentavalent organic arsenicals are used for animal drugs.

Elemental arsenic and arsenic compounds are used in pesticides, glass, ceramics, paints, dyes, and the preservation of hides. Arsenic occurs naturally in a number of ores and in food. The chemical form of arsenic in food has not been clearly established. Metabolically, it behaves as a pentavalent organic arsenical.

Approximately 70 million lb of arsenic and inorganic arsenic compounds are produced in the United States. Over 95 percent of the arsenic produced is a byproduct of copper and lead ore smelting. About 13.5 million lb of arsenic are imported, primarily as arsenic trioxide. EPA reported one producer of potassium arsenite in one region (Toxic Substances Control Act. Chemical Substance Inventory, 1979, public record).

MONS 222692

Industrial workers may be exposed to arsenic and its compounds during manufacturing and processing operations. An estimated 545,000 workers are potentially exposed. Higher-than-average worker exposure occurs during the smelting of arsenic-containing ores and during pesticide application.

Direct consumer exposure to arsenic and arsenic compounds may occur in the consumption of foods. The FDA estimates that food provides an intake of approximately 0.02 mg/day/person. Trace levels of arsenic have been reported in the tissues of livestock that were administered arsenic drugs and feed additives. Consumer exposure to arsenic may occur through the consumption of contaminated drinking water. EPA has established interim regulations to minimize exposure risks.

The general population may be exposed to arsenic compounds through air emissions from pesticide manufacturing facilities, cotton gins, glass manufacturing operations, and other sources. EPA estimated total environmental emissions to be 9000 tons.

The Consumer Product Safety Commission reports that a small number of arsenic compounds are used extensively as wood preservatives. In 1978, approximately 63.5 million cubic feet of wood products, which include lumber, timber, playground equipment, and fence posts, were treated with arsenicals. A large portion of the total products treated was lumber used for residential construction, such as decks, patios, greenhouses, and housing foundations. The CPSC staff is coordinating efforts with the EPA staff to assess the need for controls on consumer use of treated wood.

EPA, FDA, and OSHA have regulated the use of arsenic and its compounds. The EPA limits arsenic in drinking water to a maximum level of 0.05 mg/l. The Agency established effluent guidelines controlling the environmental release of such compounds for certain industrial categories. EPA issued a Rebuttable Presumption Against Registration for 11 inorganic arsenic pesticide products and regulates arsenic under the Resource Conservation and Recovery Act. FDA has set tolerances for residues of arsenic-containing pesticides in fruits and vegetables (0.35-7 mg/kg), field crops (cotton, 0.7-2.8 mg/kg), and livestock (cattle and horses, 0.7-2.7 mg/kg). OSHA promulgated a final standard in 1978 limiting occupational exposure to inorganic arsenic compounds to 10 ug/m^3. The PEL of 0.5 mg/m^3 for organic arsenic as an 8-hour time-weighted average was adopted by OSHA in 1971. In addition, this standard requires personal protective equipment, training, medical surveillance, signs and labeling, and engineering controls.

MONS 222693

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Arsenic Staff coordinating efforts with EPA TSCA/FIFRA staff to assess need for controls for consumer uses of wood-treated lumber. (CPSC)		
CWA, 301: Effluent guidelines for certain industrial categories address arsenic.	Control established through conditions in NPDES permits. Carcinogenicity was a direct factor in establishing guidelines.	40 CFR 415, 421, 429, 430 (portions)
CWA, 304(a). Water quality criteria document published in final, 11/28/80.		45 FR 231, p. 79318
CAA, 112: Inorganic arsenic listed for NESHAP, 6/5/80.	Chronic toxicity, including potential carcinogenicity.	45 FR, p 37886
First regulation would have affected two primary copper smelters, one of which closed permanently in 9/80. The second is voluntarily complying with the controls that would have been proposed for the source.	EPA is monitoring compliance and efficacy of the controls before determining if the results should be codified.	OAQPS, personal communication, 4/82
	Other sources are being evaluated to determine if NESHAPs should be set for them. This determination and a ranking, if deemed appropriate, should be completed by 1982.	OAQPS, personal communication, 4/82
	New York State has sued EPA for not having proposed NESHAPs for inorganic arsenic. No hearing date has been set.	OAQPS, personal communication, 4/82
CAA, 110: New source performance standards for smelters are being studied for revision. No target completion date has been set.	Would normally apply to new or expanded/remodeled facilities. Could be extended to all sources under a special provision of existing CAA.	OAQPS, personal communication, 4/82
RCRA, 3001-3004: Designated as a toxic waste. Requires testing to determine presence of arsenic. Wastes containing arsenic are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.	Concentration triggering compliance requirements, 5.0 mg/l.	40 CFR 261.24
SDWA, 1412: Primary drinking water regulation, Promulgated 12/24/75.	Establishes maximum contaminant level of 0.05 mg/l. Does not address carcinogenicity. Under review for possible revision.	40 CFR 141.11
SDWA, 1412: Revision of drinking water maximum contaminant level scheduled for proposal 6/83.	Existing maximum contaminant level of 0.05 mg/l remains in force. Chronic toxicity, including carcinogenicity, is under review and will be considered (EPA)	OJW, Memorandum, 10/81 (EPA)
TSCA Under continuing assessment to determine if other controls may be needed.		
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

(Continued)

MONS 222694

REGULATIONS		
Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Arsenic (Concluded) FDA Bureau of Foods and Bureau of Veterinary Medicine, FDA. None of the regulated arsenic compounds are those that have been associated with occupational cancer. There are extensive toxicity studies on arsenicals used as pet drugs which have shown any carcinogenic potential. (FDA)	Withdrawal requirements for meat-producing animals exposed to arsenicals should ensure that the levels are similar to normal background levels for arsenicals. (FDA)	Both organic and inorganic arsenics are regulated under CFR 21 558.60, 558.62, 558 120, 558.530, 561.334, 146.335 (FDA)
PEL: 0.5 mg/m^3 8-hr TWA as arsenic (organic), 10 ug/m^3 8-hr TWA (inorganic). No skin or eye contact with arsenic trichloride or liquid or particulate inorganic arsenic that is likely to cause skin or eye irritation.	Regulatory history: 1952: walsh-healy, 0.5 mg/m^3 maximum allowable concentration. 8/27/71: OSHA Takeover Standard--current limit effective.	29 CFR 1910.1000 (organic arsenic)
Protective clothing, respirator, hygiene training, and medical surveillance requirements for workers, monitoring requirements, housekeeping requirements, sign requirements for regulated areas, labeling requirements for containers. (OSHA)	6/30/78. Final Standard--current limit effective. (OSHA)	29 CFR 1910.1018 (inorganic arsenic) (OSHA)
Arsenic Trioxide CWA, 311. Hazardous spill regulation establishing reportable quantity (5000 lb, 2270 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping of chemicals and should result in reduction of accidental exposures.	40 CFR 117.3, 117.13
FIFRA: Ban on use of formulations containing more than 1.5 percent arsenic trioxide in households and grazing areas. 8/68.	Some reduction in use.	Written notice to registrants
FIFRA, 6: Voluntary cancellation by producers of three products. 9/11/77.	Minimal reduction in use.	42 FR 177, p. 45944
FIFRA, 6: RPAR issued regarding 11 inorganic arsenical pesticides. 10/19/78	Uses other than as a wood preservative are still under consideration for regulation. (EPA)	43 FR 202, p. 43267
RCRA, 3001-3004: Subjects waste products, off-specification products, and spill residues in excess of 1000 kg to handling and reports/recordkeeping requirements. Also designated as a hazardous constituent of waste. Wastes known to contain arsenic trioxide are subject to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
See regulations under arsenic. (OSHA)		29 CFR 1910.1018 (OSHA)

(Continued)

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REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Potassium Arsenate: CWA, 311: Hazardous spill regulation establishing reportable quantity (1000 lb, 454 kg) and imposing reporting requirements. Promulgated 3/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures. (EPA)	40 CFR 117.13
RCRA, 3001-3004: Arsenical compounds not otherwise specified are listed as hazardous constituents of waste. Wastes known to contain any of these are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.11 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
See regulations under arsenic. (OSHA)		29 CFR 1910.1018 (OSHA)
Sodium Arsenate: CWA, 311: Hazardous spill regulation establishing reportable quantity (1000 lb, 454 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures.	40 CFR 117.3, 117.13
FIFRA, 6: RPAR issued regarding 11 inorganic arsenical pesticides, 10/18/78.	Proposed determination in development will address uses other than as a wood preservative. (EPA)	43 FR 202, p. 48267
RCRA, 3001-3004: Arsenical compounds not otherwise specified are listed as hazardous constituents of wastes. Wastes known to contain any of these are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.11 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
See regulations under arsenic. (OSHA)		29 CFR 1910.1018 (OSHA)
Sodium Arsenite: CWA, 311: Hazardous spill regulations establishing reportable quantity (1000 lb, 454 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity.	40 CFR 117.3, 117.13
FIFRA: Ban on use of formulations containing more than 2 percent of sod. m arsenite in households or on grazing area, 8/68.	Some reduction in use.	Written notice to all affected registrants
FIFRA, 6: Registrations of two products voluntarily canceled by producers, 3/8/77.		
FIFRA, 6: RPAR issued regarding 11 inorganic arsenical pesticides, 10/18/78.	Determined not to be a wood preservative, but is under consideration for regulation.	43 FR 202, p. 48267

(Continued)

MONS 222696

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Sodium Arsenite: (Concluded) RCRA, 3001-3004: Arsenical compounds not otherwise specified are listed as hazardous constituents of waste. Wastes known to contain any of these are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.11
TSCA, 8(a): Reporting rule requiring process and use data. Proposed 2/29/80.		45 FR 12646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
See regulations under arsenic. (OSHA)		29 CFR 1910.1018 (OSHA)
Arsenic Pentoxide: CWA, 311: Hazardous spill regulation establishing reportable quantity (5000 lb, 227C kg) and imposing reporting requirements. Promulgated 8/29.	Not based on carcinogenicity.	40 CFR 1.7.3, 117.13
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designated as a hazardous constituent of waste. Wastes known to contain arsenic pentoxide are subject to the same requirements. Promulgated 5/19/80		40 CFR 261.11, 261.33
FIFRA, 3: Classification for restricted use as a wood preservative, 2/19/81, proposed.	Oncogenicity, mutagenicity, and teratogenicity. Would reduce user/worker exposure.	46 FR, p. 13020
FIFRA, 6: RPAR issued regarding 11 inorganic arsenical pesticides. 10/18/78.	Proposed determination in development will address uses other than as a wood preservative. (EPA)	43 FR 202, p. 48267 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
See regulations under arsenic. (OSHA)		29 CFR 1910.1018 (OSHA)
Calcium Arsenate, Calcium Arsenite, Disodiumhydrogen Arsenate, Lead Arsenate, and Potassium Arsenite: RCRA, 3001-3004: Arsenic compounds not otherwise specified are listed as hazardous constituents of waste. Wastes known to contain any of these are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.11 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 222697

ASBESTOS

There is sufficient evidence for the carcinogenicity of asbestos both in humans and in experimental animals.[1]

All types of commercial asbestos fibers that have been tested are carcinogenic in mice, rats, hamsters and rabbits, producing mesotheliomas and lung carcinomas after inhalation, and after intrapleural, intratracheal and intraperitoneal administration.[2]

Occupational exposure to chrysotile, amosite, anthophyllite, and mixtures containing crocidolite has resulted in a high incidence of lung cancer. A predominantly tremolitic material mixed with anthophyllite and small amounts of chrysotile has also caused an increased incidence of lung cancer. Pleural and peritoneal mesotheliomas have been observed after occupational exposure to crocidolite, amosite and chrysotile asbestos. Gastrointestinal tract cancers were increased in groups exposed occupationally to amosite, chrysotile or mixed fibers containing crocidolite. An excess of cancer of the larynx was also observed in exposed workers. Mesotheliomas have occurred in individuals living in the neighborhood of asbestos factories and crocidolite mines, and in persons living with asbestos workers. Both cigarette smoking and occupational exposure to asbestos fibers increase lung cancer incidence independently. When present together, they act multiplicatively.[1,2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 1. Lyon, France: 1979.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 14. Lyon, France: 1977, pp. 1-106.

Asbestos is the generic name of a class of natural fibrous silicates. There are four commercially important forms: chrysotile, amosite, anthophyllite, and crocidolite. Chrysotile represented 94 percent of U.S. consumption in 1974.

Asbestos is currently used in more than 5000 products, some of which are roofing, thermal and electrical insulation, cement pipe and sheet, flooring, gaskets, friction materials, coatings, plastics, textiles, and paper products.

Total production of asbestos in 1976 was estimated at 250 million lb; 1979 production was reported to be 200 million lb. Some producers are developing suitable substitutes for asbestos, and production is expected to decline in the 1980s.

MONS 222698

Human exposure to asbestos is primarily through inhalation or ingestion of fibers. Asbestos may occur as a contaminant of food or beverages that come in contact with materials such as adhesives and repeatedly used polyester-resin, rubber, and phenolic-resin molded plastic articles. FDA is aware that asbestos might be used in dental filling material, especially temporary cements. Exposure to asbestos in dental filling materials is assumed to be very low to virtually nil. Asbestos is so widely used that the entire population is exposed to some degree. Worker exposure has been a concern in the mining and milling of asbestos, during the manufacture of all asbestos products, and in the construction and shipbuilding industries. OSHA reported that about 2.5 million workers are estimated to have some exposure to asbestos.

The general population is exposed to asbestos fibers from air, beverages, drinking water, food, pharmaceutical and dental preparations, and asbestos-conteining consumer products. Families of asbestos workers have been exposed to high fiber levels through contaminated clothing brought home for laundering.

Asbestos fibers are released into the environment from the natural occurrence of asbestos in the earth and as a result of wear and deterioration of asbestus products. Asbestos minerals are emitted into the atmosphere and water systems from the mining and milling of asbestos ores. Applications of asbestos materials to buildings and vehicle brake linings account for a significant amount of emissions to the atmosphere. The demolition of buildings with asbestos insulation or fireproofing can cause high atmospheric concentrations for relatively short periods of time. The disposal of mining and building material wastes in landfills also increases the distribution of asbestos into the environment, but no estimates of the quantity of material released in this manner are available.

The 1977 banning by the Consumer Product Safety Commission (CPSC) of asbestos in patching compounds and in gas fireplaces prevented additional exposure of several million consumers who were exposed to asbestos from these sources. U.S. manufacturers of hand-held dryers cooperated with CPSC by voluntarily ceasing to use asbestos liners. This voluntary program resulted in the repair by manufacturers of 2 million dryers. CPSC has published advance notice of proposed rulemaking stating an intent to further regulate the uses of asbestos. The Commission will convene a Chronic Hazard Advisory Panel to assess the carcinogenicity, mutagenicity, and teratogenicity of asbestos and, if feasible, estimate the probable harm to human health that will result from exposure to asbestos. The panel will meet for the first time in January 1983. A report is expected from the panel in early summer 1983. Studies in progress are looking at asbestos release from products; another study in progress is examining asbestos substitutes. EPA proposed an asbestos water quality criteria document for the protection of human health in October 1979. EPA regulates asbestos under the Clean Air Act, the Clean Water Act, and the Resource Conservation and Recovery Act, and proposes to do so under the Toxic Substances Control Act. A voluntary EPA program is removing or encapsulating sources of asbestos release in school buildings.

MONS 222699

EPA published advance notices of proposed rulemaking that stated an intent to further regulate the uses of asbestos. FDA action concerning asbestos (and talc) restricted the utilization of asbestos filters in the manufacture of parenteral drugs and parenteral drug ingredients. FDA has taken no action to date with regard to asbestos in food, because there is no evidence that the ingestion of small amounts of asbestos found in food poses any human health risk. The OSHA standard for asbestos fibers permitted in the workplace is two fibers/cc of air for fibers longer than 5 μm. In addition, this standard requires personal protective equipment, training, medical surveillance, signs and labeling, and engineering controls.

In April 1980, a NIOSH/OSHA work group reviewed the most recent scientific information and recommended that a new standard for asbestos be promulgated. Recommendations included reduction of the current environmental limit and elimination of nonessential asbestos exposures with substitution of less hazardous alternatives.

MONS 222700

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Ban in effect on general-use garments (1972) containing asbestos.	Essentially eliminated that type of exposure.	1600 CFR 1500.17 (a)(7)
Voluntary recall of hair dryers.	(1979) 1.5 million units returned.	
Advance notice of proposed rulemaking describing proposed approach of seeking elimination of all nonessential uses of asbestos in consumer products from which asbestos fibers are released during use.		FR 46, p. 60056
Ban (1978) on patching compounds and gas log embedding materials containing respirable free asbestos.	Between 1 and 3 million persons had been exposed to patching compounds; no subsequent exposures. 0.5 - 1.5 x 10^6 persons exposed to embedding materials; no additional exposures. (CPSC)	1600 CFR 1304
Staff developing proposal to ban asbestos paper for consumer use. (CPSC)		1600 CFR 1305 (CPSC)
CAA, 112: NESHAP addressing several industrial categories. Promulgated 4/6/73 and 10/14/75.	Some reduction in emissions largely through engineering and practice controls. Numerical limits were not set because of the absence of reliable and economically feasible analytical methods.	40 CFR 61.20-60.26
CWA, 301: Effluent guidelines for the asbestos industry and for asbestos mining/milling operations. Promulgated 2/20/74, 2/11/75, and 10/16/75.	Control through NPDES permit conditions. Asbestos is not directly addressed. Control of suspended solids would afford a degree of control over asbestos.	40 CFR 427, 436.70
CWA, 304(a): Water quality criteria published in final form, 11/28/80.		45 FR 231, p. 79318
TSCA, a: Voluntary program of abatement of asbestos in schools, published 3/20/79	High interest in acting to encapsulate or replace asbestos-containing materials.	44 FR 58, p. 17701
ANPR seeking comments on regulation of several sources, published 10/17/79. Issued in conjunction with CPSC. Meetings ongoing;		44 FR 202, p. 60056
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.33
TSCA, 4a and Department of Education-Asbestos School Hazard Detection and Control Act of 1980.		
Proposed rule requiring state plans to inspect schools for friable asbestos, and authorizing grants and loans to cover 50 percent of the cost of inspection and control.	Ties to NESHAP and OSHA rules related to asbestos. Stipulates compliance during control activities. (EPA)	45 CFR 382, p. 61950 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

(Continued)

MONS 222701

REGULATIONS		
Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
FDA Bureau of Foods, FD&CA: Most permitted uses approved when asbestos was not known to be implicated as a carcinogen. At present there is no data available to estimate the levels of migration of asbestos into foods from the regulated uses. It is assumed that under good manufacturing practice, there will be "virtually all or de minimis" migration of asbestos into human foods. FDA Bureau of Medical Devices, FD&CA: No regulatory history and no regulations issued to date. (FDA)	Further reductions would require new estimates of how much asbestos is actually getting into food and development of sensitive detection methods. Increased awareness of product, with asbestos achieved by inclusion in Medical Device Inventory. (FDA)	21 CFR 175 (05, 177.2420 177.2910, 177.2600 (FDA)
PEL: 2 fibers/cc > 5 um in length, 8-hr TWA. 10 fibers/cc > 5 um in length, ceiling.	Regulatory History: 1951 Walsh-Healy: 5 mppcf maximum allowable concentration. 6/7/71: OSHA Inherent Standards--Tremolite 20 mppcf or (20 mg/m^3)/(%SiO$_2$) 8-hr TWA; asbestos 12 fibers/cc > 5 um in length or 2 mppcf 8-hr TWA.	29 CFR 1910.1001 (OSHA)
Medical surveillance requirements for workers; monitoring requirements; housekeeping and waste disposal requirements; protective clothing, respirator, and change room requirements in areas where engineering and work practice controls are not sufficient to lower asbestos to permissible levels; sign requirements for regulated areas. (OSHA)	12/7/71: Emergency Temporary Standards--5 fibers/cc > 5 um in length 8-hr TWA; 10 fibers/cc > 5 um in length, ceiling, 30 minutes for up to 15 min/hr, 5 hr/day. 1/11/72: Standard coverage expanded to include ship repairing, shipbuilding, ship-breaking, and longshore workers. 7/7/72: Revised Standards--5 fibers/cc > 5 um in length, 8-hr TWA, 10 fibers/cc > 5 um in length, ceiling 7/1/76: Final Standard--current limit effective.	
	(OSHA)	

MONS 222702

AURAMINE AND THE MANUFACTURE OF AURAMINE

There is sufficient evidence that the manufacture of auramine is carcinogenic in humans. The evidence for the carcinogenicity of technical grade auramine in humans and in experimental animals is considered as limited.[1]

When given in the diet, commercial auramine of unknown purity was tumorigenic in two strains of mice and in Wistar rats after oral administration, producing liver tumors, and after subcutaneous injection in rats, producing local sarcomas.[1]

The manufacture of auramine (which also involves exposure to other chemicals) is judged to be causally associated with increased incidence of bladder cancer. The actual carcinogenic compound(s) has not been specified precisely.[1,2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 1. Lyon, France: 1972, pp. 69-73.

Auramine (Basic Yellow 2), an aromatic amine, appears as yellow leaves or needles, which are insoluble in water.

Auramine (hydrochloride salt) is used industrially as a dye or dye intermediate for coloring inks, textiles, wool, paper, and leather. According to 1979 U.S. International Trade Commission data, auramine was not domestically produced; however, 165,000 lb were imported.

Human exposure to auramine occurs principally through skin absorption or vapor inhalation. Approximately 3000 workers in the textile, paper, and leather industries may be exposed to auramine. Low-level dermal exposure to the consumer may occur but would be limited to any migration of auramine from fabric, leather, or paper goods.

Auramine is regulated by the EPA under the Resource Conservation and Recovery Act. NIOSH is currently preparing a special hazard review for auramine and the manufacture of auramine.

MONS 222703

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Based on toxicologic and economic evaluation conducted in 1981 and 1982, staff recommendations will be presented to FTC. (CPSC)		
RCRA, 3001-3004. Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also, listed as a hazardous constituent of waste. Wastes known to contain auramine are subject to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, §8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 42, p. 13646 (EPA)
See the Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
NIOSH Special Hazard Review in preparation. (NIOSH)		

MONS 222704

BENZ(a)ANTHRACENE

There is sufficient evidence of the carcinogenicity of benz(a)-anthracene (BA) in experimental animals.[1] BA given by several routes of administration has proved to be carcinogenic in the mouse. It produced hepatomas and lung adenomas following repeated oral administration to young mice. In a parallel experiment with methylcholanthrene, the carcinogenic effect upon the liver and lung was similar for the two compounds at the same dose level. In the same experiment, BA did not produce tumors of the gastrointestinal tract, whereas methyl-cholanthrene induced them consistently.[2]

BA is a complete carcinogen for the mouse skin. The fact that the tumor yield was higher when using a dodecane solution than with toluene is related to the co-carcinogenic effect of dodecane. Benzo(a)pyrene given at a lower dose level produced more skin tumors with a shorter latency period than did BA. BA is also an initiator of skin carcinogenesis in mice.[2]

BA produced tumors in mice following subcutaneous injections. Fifty ug BA was the lowest dose tested, and it was effective in newborn and in adult animals. It produced bladder tumors in mice following implantation.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1976, pp. 45-68.

BA belongs to the class of chemicals known as polycyclic aromatic hydrocarbons (PAHs), which are formed under geothermal conditions leading to coal and petroleum and as a result of incomplete combustion. BA is slightly soluble in water and soluble in most organic solvents, except alcohol.

BA is a contaminant and does not have any reported commercial use or application, although one producer did report the substance for the Toxic Substances Control Act Inventory.

MONS 222705

BA has been reported present in cigarette smoke condensate, automobile exhaust gas, soot, and emissions from coal and gas works and electric plants. BA also occurs in the aromatic fraction of mineral oil, commercial solvents, waxes, petrolatum, creosote, coal tar, petroleum asphalt, and coal tar pitch. Microgram quantities of BA can be found in various foods such as charcoal broiled, barbecued, or smoked meats and fish; certain vegetables and vegetable oils; and roasted coffee and coffee powders.

Human subjects are exposed to BA through either inhalation or ingestion. Workers at facilities with likely exposure to fumes from burning or heating of organic materials have a potential for exposure to BA. Consumers can be exposed to this chemical through ingestion of various foods, with concentrations of 100 ug/kg in some instances. Cigarette smoke condensate has quantities of BA that range from 0.03 to 4.6 ug/g.

BA is found in the atmosphere at levels that vary with geographical features and climate. These values can range from up to 136 ug/1000 m^3 in summer to 361 ug/1000 m^3 in winter. Drinking water samples may contain up to 23 ng/l BA, and surface waters have been found to contain 4-185 ng/l. The soil near industrial centers has been shown to contain as much as 390 ug/kg of BA, whereas soil near highways can have levels of up to 1500 ug/kg, and areas polluted with coal tar pitch can reach levels of 2500 mg/kg.

The Carcinogen Assessment Group at EPA lists BA as a carcinogen, and the water quality criteria for PAHs apply by inference to BA. There have been few attempts to develop exposure standards for PAHs either individually or as a class; however, NIOSH has recommended a workplace standard for coal tar products of 0.1 mg/m^3 as a time-weighted average for a 10-hour workshift in a 40-hour workweek. OSHA indirectly limits exposure to BA by requiring that occupational exposure to coal tar pitch volatiles not exceed 0.2 mg/m^3 over an 8-hour period as a time-weighted average.

MONS 222706

Benzo(a)anthracene

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
RCRA, 3001-3004 Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designated as a hazardous constituent of waste.	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261.33
CWA, 304(a): Water quality criteria available in final form, 11/28/80. Total PAH addressed, as indicator nor surrogate.		45 FR 231, p. 79318
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/27/80.	Would, if promulgated, permit a basis for estimating exposure (EPA)	45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
PEL: 0.2 mg/m³ 8-hr TWA (cyclohexane soluble fraction of coal tar pitch volatiles) (limited coverage). (OSHA)	Regulatory History: 8/21/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000, 1910.1002 (OSHA)

MONS 222707

BENZENE

The evidence that benzene is carcinogenic in experimertal animals is limited.[1] Administered by stomach tube to rats, benzene increased the incidence of Zymbal gland carcinomas. An increased incidence of lymphoid tumors occurred in male mice exposed to benzene by inhalation. In similar studies with another strain of mice and with rats, no leukemic response was observed.[2]

There is sufficient evidence that benzene is carcinogenic to man.[1] Several case reports as well as an epidemiological case control study establish a relationship between benzene exposure and leukemia. Two cohort studies showed an increased incidence of acute nonlymphocytic leukemia in workers exposed to benzene. There has been an additional report of a large number of leukemia cases (most of which were acute nonlymphocytic) among a group of workers exposed to benzene.[1,2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 29. Lyon, France: 1982. pp. 93-148.

Benzene, a volatile, colorless, flammable liquid, is a major raw material of the chemical industry.

Benzene is used extensively as a solvent in the chemical and drug industries, as a starting material and intermediate in the synthesis of numerous chemicals, and as a gasoline additive. Eighty percent of the benzene is consumed in the production of ethylbenzene, cumene, and cyclohexane.

Benzene is domestically produced in the United States in over 50 locations, and in 1979, approximately 12 billion lb were produced. An additional 1.6 billion lb were imported, whereas exports were 1.3 million lb. Benzene is expected to remain one of the industry's most important chemicals. Increasing market demands are forecast at approximately 5 percent annually.

An estimated 3 million workers may be exposed to benzene. Exposure may occur during the production of benzene or during the use of substances containing the chemical as an ingredient or contaminant. Human exposure to benzene is primarily through inhalation of the vapor or through skin absorption.

MONS 222708

Due to the ubiquitous nature of benzene, over 75 percent of the population has probably been exposed to this chemical. In 1976, an estimated 1.3 billion lb of benzene were released into the atmosphere from 132 million stationary and mobile sources. This included an estimated 240 million lb/yr from the production, transport, storage, and use of benzene; 1 billion lb/yr from the refueling and operation of motor vehicles; and 22 million lb/yr from oil spills. It has been estimated that 800,000 persons may be exposed to benzene from coke oven emissions at levels greater than 0.1 ppm; 5 million persons from petroleum refinery emissions at levels of 0.1-1.0 ppm.

Information on the levels of benzene in the atmosphere is limited. Ambient monitoring data indicate that levels of benzene range from 1 ppb to 100 ppb. The highest values were reported in metropolitan areas and may be due to exhausts from motor vehicles. Benzene has been identified in drinking water and in subsurface water at concentrations to 10 ppm. Benzene occurs in fruits, fish, vegetables, nuts, dairy products, beverages, and eggs. The National Cancer Institute estimated that an individual could ingest up to 250 ug/day.

In May 1981, the Consumer Product Safety Commission (CPSC) withdrew its proposed ban of consumer products, except for gasoline and laboratory reagents, which contained benzene as an intentional ingredient or as a contaminant at 0.1 percent or greater by volume. The decision to withdraw the rulemaking was based on CPSC findings that benzene is no longer used as an intentional ingredient in consumer products and that the contaminant levels remaining in certain consumer products are unlikely to result in significant consumer exposure to benzene vapor. A labeling regulation, established in 1962 for products containing more than 5 percent benzene, and a 1977 safety packaging requirement for paint solvents and thinners containing 10 percent or more of petroleum distillates, such as benzene, remains in effect.

In 1977, EPA listed benzene as a hazardous air pollutant under Section 112 of the Clean Air Act. Emission standards for ethylbenzene-styrene plants, benzene storage and fugitive emissions, and coke byproduct plants were being assessed by EPA during 1980-81; and a standard for maleic anhydride production was proposed in 1980. EPA also regulates benzene under the Clean Water Act; the Federal Insecticide, Fungicide, and Rodenticide Act; and the Resource Conservation and Recovery Act.

OSHA's 1971 standard limited benzene to 10 ppm in the air for an 8-hour time-weighted average (TWA). This was lowered in 1977 by an emergency temporary standard to a 1 ppm TWA with a maximum of 5 ppm for 15 minutes. A final standard establishing a permissible exposure limit (PEL) of 1 ppm 8-hour TWA with a 5 ppm upper level limited to 15 minutes has been overturned by the U.S. Supreme Court. Subsequent to this Supreme Court action, the OSHA regulation has reverted to a 10 ppm 8-hour TWA PEL.

MONS 222709

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
1978 Proposed ban under CPSA of benzene as an intentional ingredient in consumer products and products containing 0.1 percent or more by volume of benzene as a contaminant. Action withdrawn in 1981.	No known intentional use of benzene in consumer products. Perhaps as a result of proposed ban, 400,000-800,000 persons are no longer exposed.	46 FR, p. 27810
Under FHSA, household products containing 5 percent or more benzene by weight must bear cautionary labeling.	Difficult to assess the effectiveness of labeling.	1600 CFR 1500.14 (b)(3), (b)(3)
Safety packaging required under PPPA for prepackaged liquid solvents that contain 10 percent or more petroleum distillates, such as benzene, by weight and have viscosity less than 100 SUS at 100° F. (CPSC)	Not based on carcinogenicity. Overall safety packaging effectiveness estimated at 85 percent over 3-year period--not able to assess poisoning reduction from benzene products per se. (CPSC)	1600 CFR 1700.14 (a)(10) (CPSC)
CAA, 112: Benzene listed for NESHAP development, 6/8/77. NESHAP for benzene emissions from maleic anhydride production facilities proposed 4/18/80. NESHAP for ethylbenzene-styrene production facilities. NESHAP to address benzene emissions from other industrial sources in development.	Would establish numerical emission limits and provide guidance on means to achieve them. Schedules for proposal between early 1981 and mid-1982.	42 FR 110, p. 29332 47 FR, p. 26660
CWA, 304(a): Water quality criteria published in final form, 11/28/80.		45 FR 231, p. 79318
CWA, 311: Hazardous spill regulation establishing reportable quantity (1000 lb, 454 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipment of chemicals and should result in reduction of accidental exposure.	40 CFR 117.3, 117.13
FIFRA, 6: Voluntary cancellation of registrations of products containing benzene as an active ingredient are being processed.	Based on hematopoietic effects, oncogenicity, and mutagenicity. Would affect all but one producer. (EPA)	OPP, SPRD Status Report, 12/81
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also listed as a hazardous constituent of waste. Wastes known to contain benzene are subject to the same requirements. Promulgated 5/19/80. See the Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
Regulatory Authority: FD&CA, 201(T). (FDA)	Action pending completion of contaminants policy. (FDA)	
PEL: 10 ppm 8-hr TWA, 25 ppm ceiling, 50 ppm maximum peak for 10 min in any 8-hr period. (OSHA)	Regulatory History: 6/27/71: OSHA Takeover Standard--10 ppm 8-hr TWA. 5/21/77: Emergency Temporary Standard--1 ppm 8-hr TWA, 5 ppm 15-min TWA ceiling. 2/10/78: Revised standard promulgated. 7/2/80: U.S. Supreme Court reverted standard to 10 ppm 8-hr TWA. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 222710

BENZIDINE

There is sufficient evidence that benzidine is carcinogenic in experimental animals after oral and subcutaneous administration, producing liver tumors in mice and hamsters; liver, mammary and Zymbal's gland tumors in rats; and bladder cancers in dogs.[1,2]

There is sufficient evidence that benzidine is carcinogenic to humans.[1,2] Case reports and followup stucies of workers provide sufficient evidence that occupational exposure to benzidine is causally associated with an increased risk of bladder cancer.[1] The causal association is strengthened by data which suggest that the incidence of this cancer in workers decreased after a reduction in industrial exposure.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 29. Lyon, France: IARC, 1982, pp. 149-83.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

Benzidine, an aromatic amine slightly soluble in cold water, has been used for over 60 years as an intermediate in the production of azo dyes, sulfur dyes, fast color salts, naphthols, and other dyeing compounds. More than 250 benzidine-based* dyes have been reported. However, the general use of benzidine has fallen dramatically because of its carcinogenicity.

Benzidine was formerly produced in the United States at levels of many millions of pounds per year. In 1977, U.S. production of benzidine-based dyes was reported as 1.4 million lb; 76,300 lb were imported. The annual production of benzidine is now about 500 lb.

Human exposure to benzidine is primarily through inhalation or skin absorption. NIOSH has estimated that 700 workers may be directly exposed. OSHA has estimated that about 2200 workers are potentially exposed to benzidine.

In the fall of 1980, CPSC instructed its staff to collect additional economic and toxicological data in order to propose a ban on the use of benzidine-based dyes in direct consumer dye products. Studies are in progress to assess the dermal penetration of benzidine congener dyes and their respective bases. Economic studies are also in progress.

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* Benzidine-based means that the chemical structure of benzidine is included as part of a larger molecule, even though the method of synthesis may not require the use of benzidine as a starting material.

MONS 222711

Residual levels or trace impurities of benzidine may be present in benzidine-derived dyes and pigments and in the final consumer product. The presence of this known carcinogen, even as a trace contaminant, is a cause for concern.— Available data show that benzidine residuals in benzidine dyes range from 1 to 270 ppm.

EPA controls benzidine through both the 1977 toxic pollutant effluent standards and the water quality criteria proposed in October 1979. The OSHA standard restricts the use of benzidine in open vessels and requires protective clothing, engineering controls, and medical surveillance of workers.

Benzidine

REGULATIONS

Regulations and Other Actions	Effect of Regulation, Other Comments	Citation of Regulation
Toxicological and economic studies are in progress. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designated as a hazardous constituent of waste. Wastes known to contain benzidine are subject to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
CWA, 311: Hazardous spill regulation establishing reportable quantity (10 lb, 4.54 kg) and respective reporting requirements. Promulgated 6/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures.	40 CFR 117.3, 117.13
CWA, 307(a): Toxic pollutant effluent standards.	Manufacture has dropped considerably since 1977 promulgation.	40 CFR 129.104
CWA, 304: Water quality criteria. Published in final form, 11/28/80.		FR 45.231, p. 79319 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene (EPA)		
Protective clothing, respirator, hygiene, training and medical surveillance requirements for workers, exhaust fan requirements; open-vessel operations prohibited; contamination control requirements, sign requirements for regulated areas; labeling requirements for containers. (OSHA)	Regulatory History: 5/10/73: Emergency Temporary Standards--protective clothing and hygiene requirements for workers, open-vessel operations restricted, engineering requirements. 2/11/74: Final Standard--current regulations effective. (OSHA)	29 CFR 1910.1010 (OSHA)

MONS 222712

BENZO(b)FLUORANTHENE

There is sufficient evidence for the carcinogenicity of benzo(b)-fluoranthene (B(b)F) in experimental animals.[1] B(b)F has produced skin tumors in mice following repeated skin paintings. The lowest carcinogenic dose for the mouse skin was at least ten times higher than that of benzo(a)pyrene. B(b)F is also an initiator of skin carcinogenesis in mice and produces local sarcomas after subcutaneous injection. It has not been tested by other routes in the mouse or in other species.[2] The isomer of B(b)F, benzo(j)fluoranthene, has limited evidence of carcinogenicity in experimental animals.[1]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1973, pp. 69-90.

B(b)F is a polycyclic aromatic hydrocarbon (PAH). This compound may be used as a research chemical.

There is no commercial production reported for this substance. However, this compound is formed as a result of incomplete combustion of organic substances and is found in coke oven emissions and coal tar. No data are available on the amounts generated.

Human exposure is primarily through inhalation of smoke from the incomplete combustion of organic compounds. B(b)F has been detected in mg/kg quantities of particulates in air, coal tar, soot, automobile exhaust, road dust, and sewage water. It has been detected in cigarette smoke condensates, soil, drinking water, rivers and lakes, and food in microgram quantities.

EPA has designated B(b)F as a carcinogen and regulates the compound under the Resource Conservation and Recovery Act. In order to minimize the risk of workplace exposure to PAHs, OSHA promulgated an exposure standard of 150 $\mu g/m^3$ (8-hour time-weighted average) for coke oven emissions; NIOSH has recommended a workplace standard of 100 $\mu g/m^3$ (10-hour time-weighted average) for coal tar products (coal tar, creosote, and coal tar pitch). OSHA has indirectly limited exposure to B(b)F by requiring that occupational exposure to coal tar pitch volatiles not exceed, as a time-weighted average, 0.2 mg/m^3 over an 8-hour period.

MONS 222713

Benzo(b)fluoranthene

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
CWA, 304(a). Water quality criteria for PAHs published in final form, 11/28/80. Total PAHs accredited; no indicator no. surrogate.		45 FR 231, p. 79319
RCRA, 3001-3004: Designates this compound as a hazardous constituent of waste and subjects wastes known to contain it to handling and report/recordkeeping requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11 (EPA)
PEL: 0.2 mg/m³ p-ar TWA [coal tar pitch volatiles] [limited coverage]. (OSHA)	Regulatory History: 6/21/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910 1000, 1910.1002 (OSHA)

MONS 222714

There is sufficient evidence for the carcinogenicity of benzo(a)-pyrene (B(a)P) in experimental animals.[1] B(a)P has produced tumors in all of the nine species for which data are reported following different administrations including oral, skin, and intratracheal routes. It has both a local and a systemic carcinogenic effect. In subhuman primates, there is convincing evidence of the ability of B(a)P to produce local sarcomas following repeated subcutaneous injections and lung carcinomas following intratracheal instillation. It is also an initiator of skin carcinogenesis in mice, and it is carcinogenic in single-dose experiments and following prenatal exposure.

In skin carcinogenesis studies in mice, B(a)P was consistently found to produce more tumors in a shorter period of time than did other polycyclic aromatic hydrocarbons, with the possible exception of dibenzo(a,h)acridine (DB(a,h)A). In a dose-response study involving subcutaneous injection in mice, the minimal dose at which carcinogenicity was detected was higher for B(a)P than for DB(a,h)A and for 3-methyl cholanthrene. The latent periods were shorter for B(a)P, however, than for DB(a,h)A. In studies using intratracheal administration, B(a)P appeared to be less effective than 7H-dibenzo(c,g)carbazole in the hamster.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1973, pp. 91-136.

B(a)P is a polycyclic aromatic hydrocarbon (PAH); it is not commercially produced. One chemical company manufacturers B(a)P, and several specialty chemical companies distribute it for research purposes in quantities from 100 mg to 5 g.

B(a)P also occurs as a product of combustion. An estimated 1.8 million lb/yr are released from stationary sources. Ninety-six percent of this amount comes from coal refuse piles, outcrops, abandoned coal mines, residential external combustion of bituminous coal, coke manufacture, and residential external combustion of anthracite coal.

Human exposure can occur from the presence of B(a)P in polluted air, in some foods, and in the occupational environment. The number of persons exposed is not known. Persons working at airports, in tarring operations, in refuse incinerator operations, in power plants, and in coke manufacturing

NONS 222715

operations may be exposed to higher B(a)P levels than the general population. Scientists involved in cancer research or in sampling toxic materials may also be occupationally exposed. The general population may be exposed to B(a)P from air pollution, cigarette smoke, and food sources. B(a)P has been detected in cigarette smoke at levels ranging from 0.2 to 12.2 ug/100 cigarettes. B(a)P has also been detected in foods at low levels ranging from 0.1 to 50 ppb.

On October 18, 1978, EPA issued a notice of Rebuttable Presumption Against Registration for coal tar, creosote, or neutral oils. B(a)P is one of many constituents in these products. The EPA Carcinogen Assessment Group has designated B(a)P as a carcinogen, and EPA regulates the compound under the Resource Conservation and Recovery Act. Under the Clean Air Act, B(a)P is considered both a surrogate for particulate organic matter and an indicator of coke oven emissions. Water quality criteria for the protection of human health address total PAHs. OSHA indirectly limits exposure to B(a)P by requiring that occupational exposure to coal tar pitch volatiles not exceed a time-weighted average of 0.2 mg/m^3 over an 8-hour period.

Benzo(a)pyrene

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
CWA, 304(a): Water quality criteria for PAH published in final form, 11/2/80. Total PAH addressed, no surrogate nor indicator.		45 FR 231, p. 79318
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates benzo(a)pyrene as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring use and process data, published 2/29/80.		45 FR 82, p. 13644
CAA EPA has been working to determine what controls over both PAH and coke emissions may be appropriate. Benzo(a)pyrene has been the surrogate for polycyclic organic matter, and is an indicator in the assessments of coke oven emissions. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		DAQPS, personal communication, 8/80 (EPA)
PEL: 0.2 mg/m^3 8-hr TWA (coal tar pitch volatiles) (limited coverage). (OSHA)	Regulatory History: 8/21/71: OSHA Takeover Standards--current limit effective. (OSHA)	29 CFR 1910.1000, 1910.1002 (OSHA)

MONS 222716

BERYLLIUM AND CERTAIN BERYLLIUM COMPOUNDS

There is limited evidence for the carcinogenicity of beryllium in humans, and sufficient evidence of carcinogenicity of some beryllium compounds in experimental animals.[1]

Beryllium compounds were carcinogenic in rats, rabbits and monkeys. Beryllium metal, beryllium-aluminum alloy, beryl ore, beryllium chloride, beryllium fluoride, beryllium hydroxide, beryllium sulfate (or its tetrahydrate) and beryllium oxide, all produced lung tumors in rats exposed by inhalation or intratracheally. Beryllium oxide and beryllium sulfate produced lung tumors in monkeys after intrabronchial implantation or inhalation. Beryllium metal, beryllium carbonate, beryllium oxide, beryllium phosphate, beryllium silicate and zinc beryllium silicate all produced osteosarcomas in rabbits following intravenous and/or intramedullary administration.[2]

Four early epidemiological studies and three recent ones of occupational exposure to beryllium were considered to provide limited evidence that exposure to beryllium may lead to human lung cancer. The data for most of the studies were derived from two beryllium plants and from the Beryllium Case Registry. Although 55 new cases of beryllium disease were registered between 1973 and 1977, no further data were available on the incidence of lung cancer. An analysis of the pathology of the 47 lung cancers noted in one study confirmed the post-mortem diagnosis of lung cancer in 32 of the 37 cases available for review. Of the 47 cases, 21 were noted to have been smokers, but the smoking histories of the other cases were not given.[1]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 23. Lyon, France: IARC, 1979, pp. 143-204.

Beryllium and its compounds are widely distributed in nature. Beryllium compounds of commercial importance include beryllium oxide, beryllium sulfate, and beryl.

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Beryllium is used extensively in the manufacturing of electrical components, chemicals, ceramics, and X-ray tubes. A number of alloys are produced in which beryllium is added to yield greater tensile strength, electrical conductivity, and resistance to corrosion and fatigue. The metal is used as a neutron reflector in high-flux test reactors.

Beryllium has been produced commercially in the United States since the 1940s. In 1979, two companies were reported to produce beryllium in unknown amounts. The Toxic Substances Control Act (TSCA), Chemical Substance Inventory (public record) reported six producers and importers in 1977, with production of 74,000 lb. Imports for 1978 were approximately 1400 lb. Beryllium oxide has been produced commercially in the United States since 1958. In 1978, only minor amounts were produced by one producer. In 1977, EPA reported that 406,000 lb were produced domestically. Eleven other beryllium compounds are produced in small quantities.

Human exposure occurs mainly through inhalation of beryllium dust or fumes. OSHA has estimated that approximately 25,000 workers are exposed to beryllium. Among these are beryllium ore miners, beryllium alloy makers and fabricators, phosphor manufacturers, ceramic workers, missile technicians, nuclear reactor workers, electric and electronic equipment workers, and jewelers.

The major source of beryllium exposure of the general population is through the burning of coal. Approximately 250,000 lb of beryllium is released from coal- and oil-fired burners. EPA has estimated the total release of beryllium to the atmosphere from point sources is 5500 lb per year. The principal emissions are from beryllium-copper alloy production. Approximately 721,000 persons living within 12.5 miles (20 km) of point sources are exposed to small amounts of beryllium (median concentration, 0.005 $\mu g/m^3$). Small concentrations of beryllium have been reported in drinking water supplies and in food.

In 1973, EPA promulgated a National Emissions Standard for Hazardous Air Pollutants (NESHAP) for extraction and production sites for beryllium and for beryllium oxide and beryllium rocket-motor firing. In 1980, EPA published a water quality criteria document for beryllium for the protection of human health. In 1980, the Agency established regulations under the Resource Conservation and Recovery Act for wastes known to contain beryllium and beryllium compounds. These regulations were based on the inclusion of beryllium and its compounds in the EPA Carcinogen Assessment Group's list of chemical carcinogens. The Agency does not plan to regulate beryllium in drinking water under the Safe Drinking Water Act, but EPA has proposed a rule under TSCA requesting production and other data.

Current OSHA standards for limiting exposure to workers are a 2 $\mu g/m^3$, time-weighted average, a 5 $\mu g/m^3$ ceiling, and 25 $\mu g/m^3$ maximum peak for 30 minutes. This standard was adopted by OSHA for toxic effects other than cancer.

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REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
CAA, 112: NESHAP promulgated for extraction and production sites for beryllium and beryllium oxide, and beryllium rocket-motor firing, 4/6/73.	Under continuing assessment to determine efficacy of existing rule. Source assessment completed, 5/80.	40 CFR 61.30 et seq., 61.40 et seq.
CWA, 304(a). Water quality criteria for dissociated beryllium. Published in final form, 11/28/80.		45 FR 231, p. 79318
RCRA, 3001-3004: Subjects wastes known to contain beryllium and beryllium compounds to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.10
Subjects beryllium dust as waste products; also subjects off-specification batches and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.33
TSCA, 8(a): Proposed rule requesting production and other data (beryllium sulfate).		45 FR 42, p. 13644
SDWA: EPA does not plan to regulate beryllium in drinking water because of reports that it is not absorbed by the gastrointestinal system.		EPA, personal communication, 8/80
A standard of 2 $\mu g/m^3$ was adopted by the industry in 1949, and has "usually been met" since the early 1950s.		OHTS draft criteria document 3/79 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
PEL: 2 $\mu g/m^3$ 8-hr TWA, 5 $\mu g/m^3$ ceiling; 25 $\mu g/m^3$ maximum peak for 30 min. [Standard adopted for toxic effects other than cancer.] (OSHA)	Regulatory History: 8/27/71. OSHA Takeover Standard--Current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 222719

N,N-BIS(2-CHLOROETHYL)-2-NAPHTHYLAMINE (CHLORNAPHAZINE)

There is sufficient evidence of the carcinogenicity of N,N-bis-(2-chloroethyl)-2-naphthylamine (chlornaphazine) in humans, and limited evidence in experimental animals.[1] N,N-bis(2-chloroethyl)-2-naphthylamine produced lung tumors in mice following intraperitoneal injection, and local sarcomas in rats after subcutaneous administration.[2]

The administration of chlornaphazine together with radioactive phosphorus (^{32}P-sodium phosphate) caused bladder cancer in 10 of 61 patients treated for polycythemia vera. In 46 patients treated with ^{32}P-sodium phosphate alone, no cases of bladder cancer were found.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 4. Lyon, France: IARC, 1974, pp. 119-24.

This antineoplastic drug, sparingly soluble in water, is a nitrogen mustard. The drug is commonly called chlornaphazine.

Chlornaphazine is neither produced nor used commercially in the United States, although it has been used in other countries in the treatment of leukemia and related cancers. The drug now has no wide therapeutic application.

The EPA Carcinogen Assessment Group has included this chemical on its list of carcinogens. Under the Resource Conservation and Recovery Act, EPA requires that the use, handling, or disposal of wastes containing this substance be subject to special reporting and recordkeeping requirements. The FDA reported that N,N-bis(2-chloroethyl)-2-naphthylamine is not an approved drug for therapeutic use.

MONS 222720

REGULATIONS		
Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
No current action on known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residue in excess of 1000 kg to handling report/recordkeeping requirements. Also designates N,N-Bis(2-chloroethyl)-2-naphthylamine as a hazardous constituent of wastes, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
FDA reports that N,N-Bis(2-chloroethyl)-2-naphthylamine is not an approved drug. (FDA)		

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BIS(CHLOROMETHYL)ETHER AND TECHNICAL GRADE CHLOROMETHYL METHYL ETHER

There is sufficient evidence for the carcinogenicity of these substances both in experimental animals and in humans.[1] Bis(chloromethyl)ether (BCME) produced tumors at the site of application in mice after administration by inhalation, skin application or subcutaneous injection, and in rats after inhalation and subcutaneous administration. Technical grade chloromethyl methyl ether (CMME) (which is almost always contaminated with BCME) produced local sarcomas in mice after subcutaneous administration, and was also an initiator of skin tumors.[1,2]

Two studies of workers exposed to BCME and technical grade CMME showed an increased risk of lung cancer, mainly oat-cell carcinoma. Two subsequent studies have shown a positive association between atypical cells in bronchial excretions (abnormal pulmonary cytology) and exposure to BCME which was not related to cigarette smoking. Several studies have demonstrated a significant excess of lung cancer among BCME- or CMME-exposed workers which was directly related to intensity and duration of exposure. Oat-cell carcinoma was the predominant histological type of lung cancer. The excess respiratory cancer mortality was most marked in workers under 55 years of age. The evaluation of CMME alone is complicated by the presence of 1 percent to 8 percent of BCME as a contaminant.[1,2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 1. Lyon, France: IARC, 1979, pp. 26-27.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 4. Lyon, France: IARC, 1974, pp. 239-45.

Both BCME and CMME are water-soluble, colorless liquids.

BCME and CMME are used in the synthesis of other chemicals and in the manufacture of plastics and ion exchange resins. Domestic production of BCME by one producer is estimated by EPA to be 550,000 lb annually. BCME has been primarily used in the United States as a chemical intermediate. There are currently four producers of CMME in the United States, but the amount produced has not been reported. Technical grades of CMME are contaminated with 1 to 8 percent BCME.

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The main route of exposure to BCME and CMME is through inhalation, and less likely through skin absorption. Potential sources of human exposure to BCME and CMME exist primarily for workers, such as organic chemical synthesizers, ion exchange resin makers, laboratory workers, and polymer makers. No estimates of the number of workers exposed are available. Very low incidental exposure might occur due to metabolites of some dental materials regulated by the FDA.

Environmental exposure through water pollution is small because both chemicals rapidly decompose in water. However, the breakdown in air is less rapid. BCME can be formed whenever formaldehyde, water, and hydrogen chloride vapors are mixed at room temperature even in low concentrations.

The EPA regulates BCME under the Clean Water Act (CWA) and the Resource Conservation and Recovery Act (RCRA). BCME was deleted from the CWA hazardous substance list due to its extremely short life in water and the absence of data indicating it is a water pollution problem. RCRA lists BCME as a hazardous constituent of waste. The EPA primarily addresses BCME, although assessments are in progress regarding additional regulations for CMME in water and air. OSHA issued an emergency temporary standard covering both chemicals in 1973 and a final standard in 1974. This standard prohibits the operation in open vessels and requires exhaust fans, protective clothing and devices, and warning signs and labels.

The Consumer Product Safety Commission (CPSC) staff preliminarily determined in 1980 that BCME and CMME were not present in consumer products under CPSC jurisdiction. The Commission subsequently requested (45 FR 61344) public comment to verify the accuracy of its information. No comments were received on these chemicals. Pending the receipt of new information, the Commission plans no action on BCME or CMME.

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REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
No current action. No known presence in consumer products. (CPSC)		
CWA, 304(a): Water quality criteria published in final form, 11/28/80 (BCME and two other chloroalkyl ethers).		45 FR 231, p. 79318
CWA, 307: Deleted from hazardous substance list, 2/4/81.	Extremely short life in water and absence of data indicating BCME to be a water pollution problem. (EPA)	46 FR, p. 10723
RCRA, 3001-3004: Listed as a hazardous constituent of waste. Wastes known to contain BCME are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.33 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
FDA Bureau of Medical Devices, FD&CA: No regulations promulgated by FDA-BMD. (FDA)	Possible presence in dental restorative materials is listed, but exposure is considered incidental. (FDA)	
Protective clothing, respirator, hygiene, training and medical surveillance requirements for workers; exhaust fan requirements; open-vessel operations prohibited; contamination control requirements; sign requirements for areas; labeling requirements for containers. (OSHA)	Regulatory History: 5/10/73: Emergency Temporary Standards--protective clothing and hygiene requirements for workers; open-vessel operations restricted; engineering requirements. (OSHA)	29 CFR 1910.1008 (OSHA)

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REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products. (CPSC)		
RCRA, 3001-3004 Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates CMME as a hazardous constituent of waste and subjects wastes known to contain it to the same requirements. *Promulgated 5/19/80.		40 CFR 261 11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 42, p. 13536 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
FDA Bureau of Medical Devices, FD&CA: No regulations promulgated by FDA-BMD. (FDA)		
Protective clothing, respirator, hygiene, training and medical surveillance requirements for workers, exhaust fan requirements, open-vessel operations prohibited; contamination control requirements for areas; labeling requirements for containers. (OSHA)	Regulatory History: 6/19/73: Emergency Temporary Standards--protective clothing and hygiene requirements for workers; open-vessel operations restricted, engineering requirements. 2/22/74: Final Standard--current regulations effective. (OSHA)	29 CFR 1910.1006 (OSHA)

MONS 222725

CADMIUM AND CERTAIN CADMIUM COMPOUNDS

The evidence for the carcinogenicity of cadmium and certain cadmium compounds in experimental animals is sufficient; the evidence of carcinogenicity in humans is limited.[1]

Cadmium chloride, oxide, sulfate, and sulfide are carcinogenic in rats, causing local sarcomas after subcutaneous injection. Cadmium powder and cadmium sulfide produce local sarcomas in rats following intramuscular administration. Cadmium chloride and cadmium sulfate produce testicular tumors in mice and rats following subcutaneous administration.[1]

Studies have suggested that occupational exposure to cadmium in some form (possibly the oxide) increases the risk of prostate, respiratory, and genitourinary cancers in humans.[1,2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 11. Lyon, France: IARC, 1976, pp. 39-74.

Cadmium and certain cadmium compounds are widely used commercially in electroplating, alloys, soldering, plastic stabilizers, batteries, fungicides, and in phosphors and pigments for television tubes, inks, artists' colors, glass, ceramics, textiles, and paper.

The 1980 domestic production of cadmium and eight high-volume cadmium compounds was approximately 17 million lb, whereas an additional 2 million lb were imported. Cadmium oxide accounts for approximately 10 million lb (about 60 percent) of the total domestic production. An estimated 4-5 million lb/yr are used exclusively for jewelry and silversmithing. Plastic stabilizers utilize approximately 2 million lb/yr of cadmium and cadmium compounds.

Human exposure to cadmium and certain cadmium compounds occurs through inhalation and ingestion. OSHA estimates that 360,000 workers are potentially exposed to cadmium and its compounds. The entire population is exposed to low levels of cadmium in the diet because of the entry of cadmium into the food chain as a result of its natural occurrence. Tobacco smokers are exposed to an estimated 1.7 ug/cigarette. Cadmium is present in relatively low amounts in the earth's crust; as a component of zinc ores, cadmium may be released into the environment around smelters.

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The Consumer Product Safety Commission (CPSC) investigated the potential consumer hazard presented by materials painted with cadmium-containing inks. No cadmium was found in inks used in printed products. The CPSC staff indicates there is little cadmium found in other printed consumer products. The EPA has regulated cadmium and its compounds under the Clean Water Act (CWA), the Resource Conservation and Recovery Act, the Safe Drinking Water Act (SDWA), and the Toxic Substances Control Act; regulation is planned or proposed under the Clean Air Act. Under the CWA, water quality criteria for the protection of human health have been published that are identical to SDWA standards of 10 ug/l. The EPA has issued a Rebuttable Presumption Against Registration of cadmium-containing pesticides, but final action has not been taken. The Carcinogen Assessment Group includes cadmium oxide, cadmium sulfide, and cadmium sulfate on its list of potential carcinogens. The FDA limits leaching from pottery and enamel to 0.5 ug/ml of leaching solution for pottery (flatware) and small hollowware (0.25 ug/ml of leaching solution for large hollowware). The OSHA has adopted permissible exposure limits of 0.1 mg/m^3 as an 8-hour time-weighted average for fumes, 0.3 mg/m^3 as a ceiling for fumes, 0.2 mg/m^3 as an 8-hour time-weighted average for dust, and 0.6 mg/m^3 as a ceiling for dust. This standard was adopted by OSHA for toxic effects other than cancer. NIOSH has recommended a standard for cadmium and all cadmium compounds of 40 ug/m^3 as a time-weighted average, and 200 ug/m^3 as a 15-minute ceiling.

MONS 222727

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
FY81 investigation of materials printed with cadmium-containing inks. FY82--no current action. (CPSC)		
CWA, 301: Effluent guidelines for certain industrial categories address cadmium. Promulgated 4/8/74, 4/24/75, 11/6/75. Proposed 9/7/78, pretreatment portion promulgated.	Control established through enforcement of conditions of NPDES permits. Carcinogenicity was not considered in establishing guidelines.	40 CFR 413, 421, 440 (portions) 44 FR 176, p. 2
CWA, 304(a): Water quality criteria published in final form, 11/28/80.	Protection of human health (general toxicity) 10 ug/l.	45 FR 231, p. 79318
CWA, 307(a): Toxic pollutant effluent standards were proposed in 1973, but never promulgated.	Difficulty in identifying sources to extent required by law was cited in the 6/76 deferral.	OWRS, personal communication, 4/78
CWA, 311: Hazardous spill regulation establishing reportable quantity (100 lb, 454 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures. Addresses cadmium acetate, cadmium chloride.	40 CFR 117.3, 117.13
RCRA, 3001-3004: Designated as a toxic waste. Requires testing to determine presence. Wastes containing cadmium are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.	Concentration triggering compliance with requirements: 1.0 mg/l.	40 CFR 261.24
Designated as a hazardous constituent of waste (cadmium compounds, not otherwise specified).		40 CFR 261.33
RCRA, 4004: Prohibition on open burning, use on food croplands, or open dumping of municipal sludges designated hazardous. (CWA, 405, also authority.) Promulgated 9/13/79.	Prohibition on cropland use specifically addresses cadmium.	40 CFR 257
CWA, 405: Limitation for concentrations of cadmium and other toxic substances in sludges intended for use as soil conditioners under study.	On hold pending development of a policy regarding sludge; considering treatability and costs relevant to toxics therein.	OSW, personal communication, 4/82
SDWA, 1412: Revision of drinking water maximum contaminant level scheduled for proposal by 8/83.	Existing maximum contaminant level is 0.01 mg/l. Chronic toxicity, including possible carcinogenicity, will be addressed.	40 CFR 141.11 OGW, memorandum, 9/81
FIFRA, 6: RPAR issued addressing registered pesticides containing cadmium, 10/26/77.	Addresses cadmium carbonate and cadmium chloride. Proposed determination in developement.	42 FR 206, p. 56574

(Continued)

MONS 222728

Cadmium and Certain Cadmium Compounds (Continued)

REGULATIONS		
Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
CAA: Under assessment to determine if airborne cadmium presents a risk warranting regulation. Risk assessments are in varying stages of review.		OAQPS, personal communication, 9/80
TSCA, 8(a): Reporting rule requiring process and use data proposed.	Addresses cadmium oxide and cadmium sulfate.	45 FR 42, p. 13644 (EPA)
TSCA: Under review to determine if additional regulatory action may be warranted. No target for determination established.		
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)	Includes cadmium sulfide and cadmium sulfate. (EPA)	
FDA Bureau of Foods, FD&CA: Cadmium is an unavoidable contaminant present at low levels in most foods. Cadmium is not a permitted food or feed additive.	Limits leaching solutions from pottery and enamel to 0.5 mg. (FDA)	CFR 21 7417.02 (FDA)
FDA Bureau of Medical Devices, FD&CA: No regulatory action at present until a position is clarified on the use of colors in medical devices.		
Initiated a collaborative study with (industry, state, and university labs involved in food sample analyses to evaluate a dry-ash anodic stripping voltammetry method for detecting cadmium (lead can also be determined through this method) in March 1981.		
Participated in an international, collaborative 'hot-leach study' on leachable cadmium from cookware. Final results of this study will be presented at the fall meeting of the Association of Official Analytical Chemists.		
Participated in an international survey--'An International Assessment of Cadmium Pollution' in March 1981. The study was carried out by the Monitoring and Assessment Research Center, Chelsea College, University of London.		

(Continued)

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REGULATIONS		
Regulations and Other Action.	Effect of Regulations; Other Comments	Citation of Regulation
Colorado State University and the Denver Metropolitan Sewage Disposal District No. 1 have completed a joint contract study funded by EPA and FDA to evaluate the impact on cattle of incorporating sewage sludge into cattle feed. A final report was prepared. Survey and monitoring of grocery products for the presence of cadmium through the Total Diet Program continues. (FDA)		
PEL: 0.1 mg/m^3 8-hr TWA (fumes), 0.3 mg/m^3 ceiling (fumes), 0.2 mg/m^3 8-hr TWA (dust), 0.6 mg/m^3 ceiling (dust). (OSHA)	Regulatory History: 1951: Walsh-Healy, 0.1 mg/m^3 maximum allowable concentration. 8/27/75: OSHA Takeover Standard--current limit effective. [Standard adopted for toxic effects other than cancer.] (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 222730

CARBON TETRACHLORIDE

There is sufficient evidence for the carcinogenicity of carbon tetrachloride (CCl_4) in experimental animals; the evidence of carcinogenicity in humans is inadequate.[1]

Carbon tetrachloride is carcinogenic to mice and rats, producing liver tumors after administration by various routes. It also produced liver tumors in trout and hamsters following oral administration.[2]

Three case reports describe liver tumors associated with cirrhosis in humans exposed to carbon tetrachloride. A mortality study of laundry and drycleaning workers exposed to a variety of solvents suggested an excess of respiratory cancers, liver tumors, and leukemia.[1,2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1976, pp. 371-99.

CCl_4 is a colorless, highly volatile liquid with a strong ethereal odor similar to chloroform. The chemical mixes sparingly with water.

Most of the CCl_4 produced is used for the manufacture of Freons 11 and 12, but it is also used in industrial degreasing operations as a general solvent and as a grain fumigant.

The EPA reported 1977 domestic production as 410 million lb/yr and imports as 4 million lb/yr (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record). In 1979, nearly 730 million lb were manufactured; 5.4 million lb were imported; and 85 million lb were exported, which indicates a 100 percent increase in exports since 1978. Market reports for 1979 indicate a 5-10 percent decrease in consumption as a result of discontinued uses, such as for drycleaning and fire extinguishers. Because of the increasing concern about the general toxicity of CCl_4, a downward trend of consumption will probably continue.

Human exposure can occur by inhalation of fumes or skin absorption. Approximately 4500 workers are exposed during production processes, and 52,000 more workers are exposed during industrial use and consumption of the chemical. OSHA estimated that 3.4 million workers could be exposed to CCl_4 directly or indirectly. Under the authority of the Hazardous Substances Act, the Consumer Product Safety Commission has banned CCl_4 and CCl_4-mixtures

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as hazardous substances. This ban excludes unavoidable manufacturing residues of CCl_4 in other chemicals that do not, during use, result in an air concentration of > 10 ppm. The compound could be ingested as a contaminant of foods that were either fumigated with CCl_4 or ingested in water contaminated with CCl_4 (reported concentrations of 0.2-18 ppm). When used as a fumigant on stored grain, residue levels can range from 3.0 to 72 mg/kg. CCl_4 may also be ingested as a contaminant of the chlorine used in treating drinking water. CCl_4 has been found in human tissues in concentrations of 1-13 ppm.

An estimated 5 million lb/yr of CCl_4 are emitted during manufacture and processing, and approximately 60 million lb/yr are released as solvent emissions. The amount of CCl_4 emitted to the environment indicates that a large proportion of the general population has been exposed. EPA estimated that 8 million people living within 12.5 miles of manufacturing sites are exposed to average levels of 0.5 $\mu g/m^3$, with peaks of 1530 $\mu g/m^3$. CCl_4 has been found in 10 percent of 113 surveyed public water systems at mean concentrations ranging from 2.4 to 6.4 $\mu g/l$; in 45 percent of surface water supplies; and in 25 percent of groundwater samples, at concentrations of 0.001-0.40 mg/l. Estimates indicate that 19 million people might be exposed to CCl_4 through ambient air, 20 million through contaminated drinking water, and 2 million through contaminated soil or landfills.

The EPA has regulated disposal and related handling of CCl_4 under the Resource Conservation and Recovery Act, and effluents and spills under the Clean Water Act. The World Health Organization recommends that no detectable residues (limit, 0.01 ppm) be allowed on food or feed, but permits 50 mg/kg on cooked cereals. Under the Federal Hazardous Substances Act, FDA banned the use of CCl_4 in all products except where it was an unavoidable byproduct, which would not yield ambient levels greater than 10 ppm. OSHA has adopted a permissible exposure level in the workplace of 10 ppm as an 8-hour time-weighted average, a 25-ppm ceiling, and a 200-ppm maximum peak for 5 minutes in any 4-hour period. This standard was adopted by OSHA for toxic effects other than cancer.

MONS 222732

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Containers are banned except for manufacturing research (CPSC)		16 CFR 1500.17(a)(2) (CPSC)
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/record-keeping requirements. Promulgated 5/19/80. Also designated as a hazardous constituent of waste. Wastes known to contain CCl_4 are subject to the same requirements. Promulgated 5/19/80.		40 CFR 261.31, 261.33
CWA, 311: Hazardous spill regulation establishing reportable quantity (5000 lb) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals, and should result in reduction of accidental exposures.	40 CFR 117.3, 117.11
Proposed to reduce reportable quantity to 1000 lb. 7/28/80.	Based on carcinogenicity.	45 FR 133, p. 46094
CWA, 304(a): Water quality criteria published in final form. 11/28/80.		45 FR 231, p. 79318
CAA: Exposure assessment completed. Under consideration for pollutant regulation. No completion date scheduled.		Document, 5/80 for OAQPS
SDWA, 1412: ANPR regarding volatile organics published, 5/4/82.	Seeks comments regarding establishment of of maximum contaminant level, issuance of guidance, and other courses of action. Notice discusses risk estimates and other factors.	47 FR 43, p. 9350
FIFRA, 6: RPAR issued 10/16/80.	Based on oncogenicity; renal and hepatotoxicity. Comment period closed, 11/20/80. Comments review and risk/benefit assessment in progress.	45 FR, p. 68134
FAO/WHO recommendation that no detectable residues or permits, on any food or feed, but permit up to 50 ppm in cooked cereal products. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)	Detection limit in feed/feed 0.01 ppm. (EPA)	1975, cited by OPP and OAQPS (EPA)
FDA under the authority of FHSA banned the use of CCl_4 in all products except where it was an unavoidable by-product, which now does not yield amount levels greater than 10 ppm. (FDA)		
PEL: 10 ppm 8-hr TWA; 25 ppm ceiling; 200 ppm maximum peak for 5 min in any 4-hr period. (OSHA)	Regulatory History: Walsh-Healy, 50 ppm maximum allowable concentration. 5/27/71: OSHA Takeover Standard--current limit effective. [Standard adopted for toxic effects other than cancer.] (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 222733

CHLORAMBUCIL

There is sufficient evidence of carcinogenicity of chlorambucil both in humans and in experimental animals.[1] Chlorambucil is carcinogenic in rats and mice following intraperitoneal injection, producing lymphomas in rats, and lymphosarcomas, ovarian tumors, and lung tumors in mice.[1]

Excesses of acute leukemia were reported in a number of epidemiological studies of people treated with chlorambucil, either alone or in combination with other therapies, for both non-malignant and malignant diseases. Other cancers have also been associated with the use of chlorambucil and other agents. An excess of acute leukemia in association with chlorambucil was seen in a further study in which 431 previously untreated patients with polycythemia vera were given phlebotomy alone or chlorambucil with phlebotomy, and followed for a mean of 6.5 years. Of the 26 cases of acute leukemia that occurred, 16 were in the group receiving chlorambucil. The risk increased with increasing dose and time of treatment.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 26. Lyon, France: IARC, 1981, pp. 115-36.

Chlorambucil, a drug used to treat cancer, is a derivative of nitrogen mustard. This drug is primarily used as an antineoplastic agent for the treatment of lymphocytic leukemia, malignant lymphomas, follicular lymphoma, and Hodgkin's disease. The treatments are not curative, but they do produce some marked remissions. Chlorambucil has also been tested for treatment of chronic hepatitis and rheumatoid arthritis and for use as an insect chemosterilant.

All of the chlorambucil used in this country is imported from the United Kingdom. No data are available on the quantity imported, but the FDA reported that 6.4 million prescriptions were dispensed by retail pharmacies in 1980. Exposure in the United States would be limited to workers formulating the tablets or to patients receiving the drug.

The Carcinogen Assessment Group includes this chemical on its list of carcinogens. Therefore, the EPA regulates chlorambucil under the Resource Conservation and Recovery Act. The FDA approved chlorambucil for use as a prescription drug in 1969, noting restrictive approved clinical use for the treatment of chronic lymphocytic leukemia, malignant lymphomas, and Hodgkin's disease.

MONS 222734

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates chlorambucil as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
FDA Bureau of Drugs, FD&CA: Regulated as an approved prescription drug. Approved for use 9/30/60. (FDA)	Limits use to treatment of indicated treatments of chronic lymphocytic leukemia, malignant lymphomas, and Hodgkin's disease. As with other potent antineoplastic agents, the likelihood of these drugs being carcinogenic is not surprising; and their clinical usage recognize that risk by restrictive approved clinical indications. (FDA)	CFR 21, Subchapter D (FDA)

MONS 222735

CHLOROFORM

There is sufficient evidence for the carcinogenicity of chloroform in experimental animals.[1] Chloroform was tested in three experiments in mice and in one in rats by oral administration. It produced hepatomas and hepatocellular carcinomas in mice (gavage of a solution in olive oil), malignant kidney tumors in male rats, and tumors of the thyroid in female rats. In another series of experiments in male mice, chloroform administered orally (gavage in toothpaste or in arachis oil) produced benign and malignant kidney tumors.[1,2]

[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 401-27.

Chloroform is a highly volatile liquid that is slightly soluble in water. It is used primarily as an intermediate in the manufacture of fluorocarbon compounds, dyes, drugs, and pesticides; as a solvent in the extraction and purification of some antibiotics, vitamins, and flavors; as an industrial solvent in photography and drycleaning; and as a heat transfer medium. Its use as an anesthetic has been largely discontinued. At least one grain fumigant mixture contains chloroform with carbon disulfide, and it has been formulated with other ingredients for screw worm control on animals. The consumption pattern for 1974 was as follows: 51 percent for fluorocarbon refrigerants, 24 percent for plastics, and 25 percent for other uses.

During 1971-78, 230-350 million lb of chloroform were produced in the United States. Domestic production in 1977 was reported by EPA (public record) as 176 million lb and imports as 4 million lb. U.S. exports were estimated at 20 million lb in 1977. The annual growth rate for production was forecast at 7 percent.

The wide industrial use of chloroform potentially exposes 360,000 workers (OSHA). Chemists and support workers as well as hospital workers are believed to be at a higher risk than the general population.

Chloroform has been detected in the atmosphere at < 0.05-7.3 μg/m3 (< 0.01-15 ppb); in water at < 0.1-311 μg/l; in foodstuff at 50 ppm; in aquatic life at 7-1040 μg/kg (56-1040 μg/kg--molluscs; 7-851 μg/kg--fish) (dry weight); and in human tissue samples at 1-68 μg/kg of wet tissue.

MONS 222736

EPA criteria and promulgated regulations include (1) general rules for regulating hazardous spills, (2) water quality criteria document for the protection of human health and assessment regarding carcinogenicity, (3) restriction of use as a pesticide under the Rebuttable Presumption Against Registration, (4) regulations regarding handling and disposal of chloroform production waste material, and (5) the Safe Drinking Water Act in which EPA has promulgated a regulation (1980) regarding the removal of chloroform from drinking water and established a maximum contaminant level of 100 µg/l. Chloroform was banned by FDA from use in food, drugs, and cosmetics on June 29, 1976. Prior to being banned, chloroform had been approved for use in cough preparations, liniments, toothpastes, cosmetics, and toothache drops. OSHA adopted a ceiling level of 50 ppm (240 mg/m^3) for any 10-minute period. This standard was adopted by OSHA for toxic effects other than cancer.

MONS 222737

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
CWA, 304(a): Water quality criteria published in final form, 11/28/80.		45 FR 231, p. 79318
CWA, 311: Hazardous spill regulation establishing reportable quantity (1000 lb, 2270 kg) and imposing reporting requirement. Promulgated 8/29/79.	Not based on carcinogenicity.	40 CFR 117.3, 117.13
A proposal to reduce reportable quantity to 100 lb (45.4 kg), 7/9/80.	Based on carcinogenicity.	45 FR 133, p. 46094
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and reporting/recordkeeping requirements. Also designates chloroform as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
SDWA: Regulation regarding removal of chloroform and three other trihalomethanes. Promulgated 11/29/79. Establishes technology-based maximum contaminant level of 100 ug/l.		40 CFR 141.12
FIFRA, 6: RPAR issued 6/6/76.	Based on oncogenicity. Comment period closed, 7/23/76. Comment review and risk/benefit assessment continuing. (EPA)	41 FR, p. 10580 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
FDA Bureau of Drugs, FD&CA: Regulations promulgated which removed chloroform after 7/29/76 from drugs and cosmetics that had added chloroform as an ingredient.	To prevent the addition of chloroform to foods, thus completely eliminating risk. (FDA)	
FDA Bureau of Foods: No specific regulations or tolerances for dietary exposure, which results from the presence of chloroform as a natural constituent of foods. (FDA)		
PEL: 50 ppm (240 mg/m^3) ceiling. [Standard adopted for toxic effects other than cancer.] (OSHA)	Regulatory History: 1952: Walsh-Healy, 100 ppm maximum allowable concentration. OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 222738

CHROMIUM AND CERTAIN CHROMIUM COMPOUNDS

There is sufficient evidence for the carcinogenicity of chromium and certain chromium compounds both in humans and experimental animals.[1]

Calcium chromate is carcinogenic in rats when given by several routes, producing tumors at the sites of administration. Lead chromate, sintered calcium chromate, zinc chromate, strontium chromate, sintered chromium trioxide, lead chromate oxide and cobalt-chromium alloy produce sarcomas at the sites of their subcutaneous, intramuscular and/or intrapleural administration in rats; lead chromate also produced renal carcinomas following its intramuscular administration in rats.[2]

There is sufficient evidence for increased incidence of lung cancer among workers in the chromate-producing industry and possibly also among chromium platers and chromium alloy workers. There is also a suggestion of increased incidence of cancers at other sites. However, the chromium compounds responsible cannot be specified.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 23. Lyon, France: IARC, 1980, pp. 205-323.

Chromium is a steel-gray, lustrous metal. Chromium and its compounds are used in metal alloys such as stainless steel; as protective coatings on metal; on magnetic tapes; and as pigments for paints, cement, paper, rubber, composition floor covering, and other materials. These compounds are also used as oxidants in organic chemical synthesis, in photomechanical processing, in industrial water treatment, and in medicine as an astringent and antiseptic.

The aggregate 1980 domestic production of chromium and 10 important chromium compounds was over 752 million lb. Approximately 102 million lb were imported in 1980. Sodium dichromate is the highest volume chemical of all chromium compounds. Its domestic production in 1980 was approximately 554 million lb, and imports totaled approximately 71 million lb.

MONS 222739

Chromium (in the form of unidentified chromium compounds) is widely distributed in air, water, soil, and food. In trace amounts, the trivalent form may be an essential ingredient in our diet. The entire population is thus exposed to some of these compounds, but the levels of exposure vary. Hexavalent chromium compounds are of greater health concern than trivalent compounds; however, hexavalant compounds are readily reduced to trivalent forms in the presence of organic matter. The National Occupational Hazard Survey has estimated that 2.5 million workers are exposed to chromium and its compounds.

The Consumer Product Safety Commission (CPSC) staff is investigating the potential hazard to consumers from materials printed with chromium-containing inks. Although chromium was found in some inks used in printed products, the levels found in the final product did not warrant further activity. The CPSC staff indicated that there was little chromium found in other printed consumer products. The EPA has regulated chromium and its compounds under the Clean Water Act, the Resource Conservation and Recovery Act, and the Toxic Substances Control Act. The EPA maximum level permitted in drinking water is 0.05 mg/l (Safe Drinking Water Act, 1412). The EPA Carcinogen Assessment Group has included 10 chromium compounds on its list of carcinogens. NIOSH recommends respiratory devices, protective clothing, proper housekeeping, and training for persons potentially exposed to hexavalent chromium compounds. OSHA has adopted an 8-hour TWA exposure limit of 0.5 mg/m^3 for soluble chromium compounds and 1 mg/m^3 for chromium metal and insoluble compounds as an 8-hour time-weighted average. For chromic acid and chromates, the permissible exposure limit is 0.1 mg/m^3 ceiling. NIOSH recommends exposure limits of 1 ug/m^3 for carcinogenic hexavalent chromium compounds, 25 ug/m^3 as an 8-hour time-weighted average, and 50 ug/m^3 ceiling for other hexavalent chromium compounds.

MONS 222740

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (FDSC)		
Chromium		
CWA, 301. Effluent guidelines for certain industrial categories control chromium. Proposals for additional categories 7/2, 9/7, 10/75, and 12/21/79. Pretreatment part of one category. Promulgated 9/7/79.	Establishes control through NPDES permits. Carcinogenicity was not addressed in setting guidelines, although the generally higher risks associated with hexavalent chromium were considered.	40 CFR 409, 413, 415, 419, 420, 421, 424, 425, 426, 429 (portions)
	Proposed guidelines for textiles and leather tanning and finishing item, still seek comments on possible revisions of proposals in 12/80. All four are targeted for promulgation during mid- or late 1981.	44 FR 178, p. 48703 45 FR 179, p. 1 44 FR 210, p. 62704 46 FR 247, p. 189/6
CWA, 304(a)1: Water quality criteria published in final form, 11/28/80.	The health-based criterion is general toxicity (smallest 170 ug/l; hexavalent 50 ug/l).	45 FR 231, p. 79318
RCRA, 3001-3034: Designated as hazardous constituent of waste (chromium and compounds, not otherwise specified). Requires testing to determine presence of chromium. Wastes known to contain chromium are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.	Concentration triggering compliance requirements is 5.0 mg/l.	40 CFR 261.11
SDWA, 1412: Primary drinking water standard. Promulgated 12/24/75.	Existing maximum contaminant level is 0.05 mg/l, total chromium. Chronic toxicity and carcinogenicity of hexavalent chromium was considered in setting this level.	40 CFR 141.11
TSCA: Assessment completed, 5/78.	Problems not being addressed were determined to be workplace related. (EPA)	9TS, personal communication, 8/79 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
FDA Bureau of Foods: No specific regulations or tolerances for dietary exposure. No action has been taken on chromium as a carcinogen because the data available are not adequate to assess its carcinogenicity through dietary exposure.	Not applicable for dietary sources. Regulated uses are based on an assumption that "all" migration of chromium will occur.	Regulated under 21 CFR 175.105 for adhesives; 21 CFR 177.2600 for rubber products, and 21 CFR 175.300 for paper and paperboard in contact with dry food (FDA)
FDA Bureau of Medical Devices, FD&CA: No regulations have been promulgated. Testing the carcinogenic potential of chromium salts liberated by corrosion has been suggested to OC). (FDA)	Hexavalent compounds have not been regulated for us.. (FDA)	

(Continued)

MONS 222741

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Chromium (Continued) PEL 0.1 mg/m³ ceiling (chromic acid and chromates), 0.6 mg/m³ 8-hr TWA (soluble chromic or chromous salts), 1 mg/m³ 8-hr TWA (metal and insoluble salts). (OSHA)	Regulatory History 1952. Walsh-Healy, 0.1 mg/m³ maximum allowable concentrations (chromic oc d and chromates). 8/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)
Calcium Chromate See RCRA, 3001-3004, under chromium See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA) See recommended standard for chromium (VI). (NIOSH) See regulations for chromium. (OSHA)		29 CFR 1910.1000 (OSHA)
Chromium Acetate. CAA, 111: hazardous air(1) regulation establishing quantity (5000 lb, 850 kg) and imposing reporting requirements (8/28/79). See RCRA, 3001-3004 under chromium. (EPA)	Based on aquatic toxicity. Fosters greater care in handling and shipping chemicals. (EPA)	40 CFR 117.3, 117.1) (EPA)
Chromium Carbonate FY81 evaluation of consumer exposure to chromium from printed materials. FY82 evaluation of exposure to chromium from nonprinted consumer products. (CPSC) See RCRA, 3001-3004, under chromium. (EPA)		
Barium Chromate See RCRA, 3001-3004 See the Carcinogen Assessment Group statement under 2-acetylaminofluorene (EPA)		

(Continued)

MONS 222742

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Chromic Oxide:		
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 82, p. 13646 (EPA)
See RCRA, 3001-3004, under chromium. (EPA)		
See recommended standard for chromium (VI). (NIOSH)		
See regulations for chromium. (OSHA)		29 CFR 1910.1000 OSHA
Chromium Phosphate:		
See RCRA, 3001-3004. (EPA)		
Chromium Trioxide:		
See RCRA, 3001-3004, under chromium.		
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 82, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Lead Chromate		
See RCRA, 3001-3004, under chromium.		
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Potassium Chromate:		
See RCRA, 3001-3004, under chromium.		
CWA, 311: Hazardous spill regulation quantity (1000 lb, 454 kg) and imposing reporting requirements, promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures. (EPA)	40 CFR 117.3, 117.11
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 82, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
See recommended standard for chromium (VI). (NIOSH)		
See regulations for chromium. (OSHA)		29 CFR 1910.1000 (OSHA)

(Continued)

MONS 222743

REGULATIONS		
Regulations and Other Action	Effect of Regulations/ Other Comments	Citation of Regulation
Potassium Dichromate[1]		
See RCRA, 3001-3004, under chromium.		
CWA, 311: Hazardous spill regulation quantity (1000 lb, 454 kg) impacting reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reductions of accidental exposures.	40 CFR 117.4, 117.11 (EPA)
CWA, 301: Effluent guidelines address manufacture of potassium and sodium dichromate. Promulgated 3/12/74; amended subsequently.	Control of chromium through NPDES permits. (EPA)	40 CFR 415.120, 415.126, 415.170, 415.176
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
See recommended standard for chromium (VI). (NIOSH)		
See regulations for chromium. (OSHA)		29 CFR 1910.1000 (OSHA)
Sodium Chromate[1]		
See RCRA, 3001-3004, under chromium.		
CWA, 311: Hazardous spill regulation establishing reportable quantity (1000 lb, 454 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures. (EPA)	CFR 117.3, 117.11
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
See recommended standard for chromium (VI). (NIOSH)		
See regulations for chromium. (OSHA)		29 CFR 1910.1000 (OSHA)
Sodium Dichromate.		
See RCRA, 3001-3004, under chromium.		
CWA, 311: Hazardous spill regulation establishing reportable quantity (1000 lb, 454 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures.	40 CFR 117.3, 117.11 (EPA)
CWA, 301: Effluent guidelines address manufacture of potassium and sodium dichromate. Promulgated 3/12/74; amended subsequently.	Control of chromium through NPDES permits. (EPA)	40 CFR 415.120, 415.126, 415.170, 415.176 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

(Continued)

MONS 222744

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Sodium Dichromate (Continued) See recommended standard for chromium (VI). (AIOSH)		
See regulations for chromium. (OSHA)		29 CFR 1910.1000; 1050(a) (OSHA)
Strontium Chromate See RCRA, 3001-3004, under chromium.		
CWA, 311: Hazardous spill regulation establishing reportable quantity (1000 lb, 454 kg) and imposing reporting requirements. Promulgated 3/29/80.	Rec based on carcinogenicity. Lacqueres greater care in handling and shipping chemicals and should result in reduction of accidental exposures. (EPA)	40 CFR 117.3, 117.13
TSCA, 8(a): Reporting rule requiring process and use data, proposed 3/29/80. (EPA)		45 FR 67, p. 13644 (EPA)
See recommended standard for chromium (VI). (AIOSH)		
See regulations for chromium. (OSHA)		29 CFR 1910.1000 (OSHA)
Zinc Chromate Hydroxide: See RCRA, 3001-3004, under chromium.	Although this compound is not believed to be commercially available in the United States, knowledge that it is present in waste would afford a degree of control over it. (EPA)	
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 222745

COKE OVEN EMISSIONS

The overwhelming scientific evidence supports the finding that coke oven emissions are carcinogenic. This finding rests on epidemiological surveys as well as animal studies and chemical analyses of coke oven emissions. Coke oven workers have an increased risk of developing cancer of the lung and urinary tract. In addition, observations on animals and of human populations have shown that skin tumors can be induced by the products of coal combustion and distillation. Chemical analyses of coke oven emissions reveal the presence of a large number of known carcinogens as well as several agents known to enhance the effect of chemical carcinogens especially on the respiratory tract.[1]

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[1]Occupational Safety and Health Administration: Exposure to Coke Oven Emissions. Federal Register. Vol. 41(206), 1976, pp. 46742-90.

Coke oven emissions are a complex mixture of coal and coke particles, various vapors, gases, and tars that include polycyclic aromatic hydrocarbons. OSHA defines these emissions as the benzene-soluble fraction of total particulate matter present during the destructive distillation or carbonization of coal for the production of coke. Polycyclic aromatic hydrocarbons generally constitute about 2-3 percent of the total particulates and 3-6 percent of the benzene-soluble fraction.

According to the Bureau of Mines, 64 domestic plants operated about 13,000 coke ovens in 1970. Most of the coke produced in this country is used in the extraction of metals from their ores, especially iron. As a raw material, coke is used in the synthesis of calcium carbide and in the manufacture of graphite and electrodes.

Workers and those living in industrial areas where coke oven emissions occur have a high risk of exposure. Oven-charging operations and leakage around poorly sealed coke oven doors are the major sources of gaseous emissions from byproduct ovens. OSHA estimated that 10,000 coke oven workers are exposed to these emissions. Worker exposures to the benzene-soluble fraction were reported in air sampling studies to range from 0.40 mg/m^3 to 3.0 mg/m^3.

The OSHA standard for coke oven emissions, which was promulgated in 1977, established a permissible exposure limit of 150 $\mu g/m^3$ averaged over any 8-hour period. Under this standard, specific engineering and work practice control requirements became effective in January 1980.

MONS 222746

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
CAA: Coke oven emissions are under assessment to determine if regulations are warranted and feasible.		OAQPS, personal communication, 8/80. (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)	Addresses PAH constituent. (EPA)	
PEL: 150 ug/m^3 8-hr TWA. Additional Regulation: Protective clothing, training, and medical surveillance requirements for workers; respirator requirements where engineering and work-practice controls not sufficient or feasible; monitoring requirements; specific engineering-control requirements for charging and coking operations; specific work-practice control requirements for charging, coking, pushing, and maintenance and repair operation; sign requirements for regulated areas and areas where respirators required; labeling requirements for containers of contaminated clothing. (OSHA)	Regulatory History: 1969: Walsh-Healy, 0.2 mg/m^3 maximum allowable concentration of coal tar pitch volatiles. 8/27/71: OSHA Takeover Standard--0.2 mg/m^3, 8-hr TWA for coal tar pitch volatiles. 1/20/77: Final Standard--effective. 1/20/80: Specific engineering and work-practice control requirements effective. (OSHA)	29 CFR 1910.1029 (OSHA)

MONS 222747

p-CRESIDINE

When administered in the diet, p-cresidine was carcinogenic to Fischer 344 rats, causing increased incidences of carcinomas and papillomas of the urinary bladder in both sexes, increased incidences of olfactory neuroblastomas in both sexes, and of liver tumors in males. p-Cresidine was also carcinogenic in B6C3F1 mice, causing carcinomas of the urinary bladders in both sexes and hepatocellular carcinomas in females.[1]

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[1]National Cancer Institute. Bioassay of p-Cresidine for Possible Carcinogenicity. CAS No. 120-71-8. Technical Report Series No. 142. DHHS Publication No. (NIH) 78-1394. Bethesda, Maryland, 1979.

p-Cresidine is an aromatic amine that is insoluble in water but very soluble in organic solvents.

p-Cresidine appears to be used solely as an intermediate in the production of various azo dyes and pigments, including 11 dyes that are produced commercially in the United States.

The average annual production is not known, but one manufacturer has reported a production of about 590,000 lb during 1971-76. The EPA in 1977 reported 14 manufacturers and/or importers.

Human exposure to p-cresidine occurs primarily through inhalation of vapors or skin absorption of liquids, and this exposure is believed to be limited to workers in dye-production facilities. The Consumer Product Safety Commission stated that residual levels or trace impurities of p-cresidine may possibly be present in some dyes based on this chemical and in the final consumer product. The presence of p-cresidine, even as a trace contaminant, may be cause for concern. But no data are available describing the actual levels of impurities in the final product, the potential for consumer exposure, and the potential uptake.

Under the Toxic Substances Control Act, EPA has proposed a rule to require data reporting on the process and the use of p-cresidine. p-Cresidine is not currently regulated under the Food, Drug, and Cosmetic Act (FD&CA). The chemical is a potential contaminant in the FD&CA Red 40 (Allura Red), however, and regulatory action is pending.

MONS 222748

p-Cresidine

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)		45 FR 42, p. 13646 (EPA)
Not currently regulated under FHSCA. Regulation is pending due to its potential to contaminate FDSCA food -0. (FDA)		

MONS 222749

CUPFERRON

Cupferron, given in the diet, was carcinogenic to Fischer 344 rats, causing hemangiosarcomas, hepatocellular carcinomas, and squamous-cell carcinomas of the forestomach in males and females, as well as carcinomas of the auditory sebaceous gland in females. The chemical was also carcinogenic to B6C3F1 mice, causing hemangiosarcomas in males; and hepatocellular carcinomas, carcinomas of the auditory sebaceous gland, a combination of hemangiosarcomas and hemangiomas, and adenomas of the Harderian gland in females.[1]

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[1]National Cancer Institute. Bioassay of Cupferron for Possible Carcinogenicity. Technical Report Series No. 100. DHEW Publication No. (NIH) 78-1350. Bethesda, Maryland, 1978.

Cupferron, a laboratory chemical, is a crystalline solid that is very soluble in water and alcohol. This compound is an N-nitrosohydroxylamine derivative.

Cupferron is used to separate tin from zinc, and copper and iron from other metals. Cupferron also finds application as a quantitative reagent for vanadates and titanium and for the colorimetric determination of aluminum.

EPA has indicated that two companies currently produce cupferron in two regions. Domestic production has been estimated as 37,000 lb. Imports were not reported (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). The 1980 production of cupferron was reported to the U.S. International Trade Commission as greater than 5000 lb.

Human exposure to cupferron occurs mainly through ingestion or inhalation of the dust from the dry salt. Skin absorption is a secondary route of exposure. The potential for exposure appears to be greatest for those engaged in analytical or research studies involving use of the chemical. Workers may also be exposed to the compound during manufacturing processes.

The National Occupational Hazard Survey in 1974 estimated that 4000 workers were potentially exposed to cupferron.

Cupferron is currently proposed for regulation by EPA under the TSCA, 8(a), reporting rule, which would provide detailed production and marketing data.

MONS 222750

Cupferron

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/30. (EPA)	could provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)

MONS 222751

CYCASIN

There is sufficient evidence for the carcinogenicity of cycasin in experimental animals.[1] Cycasin was carcinogenic in five animal species, inducing tumors in several organs. When administered in the diet, it was carcinogenic to the rat, guinea-pig and fish. Administered by gavage, it was carcinogenic to the hamster. It was also active in single-dose experiments and following prenatal exposure. The carcinogenicity of its metabolite, methylazoxymethanol, has been demonstrated in the rat and hamster and that of a closely related synthetic substance, methylazoxymethanol acetate, in the rat.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 1. Lyon, France: IARC, 1972, pp. 157-63.

Cycasin occurs naturally in the seeds, roots, and leaves of cycad plants, which are found in the tropical and subtropical regions of the world. Nuts from the cycads are used to make chips, flour, and starch.

Cycasin is not produced or used commercially. The major potential exposure is the ingestion of the foods containing cycasin. It is estimated that about 50-55 percent of the inhabitants of Guam are potentially exposed (50,000-60,000 persons) to cycasin. Wastewater from the preparation of the cycad nuts contains large amounts of cycasin and represents a potential secondary exposure source.

The EPA regulates cycasin under the Resource Conservation and Recovery Act. Cycasin is designated as a hazardous constituent of waste, and wastes known to contain it are subject to handling and report/recordkeeping requirements.

Cycasin

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004: Designates cycasin as a hazardous constituent of waste, and subjects wastes known to contain it to handling and report/recordkeeping requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11 (EPA)

MONS 222752

CYCLOPHOSPHAMIDE

There is sufficient evidence for the carcinogenicity of cyclophosphamide both in humans and in experimental animals.[1] Cyclophosphamide was carcinogenic in rats following administration in drinking water and intravenous injection, and in mice following subcutaneous injection. Dosages were comparable to those used in clinical practice. The chemical produced benign and malignant tumors at various sites, including bladder tumors in the rat.[2]

Five epidemiological studies are available in which persons treated with cyclophosphamide for a variety of medical conditions were compared with similarly afflicted controls. These studies consistently demonstrate an excess of various neoplasms and leukemias in the treated groups, although the number in all five studies was small.[1]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 26. Lyon, France: IARC, 1981, pp. 165-202.

Cyclophosphamide, a chemical related to the nitrogen mustards, is a widely used synthetic antineoplastic drug that is soluble in water.

Cyclophosphamide is used in the treatment of malignant lymphoma, multiple myeloma, leukemias, and other malignant diseases. Cyclophosphamide has been tested as an insect chemosterilant and for use in the chemical shearing of sheep.

Cyclophosphamide is not produced in the United States. It is produced in the Federal Republic of Germany and exported to the United States where one company has formulated and marketed the drug since 1959. U.S. sales are approximately 1300 lb annually.

The FDA estimates that 200,000-300,000 patients per year are treated with cyclophosphamide, which is administered orally and through injection. The adult dosage is usually 1-5 mg/kg of body weight daily or 10-15 mg/kg administered intravenously every 7-10 days.

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The FDA requires an insert in the drug package to warn of secondary malignancies that may occur several years after treatment with cyclophosphamide has ended. The FDA is investigating the use of cyclophosphamide in nonmalignant diseases. EPA regulates this chemical under the Resource Conservation and Recovery Act.

Cyclophosphamide

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004: Designated as a hazardous constituent of waste. Any waste known to contain cyclophosphamide is subject to handling and report/recordkeeping requirements. Promulgated 5/19/80. See Carcinogen Assessment Group treatment under 2-acetylaminofluorene. (EPA)		40 CFR 261 33 (EPA)
FDA Bureau of Drugs, FD&CA: Prescription drug use for treatment of neoplasias. The package has clear warning of the induction of secondary malignancies that may occur several years after treatment has been discontinued. (FDA)	The physician is provided with information required for a benefit versus risk assessments on each patient. Use in nonmalignant diseases is investigational but could allow exposure of very young children, young adults, and adults to doses that might induce future malignancies. [illegible] permit reduction of exposures to this danger may be advisable. (FDA)	Crk 21, Subchapter D (FDA)

MONS 222754

2,4-DIAMINOANISOLE SULFATE

There is sufficient evidence for the carcinogenicity of 2,4-diaminoanisole sulfate in experimental animals.[1,2] In Fischer 344 rats, dietary administration of the technical-grade 2,4-diaminoanisole sulfate increased the incidence of malignant tumors of the skin and the associated glands, and of malignant thyroid tumors in each sex. In B6C3F1 mice, dietary administration of 2,4-diaminoanisole sulfate induced thyroid tumors in each sex. Fischer 344 female rats exposed in the feed to technical-grade 2,4-diaminoanisole sulfate developed tumors of the thyroid, mammary, clitoral, and pituitary glands.[2,3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 27. Lyon, France: IARC, 1982, pp. 191-98.

[3]National Cancer Institute. Bioassay of 2,4 Diaminoanisole Sulfate for Possible Carcinogenicity. Technical Report Series No. 84. DHEW Publication No. (NIH) 78-1334. Bethesda, Maryland, 1978.

2,4-Diaminoanisole sulfate (2,4-DAA sulfate) is a phenylenediamine derivative that is soluble in water and ethanol.

The principal use of 2,4-DAA sulfate is as a component of oxidation ("permanent") hair- and fur-dye formulations. Approximately three-quarters of the hair-dye formulations in 1978 contained 2,4-DAA or 2,4-DAA sulfate. These two compounds are also used as intermediates for the production of C.I. Basic Brown 2, used to dye furs, acrylic fibers, cotton, wool, nylon, polyester, leather, suede, and as an ingredient of shoe polishes. The Consumer Product Safety Commission (CPSC) reported that currently the chemical is not used in consumer products under CPSC jurisdiction. It is, however, used as a component of cosmetic products under FDA jurisdiction.

Commercial production of 2,4-DAA sulfate was first reported in 1967 to the U.S. Tariff Commission. The estimated annual domestic usage of this compound in 1977 was 30,000 lb. The CPSC indicated that 2,4-DAA sulfate is no longer produced in commercial quantities or imported. However, EPA has reported two producers and importers of 2,4-DAA sulfate. No domestic production data were available. Imports of 2,4-DAA sulfate were estimated as 350 lb (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). NCI stated that production of 2,4-DAA sulfate was not

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reported to the U.S. International Trade Commission for 1979-1980; however, the 1982 Directory of Chemical Producers indicates that one U.S. company currently produces the chemical. The one company listed stated they no longer produce this chemical on a regular basis according to the information received by the CPSC.

Human exposure to 2,4-DAA sulfate may occur through skin absorption at chemical- and dye-production facilities. Dermal contact also occurs for persons using hair dyes containing 2,4-DAA sulfate. The maximum concentration of the compound in hair-dye preparations is about 1.5 percent. The National Occupational Hazard Survey in 1974 made no estimate of the potential worker exposure to 2,4-DAA sulfate (NIOSH). However, the survey estimated 7200 exposures for 2,4-DAA. NCI states that substantial exposure of the population to 2,4-DAA sulfate is questionable.

Under 21 CFR 748.18, FDA regulates 2,4-DAA sulfate as a component of hair dyes. Under 44 FR 5952, FDA requires a warning label on cosmetic products containing 2,4-DAA sulfate. However, a September 1980 court decision stayed the FDA regulation, pending a determination of the potential human health risk from dermal exposure to this compound. FDA is continuing its consideration of the matter.

2,4-Diaminoanisole Sulfate

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
2,4-Diaminoanisole sulfate is produced in small enough quantities that it is of low priority regulatory interest to EPA. (EPA)		
Regulated as a cosmetic ingredient product, as coal-tar hair dyes pose a risk of cancer.		21 CFR 748.18
A warning label required on cosmetic products containing chemical, but this regulation was stayed in a 9/22/80 court decision. (FDA)		44 FR, p. 5952 (Stayed, pending determination by FDA of risk from dermal exposure.) (FDA)

MONS 222756

2,4-DIAMINOTOLUENE

There is sufficient evidence for the carcinogenicity of 2,4-diaminotoluene in experimental animals.[1] 2,4-Diaminotoluene was carcinogenic in rats after administration in the diet, producing hepatocellular carcinomas, and after subcutaneous injection, inducing local sarcomas.[2] In another bioassay, 2,4-diaminotoluene administered in the feed of F344 rats induced hepatocellular carcinomas or neoplastic nodules in both males and females and carcinomas or adenomas of the mammary gland in females. The test chemical also produced hepatocellular carcinomas in female B6C3F1 mice.[3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 16. Lyon, France: IARC, 1978, pp. 83-95.

[3]National Cancer Institute. Bioassay of 2,4-Diaminotoluene for Possible Carcinogenicity. Technical Report Series No. 162. DHEW Publication No. (NIH) 79-1718. Bethesda, Maryland, 1979.

2,4-Diaminotoluene is a water-soluble crystalline solid.

Most of the 2,4-diaminotoluene is used as an intermediate to produce toluene diisocyanate, which is used in the production of polyurethane. Small amounts are used in the production of dyes for textiles, leathers, furs, wood, and biological stains. 2,4-Diaminotoluene is used in hair-dye formulations, but FDA has specific labeling requirements. 2,4-Diaminotoluene may be formed on hydrolysis of toluene diisocyanate-based polyurethanes (e.g., polyurethane adhesives).

2,4-Diaminotoluene has been produced commercially in the United States for over 50 years. Approximately 14 companies currently produce and import this chemical. Domestic production for 1980 has been estimated at 216 million lb. Imports in 1980 were approximately 4000 lb. Domestic production has increased 800 percent since 1967, with only 1978 production showing a decline.

Human exposure to 2,4-diaminotoluene occurs by skin contact and less frequently by inhalation. Despite a long high-volume production history, there are no data available on the number of people exposed during the production or use of 2,4-diaminotoluene. More than 99 percent of the 2,4-diaminotoluene produced in the United States is used captively to produce toluene diisocyanate, usually at the same site; hence, exposure potential is minimized. Air emissions from production are believed to be insignificant. Water solubility of 2,4-diaminotoluene may contaminate industrial wastewater discharges and result in exposure of the general population.

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The Consumer Product Safety Commission staff stated that it is possible that residual traces of 2,4-diaminotoluene are present in some dyes based on this chemical, and in the final consumer product. The presence of 2,4-diaminotoluene, even as a trace contaminant, may be a cause for concern. However, data describing the actual levels of impurities in the final product and the potential for consumer exposure are currently lacking. The EPA regulates toluenediamine (isomers not specified) under the Resource Conservation and Recovery Act.

2,4-Diaminotoluene

REGULATIONS

Regulations and Other Actions	Effect of Regulations/ Other Comments	Citation of Regulation
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues of toluenediamine (isomers) not specified) in excess of 1000 kg to handling and reporting/recordkeeping requirements. Designates toluenediamine as a hazardous constituent of waste. (EPA)	Based on chronic toxicity. Fosters greater care in handling of chemical wastes. (EPA)	40 CFR 261.11, 261.33 (EPA)
Regulatory Authority: FD&CA 601(a). (FDA)	Coal tar hair dyes may not be considered adulterated under the Act as long as they bear appropriate warning labels. (FDA)	

MONS 222758

DIBENZ(a,h)ACRIDINE

There is sufficient evidence of the carcinogenicity of dibenz-(a,h)acridine (DB(a,h)AC) in experimental animals.[1] In mice, painting with DB(a,h)AC induced skin tumors. Subcutaneous administration to mice induced local sarcomas and increased the incidence of lung tumors. Intravenous administration increased the incidence of multiple lung tumors.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1973, pp. 247-53.

DB(a,h)AC belongs to a class of organic chemicals known as heterocyclic compounds.

The compound has limited application but it may be used in biochemical and cancer research. DB(a,h)AC has been detected in air pollution emitted from coal combustion, petroleum refineries, incinerators, and automobile exhausts. No commercial production has ever been reported.

Based on the occurrence of this compound in polluted air, widespread inhalation exposure appears likely for both the occupational and the general population.

The monitoring of several air pollution sources has detected DB(a,h)AC levels of 17 mg/1000 m^3 in domestic coal combustion stack effluents, < 0.12 mg/1000 m^3 in petroleum refinery incinerator effluents, and 0.01 mg/1000 m^3 in air polluted by coal-tar pitch. DB(a,h)AC occurs in cigarette smoke condensate at concentrations up to 0.01 µg/100 cigarettes.

EPA regulates DB(a,h)AC under the Resource Conservation and Recovery Act and the Clean Water Act. OSHA indirectly limits exposure to DB(a,h)AC by requiring that occupational exposure to coal-tar pitch volatiles not exceed a time-weighted average of 0.2 mg/m^3 over an 8-hour period.

MONS 222759

Dibenz[a,h]acridine

REGULATIONS		
Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Action
CWA, 304(a): Water quality criteria for PAHs published in final form, 11/28/80. Total PAH approach, no indicator nor surrogate		45 Fd 23.1, p. 79318
RCRA, 3001-3004: Designates this compound as a hazardous constituent of waste, and subjects wastes known to contain it to handling and report/record-keeping requirements unless exempted by EPA. Promulgated 5/19/80. See Carcinogenic Assessment Group statement under 2-acetylaminofluorene (EPA)		40 CFR 261.11 (EPA)
PEL: 0.2 mg/m³ 8-hr TWA (coal tar pitch volatiles) (limited coverage). (OSHA)	Regulatory History. 6/21/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR (910.1000, 1916.1002 (OSHA)

MONS 222760

The evidence of carcinogenicity of dibenz(a,j)acridine (DB(a,j)AC) in experimental animals is considered sufficient.[1] DB(a,j)AC induced skin tumors in mice following topical application and produced local sarcomas at the highest dose tested following subcutaneous administration. It increased the incidence of lung tumors after subcutaneous administration.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1973, pp. 254-59.

DB(a,j)AC is a heterocyclic organic compound.

DB(a,j)AC is used in biochemical and toxicological research. No commercial production of this chemical for other purposes has been reported. Based on the environmental occurrence of DB(a,j)AC, there is a potential of inhalation exposure for the general population.

DB(a,j)AC has been detected in air pollutants from coal combustion and petroleum refinery incinerators, from automobile exhausts, and from cigarette smoke. DB(a,j)AC occurs in domestic coal combustion stack effluents at concentrations of 2 mg/1000 m^3, in petroleum refinery incinerator effluents at concentrations of 0.15 to 1.8 mg/1000 m^3, and in air polluted by coal-tar pitch at a concentration of 0.001 mg/1000 m^3. DB(a,j)AC also occurs in cigarette smoke condensate at levels of 0.27 ug/100 cigarettes and in motor exhaust at levels up to 300 ug/kg. In addition, trace amounts have been detected in the average U.S. urban atmosphere.

Both EPA and OSHA regulate DB(a,j)AC. The EPA regulates it under the Clean Water Act (CWA) and the Resource Conservation and Recovery Act (RCRA). Under the CWA, EPA has published a water quality criteria document for the protection of human health for PAHs, and under RCRA, EPA has designated DB(a,j)AC a hazardous constituent of waste. OSHA has indirectly limited exposure to DB(a,j)AC by requiring that occupational exposure to coal tar pitch volatiles not exceed a time-weighted average of 0.2 mg/m^3 over an 8-hour period.

MONS 222761

Dibenz[a,j]acridine

REGULATION		
Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
CWA 304(a): Water quality criteria for PAHs published in final form, 11/28/80 Total PAH concentration, an indicator nor surrogate.		45 FR 231, p. 79318
RCRA, 3001-3004: Designates this compound as a hazardous constituent of waste, and subjects wastes known to contain it to handling and report/recordkeeping requirements. Promulgated 8/19/80.		40 CFR 261.11 (EPA)
See Carcinogen Assessment Group statement for 7-methylbenz[a]anthracene. (EPA)		
PEL: 0.2 mg/m³ 8-hr TWA (coal tar pitch volatiles) [limited coverage]. (OSHA)	Regulatory History: 8/21/71: OSHA Takeover Standards--current limit effective. (OSHA)	29 CFR 1910.1000, 1910.1002 (OSHA)

MONS 222762

There is sufficient evidence of the carcinogenicity of dibenz-(a,h)anthracene (DB(a,h)A) in experimental animals.[1] DB(a,h)A has produced tumors by different routes of administration in mice, rats, guinea pigs, frogs, pigeons and chickens. It has both local and systemic carcinogenic effects. On oral administration in food, it produced tumors of the forestomach in the mouse; intratracheal administration to hamsters produced lung tumors. In repeated mouse skin painting (in several mouse strains), DB(a,h)A and benzo(a)pyrene (B(a)P) appeared to be equally effective. In a dose-response study (with C3H mice) on subcutaneous carcinogenicity with DB(a,h)A, B(a)P and 3-methylcholanthrene (MC), DB(a,h)A was shown to be effective at a lower dose than that effective for B(a)P or for MC; its latent period, however, was longer. DB(a,h)A induced local sarcomas and increased the incidence of lung adenomas following a single subcutaneous injection in newborn mice at dose levels which were ineffective with MC.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1973, pp. 178-96.

DB(a,h)A is a member of the class of chemicals known as polycyclic aromatic hydrocarbons (PAHs), which are formed as a result of incomplete combustion of organic compounds.

There is no reported commercial application for this compound. DB(a,h)A occurs in cigarette smoke condensate; gasoline engine exhaust; soot; smoke; coke and coal tars; various smoked, barbecued, or charcoal-broiled meats and fish; and certain vegetables and vegetable oils. EPA lists one producer for DB(a,h)A, but there are no data on its production.

Exposure to this chemical would occur through inhalation or ingestion. Workers near burning or energy-producing operations are more likely to be exposed to DB(a,h)A than the general public. The highest concentrations of DB(a,h)A have been reported in airborne soot and in coal tar containing 64-705 mg/1000 m^3 and 230 mg/kg, respectively.

DB(a,h)A has a widespread presence in the environment, particularly in ambient air, but it is also found in soils and water. Therefore, a large segment of the population could be potentially exposed to DB(a,h)A from environmental sources as well as from foods and cigarette smoke.

MONS 222763

There have been few attempts to develop exposure standards for PAHs, either individually or as a class. However, NIOSH has recommended a workplace standard for coal tar products of 0.1 mg/m^3 as a time-weighted average for a 10-hour shift in a 40-hour workweek. OSHA indirectly limits exposure to DB(a,h)A by requiring that occupational exposure to coal tar pitch volatiles not exceed 0.2 mg/m^3 over an 8-hour period as a time-weighted average. EPA regulates DB(a,h)A under the Resource Conservation and Recovery Act, and has proposed a reporting rule requiring process and use data under TSCA, 8(a).

Dibenz(a,h)anthracene

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
CWA, 304(a): Water quality criteria for PAHs published in final form, 11/28/80. Total PAH addressed; no indicator nor surrogate.		45 FR 231, p. 79318
RCRA, 3001-3004: Subjects waste products, off-specification batches, and sb.ll residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates this compound as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	40 CFR 261.11
TSCA, 8(a): Proposed reporting rule requiring use data, published 2/29/80.	Would, if promulgated, permit a basis for estimating exposure. (EPA)	45 FR 12, p. 13646 (EPA)
See Carcinogen Assessment Group statement for 2-acetylaminofluorene (EPA)		
PEL: 0.2 mg/m^3 8-hr TWA (coal tar pitch volatiles) [limited coverage]. (OSHA)	Regulatory History: 6/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 222764

7H-DIBENZO(c,g)CARBAZOLE

There is sufficient evidence of the carcinogenicity of 7H-dibenzo(c,g)carbazole (7H-DB(c,g)C) in experimental animals.[1] 7H-DB(c,g)C was shown to be carcinogenic in the mouse, rat, hamster, and possibly in the dog. It had both a local and a systemic carcinogenic effect. Following oral administration to the mouse, forestomach tumors and hepatomas occurred; intratracheal administration to hamsters produced tumors of the respiratory tract. In comparison with benzo(a)-pyrene, 7H-DB(c,g)C appears to be a stronger respiratory tract carcinogen for the hamster.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1973, pp. 260-68.

7H-DB(c,g)C is a member of the class of organic chemicals known as heterocyclic compounds. This chemical is soluble in most organic solvents.

7H-DB(c,g)C may be formed by incomplete combustion and has been found in cigarette tar in concentrations of 0.07 ug/100 cigarettes. It is produced as a research chemical.

No case reports or epidemiologic studies have been made on human exposure to 7H-DB(C,g)C. But because this chemical has been detected in cigarettes, some persons, especially smokers, may be exposed.

EPA regulates 7H-DB(c,g)C under the Resource Conservation and Recovery Act. In addition, OSHA indirectly limits exposure to 7H-DB(c,g)C by requiring that occupational exposure to coal tar pitch volatiles not exceed 0.2 mg/m^3 over an 8-hour time-weighted average.

MONS 222765

REGULATIONS

Regulations and Other Actions	Effect of Regulation Other Comments	Citation of Regulation
CWA, 304(a). Water quality criteria for PAHs published in final form, 11,28/80. Total PAH approaches, no indicator nor surrogate.		45 FR 2311, p. 79318
RCRA, 3001-3004 Designates this compound as a hazardous constituent of waste, and subjects wastes known to contain it to handling and reporting/recordkeeping requirements unless exempted by EPA. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylamin.fluorene. (EPA)	Regulation based on reports of carcinic hazard. (EPA)	40 CFR 261.11 (EPA)
PEL. 0.2 mg/m³ 8-hr TWA (coal tar pitch volatiles) [limited coverage]. (OSHA)	Regulatory History 6/21/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000, 1910 1002 (OSHA)

MONS 222766

DIBENZO(a,h)PYRENE

There is sufficient evidence for the carcinogenicity of dibenzo-(a,h)pyrene (DB(a,h)P) in experimental animals.[1] Carcinogenic effects of DB(a,h)P were demonstrated following repeated skin painting in mice and injections in mice and rats. In the skin painting experiment, DB(a,h)P was less active than benzo(a)pyrene.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1973, pp. 207-14.

DB(a,h)P is a polycyclic aromatic hydrocarbon (PAH) that is insoluble in water.

DB(a,h)P is not deliberately produced; it is a combustion product. The occurrence of DB(a,h)P in the environment is not well documented; however, it has been detected in minute amounts in coal tar pitch, engine exhaust, and in cigarette tar.

In 1974, the National Occupational Hazard Survey estimated that approximately 210,000 workers were exposed to PAHs from asphalt volatiles, coal tar pitch volatiles, and coke oven emissions, all of which may contain DB(a,h)P. An unspecified additional number of workers may be exposed to DB(a,h)P in the products of combustion from fuel oil, diesel fuel, kerosene, and wood.

The EPA has included DB(a,h)P on the Carcinogen Assessment Group list of carcinogens, and EPA regulates this chemical under the hazardous waste disposal rule of the Resource Conservation and Recovery Act. OSHA indirectly limits exposure to DB(a,h)P by requiring that occupational exposure to coal tar pitch volatiles not exceed 0.2 mg/m^3 over an 8-hour period as a time-weighted average.

MONS 222767

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
CWA, 304(a): water quality criteria for polynuclear aromatic hydrocarbons published in final form, 11/28/80 Total PAH concentration, an indicator nor surrogate.		45 FR 231, p 79318
RCRA, 3001-3004: Designates this compound as a hazardous constituent of waste, and subjects wastes known to contain it to handling and report/recordkeeping requirements unless exempted by EPA. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)	Regulation based on reports of chronic hazard. (EPA)	40 CFR 261.33 (EPA)
PEL: 0.2 mg/m^3 8-hour TWA (coal tar pitch volatiles) (limited coverage). (OSHA)	Regulatory History: 8/.1/71: OSHA Takeover Standards--current limit effective. (OSHA)	29 CFR 1910.1000, 1910.1002 (OSHA)

MONS 222768

DIBENZO(a,i)PYRENE

There is sufficient evidence of the carcinogenicity of dibenzo-(a,i)pyrene (DB(a,i)P) in experimental animals.[1] Subcutaneous injections of DB(a,i)P resulted in a rapid appearance of local sarcomas in the hamster and the mouse. The smallest single dose which produced sarcomas in mice was 50 ug. Repeated skin application in mice was also effective, but DB(a,i)P was less active than benzo(a)pyrene.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1973, pp. 215-23.

DB(a,i)P is a polycyclic aromatic hydrocarbon (PAH) that is insoluble in water.

DB(a,i)P is not commercially produced but is found as a combustion product. DB(a,i)P is the byproduct of poorly controlled combustion encountered in coal or refuse burning, in the exhaust of diesel-powered vehicles, and in coke oven emissions. It has also been detected in tobacco smoke at concentrations of 0.002-0.27 ug/100 cigarettes and in smoked foods.

In 1974, the National Occupational Hazard Survey estimated that about 210,000 workers were exposed to PAHs from asphalt and coal tar pitch volatiles and from coke oven emissions, all of which contain DB(a,i)P.

The EPA has included DB(a,i)P on the Carcinogen Assessment Group list of carcinogens. Under the Resource Conservation and Recovery Act, this chemical has been included in the hazardous waste disposal rule. OSHA indirectly limits exposure to DB(a,i)P by requiring that occupational exposure to coal tar pitch volatiles not exceed 0.2 mg/m^3 over an 8-hour period as a time-weighted average.

MONS 222769

Dibenz[a,i]pyrene

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates dibenz[a,i]pyrene as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261.33
CWA, 304(a): Water quality criteria document for polynuclear aromatic hydrocarbons published in final form, 11/28/80. Total PAH addressed; no indicator nor surrogate.		45 FR 231, p. 79318 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
PEL: 0.2 mg/m³ 8-hr TWA (coal tar pitch volatiles) [limited coverage]. (OSHA)	Regulatory History: 8/21/71. OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000, 1910.1002 (OSHA)

MONS 222770

There is sufficient evidence for the carcinogenicity of 1,2-dibromo-3-chloropropane (DBCP) in experimental animals.[1] DBCP administered in corn oil by gavage to Osborne-Mendel rats and B6C3F1 mice was carcinogenic, producing squamous-cell carcinomas of the forestomach in both sexes and carcinomas of the mammary gland in female rats.[2] In an inhalation experiment, DBCP was carcinogenic in male and female F344 rats, inducing increased incidence of nasal cavity tumors and tumors of the tongue in both sexes, and cortical adenomas in the adrenal gland of females.[3] DBCP was also carcinogenic in B6C3F1 mice of both sexes, producing increased incidence of nasal cavity tumors and lung tumors.[4]

[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 83-86.
[3]National Toxicology Program. Carcinogenesis Bioassay of 1,2-Dibromo-3-Chloropropane (Cas No. 96-12-8) in F344 Rats and B6C3F1 Mice (Inhalation Study). Technical Report Series No. 206. NIH Publication No. 82-1762. NTP, Research Triangle Park, N.C., and Bethesda, Maryland, 1982.
[4]National Cancer Institute. Bioassay of Dibromochloropropane for Possible Carcinogenicity. Technical Report Series No. 28. DHEW Publication No. (NIH) 78-828. Bethesda, Maryland, 1978.

DBCP is a dark amber to dark brown liquid that is slightly soluble in water.

DBCP has been registered by EPA as a soil fumigant to control nematodes during plant growth that include field crops, vegetables, fruits and nuts, greenhouse and nursery crops, and turf. In 1974, U.S. farmers used 9.8 million lb of DBCP on crops. In 1977, 831,000 lb were used in California alone, mostly on grapes and tomatoes. The Agency, however, suspended all registrations of end-use products during 1977, except for use on pineapples in Hawaii.

DBCP was first produced commercially in the United States in 1955. The annual production estimated during 1974 and 1975 was 18-20 million lb. In 1979, EPA prohibited the sale, distribution, or movement of DBCP in commerce for all suspended uses. No data are currently available on the amount of DBCP produced in the United States nor in existing stockpiles.

MONS 222771

Human exposure to DBCP can occur by inhalation and skin contact, primarily during the pesticide's manufacture, formulation, and storage. According to OSHA, approximately 17,500 workers have been exposed to the chemical. Pesticide applicators as well as farm workers were the high risk exposure groups during formulation and application. Exposure of the general population through soil is considered negligible because DBCP is moderately volatile and is degraded in moist soil. According to a 1977 EPA report, human dietary exposure to DBCP was estimated to be in the range of 2.2 to 61.0 x 10^{-6} mg/kg/day. The chemical has been detected in carrots (0.009-1.5 mg/kg) and in radishes (0.03-0.194 mg/kg) that were treated with DBCP.

On October 29, 1979, the EPA suspended, unconditionally, all DBCP-containing products for end uses except for use on pineapples in Hawaii. It further issued a notice of intent to cancel unconditionally all remaining end uses of all registered DBCP-containing pesticide products. The FDA established maximum residue levels of 1.5 mg/l in raw milk and 0.05 mg/kg in all other raw agricultural commodities. The current OSHA standard for DBCP established in April 1978 is 1 ppb (0.01 mg/m^3) as an 8-hour time-weighted average permissible exposure limit for workers. In addition, this standard requires personal protective equipment, training, medical surveillance, signs and labeling, and engineering controls.

MONS 222772

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current attic). No known presence in consumer products under CPSC jurisdiction. (CPSC)		
FIFRA, 6: Notice of intent to cancel all uses and suspension order affecting all uses except on pineapples in Hawaii, published 10/29/79. Final action after APAR, except for hearings now in progress.	An estimated 7000 cancers/year could result from use of DBCP as registered and without cancellation action. Two major producers had discontinued pesticide production and received supplies in August 1977.	44 FR, p. 65131
FIFRA, 3: Classifies remaining use as restricted.	Based on oncogenicity and reproductive effects. Minimizes exposure to users. (EPA)	44 FR, p. A5135
RCRA, 3001-3004. Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/record-keeping requirements. Also designates DBCP as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting requirement for submission of use and related data, published 2/29/80.		45 FR 42, p. 13648 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
PEL: 1 ppb, 8-hr TWA airborne concentration. No skin or eye contact.	Regulatory History: 9/8/77: Emergency Temporary Standards--10 ppb 8-hr TWA; 50 ppb, 15-min TWA ceiling.	29 CFR 1910.1044 (OSHA)
Protective clothing, respirator, hygiene, training, and medical surveillance requirements for workers; monitoring requirements; recordkeeping and waste disposal requirements; sign requirements for regulated areas; labeling requirements for containers. (OSHA)	6/17/78: Final Standards--current limit effective. (OSHA)	

MONS 222773

1,2-DIBROMOETHANE

There is sufficient evidence for the carcinogenicity of 1,2-dibromoethane (ethylene dibromide, EDB) in experimental animals. The evidence of carcinogenicity in humans is inadequate.[1]

When administered by gavage in corn oil, 1,2-dibromoethane (technical grade) was carcinogenic to Osborne-Mendel rats, inducing squamous-cell carcinomas of the forestomach in both sexes, hepatocellular carcinomas in females and hemangiosarcomas in males. The compound induced squamous-cell carcinomas of the forestomach and alveolar/bronchiolar adenomas in B6C3F1 mice of both sexes.[2] When inhaled, EDB was carcinogenic in male and female F344 rats, increasing the incidence of nasal cavity tumors and tumors of the circulatory system. EDB also increased the incidence of lung tumors in both sexes of B6C3F1 mice.[3] Topical application to mice produced tumors of the skin, lung and forestomach.[1]

There was only one epidemiological study of carcinogenic effects of occupational exposure to EDB; it did not produce adequate information.[1]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982, pp. 124-126.

[2] National Cancer Institute. Bioassay of 1,2-Dibromoethane for Possible Carcinogenicity. Technical Report Series No. 86. U.S. Department of Health, Education, and Welfare. Bethesda, Maryland, 1978.

[3] National Toxicology Program. Carcinogenesis Bioassay of 1,2-Dibromoethane (CAS NO. 106-93-4) in F344 Rats and B6C3F1 Mice (Inhalation Study). Technical Report Series No. 210. U.S. Department of Health and Human Services. National Institutes of Health (NIH Publication 82-1766, NTP-80-28). Research Triangle Park, North Carolina, and Bethesda, Maryland, 1982.

EDB, an industrial chemical, is a good solvent for resins, gums, waxes, and many organic chemicals; however, its major use (85 percent) is as an additive in leaded gasoline, where it scavenges lead oxide residues from the combustion chambers of gasoline engines. Other uses are in fumigants; in agricultural insecticide formulations; and in the production of certain dyes, drugs, and vinyl bromide.

MONS 222774

Production of EDB was first reported in the United States in 1923. EPA indicated in 1977 that about 300 million lb of EDB were produced annually (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record). Estimated exports were 99 million lb in 1973. Imports in 1976 were reported as less than 3000 lb. Demand for EDB is expected to fall sharply because of the decline in the consumption of gasoline lead additives.

Human exposure is primarily through inhalation, ingestion, or skin absorption. NIOSH has estimated that approximately 9000 employees at production facilities are potentially exposed to ethylene dibromide. OSHA has estimated that 218,000 workers are potentially exposed in processes using this compound. The National Occupational Hazard Survey (1974) indicated that 126,000 workers may be exposed. In addition to these potential industrial exposures, NIOSH (1977) estimated that 650,000 gas station attendants may have a potential risk of exposure.

Emission concentrations of ethylene dibromide were monitored at a bulk transfer site at levels of 0.2-17 $\mu g/m^3$. An EPA study (1975) measured levels of 90-115 $\mu g/m^3$ for one ethylene dibromide production facility. Emission samples taken adjacent to gas stations and traffic arteries contained 0.07-0.11 $\mu g/m^3$.

Between 13 and 15 million lb are applied annually to soil as a pesticide, and it can be assumed that as a result of this application the chemical enters the environment through leaching. Concentrations of 0.2-31 $\mu g/l$ were measured in raw water, and finished water contained concentrations of 0.2-6 $\mu g/l$. NIOSH (1978) estimated that 304,000 lb/yr were released to the atmosphere from all sources. The low vapor pressure and rather high water solubility of the compound tend to promote its environmental presence in air, water, and soil. However, with a half-life in the atmosphere of 45 days and 5-10 days in water, no appreciable environmental accumulation would be expected.

The EPA has regulated ethylene dibromide under the Resource Conservation and Recovery Act and the Clean Water Act; and the Agency has issued a notice of Rebuttable Presumption Against Registration (1977) under the Federal Insecticide, Fungicide, and Rodenticide Act, and is considering regulation under the Clean Air Act. In 1971, OSHA adopted a permissible exposure limit of 20 ppm as an 8-hour time-weighted average, a 30 ppm ceiling, and 50 ppm maximum peak for 5 minutes in an 8-hour time period. This standard was adopted by OSHA for toxic effects other than cancer.

MONS 222775

1,2-Dibromoethane

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSA jurisdiction. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.33
FIFRA, 6: RPAR issued 12/14/77.	Comments have been reviewed. Remaining use is as a soil fumigant (80%); proposed restricted use, 12/10/80.	42 FR, p. 63134 45 FR, p. 81506
CWA, 311: Hazardous spill regulation establishes reportable quantity (1000 lb, 454 kg) and imposes reporting requirements, 4/28/79.	Based on aquatic toxicity. Fosters greater care in handling and shipping chemicals. (EPA)	40 CFR 117.3, 117.11
CAA: Under assessment to determine if sources pose a hazard sufficient to warrant control.		OAQPS, personal communication, 8/80
FAO/WHO: Recommended that no detectable residues be allowed on foods. Detection limit cited as being 1 ppm. (EPA)		FAO/WHO: Evaluation of the Hazard to Consumers Resulting from the Use of Fumigants in the Protection of Food, 1967 (EPA)
PEL: 20 ppm 8-hr TWA, 30 ppm ceiling, 50 ppm maximum peak for 5 min in an 8-hr time period. [Standard adopted for toxic effects other than cancer.] (OSHA)	Regulatory History: 6/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 222776

There is sufficient evidence for the carcinogenicity of 3,3'-dichlorobenzidine (DCB) in experimental animals. The evidence of carcinogenicity in humans is inadequate.[1]

3,3'-Dichlorobenzidine was carcinogenic in rats, hamsters, and dogs. In rats it produced tumors of the skin, mammary gland, Zymbal gland and hematopoietic tissues following administration in the diet or subcutaneous injection. In mice it produced liver cell tumors and leukemias following dietary and transplacental exposure, respectively. In dogs and hamsters, it produced malignant tumors of the liver and bladder following administration in the diet.[1,2]

In three retrospective epidemiological studies, no bladder tumors were reported in men occupationally exposed to dichlorobenzidine, but the studies were of insufficient quality to permit confident exclusion of carcinogenicity.

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 29. Lyon, France: IARC, 1982, pp. 239-56.

DCB is used commercially in the United States primarily as a base (3,3'-dichlorobenzidine) and as a salt (3,3'-dichlorobenzidine dihydrochloride). Both are essentially insoluble in cold water.

The major uses of DCB are in the manufacture of pigments for printing ink, textiles, and plastics, and as a curing agent for solid urethane plastics.

DCB has been produced commercially in the United States since 1938. An estimated 5 million lb of DCB (base and salt) were produced in 1972. No production data are available after 1972. According to estimates from the U.S. International Trade Commission, 208,000 lb of DCB were imported into the United States in 1979.

Human exposure to DCB occurs through inhalation and probably through percutaneous absorption, primarily during industrial operations. NIOSH estimated in 1974 that 1100 people were exposed to DCB. However, no data are available on the number of workers exposed to DCB during manufacturing, processing, storing and handling, and repackaging operations.

MONS 222777

According to the EPA in 1980, there are limited data on the presence of DCB in the environment. The Agency did, however, report that a survey detected DCB levels of 0.13-3.0 mg/l at one DCB production waste disposal site.

CPSC staff has stated that residual levels or trace impurities of DCB may be present both in DCB-based dyes and pigments and in the final consumer products. The presence of this potential carcinogen, even as a trace contaminant, is cause for concern. However, no data are available to describe the actual levels of impurities in the final product, the potential for consumer exposure, and the potential uptake.

EPA regulates DCB under the Toxic Substances Control Act (TSCA), the Clean Water Act (CWA), and the Resource Conservation and Recovery Act. Under the CWA, the Agency has published a water quality criteria document for the protection of human health (1980). Under TSCA, the Agency conducted a pre-regulatory assessment of DCB based on its suspected carcinogenicity. Waste disposal guidelines were promulgated May 19, 1980, for DCB. Although the EPA has classified DCB as a carcinogen, no regulatory guidelines have been enacted by the Agency. OSHA also regulates this carcinogen. The standard includes requirements for personal protective equipment, training, medical surveillance, signs, labeling, and engineering controls.

MONS 222778

REGULATIONS

Regulations and Other Actions	Effect of Regulations/ Other Comments	Citation of Regulation
No current action. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Promulgated 5/19/80. Also designates 3,3'-dichlorobenzidine as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements.		40 CFR 261 11, 261 33
CWA, 304(a): Water quality criteria published in final form, 11/28/80. (Heading indicates 3,3'-dichlorobenzidine, text does not specify isomer.)		45 FR 231, p. 79116
CWA, 311: Hazardous spill regulation designating reportable quantity (10 lb, 4.54 kg) proposed 7/9/80 (no isomer specified).	Based on carcinogenicity. (EPA)	45 FR 133, p. 46094 (EPA)
TSCA, 8(a): Proposed reporting rule requiring use and exposure data, published 2/29/80 (3,3'-dichlorobenzidine).		
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Protective clothing, respirator, hygiene, training, and medical surveillance requirements for workers; asbestos fact requirements; open-vessel operations prohibited; contamination control requirements; sign requirements for regulated areas; labeling requirements for containers. (OSHA)	Regulatory history: 5/20/73: Emergency temporary standards--protective clothing and hygiene requirements for workers, open-vessel operations restricted, engineering requirements. 3/11/74: Current regulations effective. (OSHA)	29 CFR 1910.1007 (OSHA)

MONS 222779

1,2-DICHLOROETHANE

There is sufficient evidence that 1,2-dichloroethane is carcinogenic in experimental animals.[1,2] 1,2-Dichloroethane (technical grade) was tested in one experiment in mice and in one in rats by gavage in corn oil. In B6C3F1 mice, it produced benign and malignant tumors of the lung and malignant lymphomas in animals of both sexes, hepatocellular carcinomas in males and mammary, and uterine adenocarcinomas in females. In Osborne-Mendel rats, it produced carcinomas of the forestomach in male animals, benign and malignant mammary tumors in females, and hemangiosarcomas in animals of both sexes.[2,3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 429-44.

[3]National Cancer Institute. Bioassay of 1,2-Dichloroethane for Possible Carcinogenicity. Technical Report Series No. 55. DHEW Publication No. (NIH) 78-1361. Bethesda, Maryland, 1978.

1,2-Dichloroethane, commonly known as ethylene dichloride (EDC), is a chlorinated hydrocarbon that is sparingly soluble in water.

EDC is primarily used as a component of leaded fuel and as an intermediate in the production of vinyl chloride, trichloroethane, trichloroethylene, perchloroethylene, vinylidene chloride, and ethyleneamines. Other minor uses are as an insect fumigant for stored grains and mushroom houses; as a soil fumigant in peach and apple orchards; as a cleaner for upholstery and carpets; as a solvent in textile cleaning and metal degreasing; as a dispersant for plastics and elastomers such as synthetic rubber; as an ore flotation compound; and as an extractant in certain food processes.

Commercial production of EDC was first reported in the United States in 1922. The average annual U.S. production between 1973 and 1976 was reported at 10 billion lb. In 1976, approximately 7.2 billion lb were produced, 400 million lb were exported, and negligible amounts were believed to be imported. Current production estimates are not available.

NONS 222780

Human exposure to EDC can occur through skin absorption, inhalation, or ingestion. According to NIOSH, as many as 2 million workers, including those employed in chemical manufacturing and processing industries, may have been exposed to EDC. The population at large may also be exposed through the use of EDC in food, gasoline, and agriculture. EPA reported that EDC was identified at concentrations of 1-90 ppb in 53 of 204 surface water samples taken near heavily industrialized areas across the United States.

EPA regulates EDC under the Clean Water Act and has assessments in progress under the authority of the Clean Air Act; the Safe Drinking Water Act; the Federal Insecticide, Fungicide, and Rodenticide Act; and the Toxic Substances Control Act. The FDA, Bureau of Foods, under the Food, Drug, and Cosmetic Act, has labeled EDC as an animal carcinogen. Through regulations and other actions, FDA is eliminating EDC residues in foods. OSHA has adopted permissible exposure levels of 50 ppm (200 mg/m^3) as an 8-hour time-weighted average, 100 ppm ceiling, 200 ppm maximum peak concentration for 5 minutes in any 3-hour period. OSHA adopted this standard for toxic effects other than cancer.

MONS 222781

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Preliminary economic and toxicologic review complete. Disposition recommendations to be made in FY83. (CPSC)		
CAA, 311: Hazardous spill regulation establishing reportable quantity and imposing reporting requirements. Promulgated 1/29/79. Proposal to reduce reportable quantity.	Carcinogenicity-based proposal	40 CFR 117
CWA, 304(a). Water quality criteria published in final form, 11/28/80		45 FR 231, p. 79318
FIFRA, 3: Data call-in issued regarding chronic effects. Letter sent to all registrants of record, 2/2/81.	Teratogenicity and reproductive effects data deemed inadequate in light of current registration requirements.	Not published in FR
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 100% kg to handling and report/recordkeeping requirements. Also designated as a hazardous constituent of waste and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
CAA, 109, 110, 112: Assessment of sources and exposure complete 5/80. Regulatory decision anticipated during FY84.	Based on chronic toxicity.	OAQPS, personal communication, 9/81
SDWA, 1412: ANPR regarding 1,2-dichloroethane and five other volatile organics published, 3/6/81. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)	Based on chronic effects, including carcinogenicity reviewed in draft. Criteria document complete 6/81. (EPA)	47 FR, p. 9350 (EPA)
FDA Bureau of Foods (OBCA): The compound has been labeled an animal carcinogen, and the Agency has initiated revocation of the regulations. (FDA)	To eliminate residues of 1,2-dichloroethane in foods. (FDA)	21 CFR 193 ???. 173.3(5(a)(3) 172.710, 172.560 (FDA)
PEL: 50 ppm 8-hr TWA, 100 ppm ceiling, 200 ppm maximum peak for 5 min in any 3-hr period. (Standard computed for toxic effects other than cancer.) (OSHA)	Regulatory History: 1952: 50-100-nealy, 75 ppm maximum allowable concentrations. 6/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 222782

DIEPOXYBUTANE

There is sufficient evidence for the carcinogenicity of diepoxybutane in experimental animals.[1] Two forms of 1,2:3,4-diepoxybutane (DL and meso) were carcinogenic in mice by skin application. Both compounds produced squamous-cell skin carcinomas. The D,L-racemate also produced local sarcomas in mice and rats by subcutaneous injection.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 11. Lyon, France: IARC, 1975, pp. 115-23.

Diepoxybutane (DEB) is a highly reactive industrial chemical. DEB exists in four isomeric forms (D-, L-, DL, and meso), which differ in some of their chemical and physical properties.

DEB is primarily used in research and experimental work, as a curing agent for polymers, as a crosslinking agent for textile fabrics, and in preventing microbial spoilage in substances. DEB is also used commercially as mixed stereoisomers and as individual isomers in the preparation of erythritol and other pharmaceuticals.

Annual production volumes are small. EPA indicated that 350 lb of 1,2:3,4-diepoxybutane (isomeric forms not specified) were imported by one importer (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). According to NCI, DEB apparently was not imported or produced commercially in the United States in 1979-1980.

Human exposure to DEB is principally through inhalation and skin absorption. The National Occupational Hazard Survey in 1974 made no estimate of worker exposure to DEB. No consumer product use of this chemical was found.

EPA regulates DEB under the Resource Conservation and Recovery Act. Regulation is also proposed under the TSCA, 8(a), reporting rule that would provide detailed production and marketing data.

MONS 222783

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
N: current action. (CPSC)		
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 6/19/80.	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13696 (EPA)

MONS 222784

DI(2-ETHYLHEXYL)PHTHALATE

There is sufficient evidence for the carcinogenicity of di(2-ethylhexyl)phthalate in experimental animals.[1,2] Di(2-ethylhexyl)phthalate, given in the diet, was carcinogenic to Fischer 344 rats and B6C3F1 mice, producing increased incidence of hepatocellular carcinomas in female rats, and male and female mice; and an increased incidence of hepatocellular carcinomas or neoplastic nodules in male rats.[2,3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 29. Lyon, France: IARC, 1982. pp. 269-85.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon. France: IARC, 1982.

[3]National Toxicology Program. Carcinogenesis Bioassay of Di(2-ethylhexyl)phthalate in F344 Rats and B6C3F1 Mice (Feed Study). Technical Report Series No. 217. DHHS Publication No. (NIH) 82-1773. Research Triangle Park, North Carolina, 1982.

Di(2-ethylhexyl)phthalate (DEHP) is easily soluble in body fluids, e.g., saliva and plasma.

DEHP is most commonly used as an additive to polyvinyl chloride resins for fabricating flexible products. Polyvinyl chloride polymers plasticized with DEHP are used in many types of products such as teething rings, pacifiers, soft squeeze toys, and balls; in vinyl upholstery, tablecloths, shower curtains, and raincoats; and in many other products (CPSC, EPA). DEHP is also used in adhesives, in resins and polymeric coatings, in components of paper and paperboard, in defoaming agents, in enclosures for food containers, in animal glue, in surface lubricants, and in flexible devices for administering parenteral solutions (FDA).

DEHP is used in the manufacturing of vinyl gloves used for medical examinations and surgery. Approximately 500 million pairs of these vinyl gloves are produced annually. Three million flexible bags for iv fluids and an additional 8 million medical products both containing DEHP are used annually by physicians and hospitals.

DEHP was patented in 1933 and became commercially available in the 1940s. The Society of Plastics reported 302 million lb of DEHP was consumed in the United States during 1980. Approximately 400 million lb of DEHP are produced annually.

MONS 222785

EPA reported 18 producers and importers in five regions, with domestic production of 278 million lb and imports of 1100 lb (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record). NCI estimated 1980 production of DEHP as 257 million lb.

The entire population can potentially be exposed to this widely used phthalate. Exposure depends on the amount of DEHP that is volatilized from vinyl products such as upholstery in automobiles, and on the ease with which DEHP is extracted from products into water or saliva. The human exposure estimate from all sources of ingestion is 5.8 mg/day. The FDA is currently reviewing the data to determine if a human health hazard occurs from DEHP used in food contact items. Large-volume parenteral formulations are packaged in flexible containers made from polyvinyl chloride that contains DEHP as a plasticizer. Parenteral solutions are administered intravenously. The concentration of DEHP in replenishers (fluids, nutrients, electrolytes) is estimated to be less than 5 ppm. An individual weighing 70 kg and receiving 3 liters of a replenisher per day gets less than 0.3 mg DEHP/kg/day. Individuals undergoing peritoneal dialysis are exposed to larger amounts of DEHP. But because of losses in the dialysis effluent, not all DEHP in the solutions is absorbed. Pharmaceutical manufacturers, aware of the possible carcinogenic risk from DEHP exposures, either are shifting to other flexible plastics that require no plasticizer or are replacing DEHP in polyvinyl chloride with other plasticizers (FDA). The National Occupational Hazard Survey in 1974 estimated that 612,000 workers were potentially exposed to DEHP (NIOSH).

DEHP is known to be widely distributed in the environment, having been detected in various forms of marine life, in soil samples, and in both animal and human tissues. The average estimated concentration of 1 ug/l in surface waters is 2 to 3 times below the levels that cause harmful effects in aquatic organisms. DEHP is biodegradable; however, it tends to partition into sediment where it is relatively persistent. Indirect human exposure to DEHP may occur through contamination of drinking water and aquatic organisms, which lead to contamination in the food chain. The leaching of DEHP from plastic articles placed in landfills is also a potential source of exposure.

EPA regulates DEHP under the Resource Conservation and Recovery Act. Regulation has been proposed under the Toxic Substances Control Act, 8(a). FDA regulates DEHP as an indirect food additive. OSHA has set a permissible exposure level of 2 ppm or 12 mg/m^3 time-weighted average for phthalic anhydride. DEHP is the subject of a NIOSH Special Hazard Review because of a 1980 NTP test in which DEHP was carcinogenic to rats and mice. Additional concern over DEHP is due to its use for respirator leak testing. NIOSH submitted to OSHA the preliminary hazard review in September 1981. This hazard review was part of OSHA's rulemaking to amend the respirator test provisions of the lead standard.

MONS 222786

The EPA Carcinogen Assessment Group has included DES on its list of carcinogens. In addition, EPA regulates DES under the hazardous waste disposal rule of the Resource Conservation and Recovery Act. FDA requires product labeling to state that DES is contraindicated for use during pregnancy. FDA passed a regulation in 1977 requiring a package insert to inform patients of the risks involved in taking DES, and the FDA further requires special labeling to inform physicians of the risk associated with administering estrogens. In 1979, the FDA revoked all use of DES in food-producing animals. The Court of Appeals upheld the Commissioner's decision to revoke the use of DES in all food-producing animals on November 24, 1980, and the motion to reconsider was denied on December 24, 1980.

Diethylstilbestrol

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and reporting/recordkeeping requirements. Also designates diethylstilbestrol as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirement. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
FDA Bureau of Foods, FD&CA: Because DES has been shown to be a carcinogen in animals and has been associated with carcinogenesis in humans, a regulation was published in the Federal Register on 7/8/79, to revoke all use of DES in food-producing animals. On 8/3/79, a stay of the effective date for revoking DES until 11/3/79, was published in the Federal Register. The Court of Appeals upheld the Commissioner's decision to revoke the use of DES on 11/24/80; and the motion to reconsider was denied on 12/24/80. There is presently no legal use of DES in food-producing animals.	Completely removed the risk of continuous exposure to DES as a residue to meat and meat products.	44 FR, p. 39387
In late 1940s and early 1950s DES was prescribed extensively for threatened abortion. This was doctored as epidemiologic studies demonstrated DES to be ineffective in preventing abortion accidents. In 1971, further epidemiologic data proved a relationship between DES intrauterine exposure and clear-cell adenocarcinoma of the vagina of female offspring. FDA has since required product labeling to state that DES is contraindicated for use in pregnancy. Dispensing an estrogen patient package insert with each new prescription became a regulation in 1977. Special estrogen labeling, FDA Bureau of Drugs; FD&CA (FDA)	Use use of DES in pregnant women is listed as contraindicated. Special patient package inserts and physician estrogen labeling information is required by regulation. The use of such educational material will inform both the patient and the doctor of the risks associated with DES. (FDA)	CFR 21, Subchapter B (FDA)

MONS 222789

3,3'-DIMETHOXYBENZIDINE

There is sufficient evidence for the carcinogenicity of 3,3'-dimethoxybenzidine (o-dianisidine) in experimental animals.[1] 3,3'-Dimethoxybenzidine administered by stomach tube was carcinogenic in rats, producing tumors at various sites, including intestinal, skin and Zymbal's gland carcinomas. The findings in hamsters exposed to o-dianisidine in the feed also suggest carcinogenicity.[2]

The evidence for the carcinogenicity of o-dianisidine in humans is inadequate.[1] Most of the workers exposed to this substance were also exposed to related amines, such as benzidine, which are strongly associated with urinary bladder cancer in humans.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 4. Lyon, France: IARC, 1974, pp. 41-47.

3,3'-Dimethoxybenzidine (DMOB) (o-dianisidine), an aromatic amine, is slightly soluble in water and soluble in most organic solvents and lipids.

DMOB or its dihydrochloride is used principally as a chemical intermediate for the production of azo dyes. The Society of Dyers and Colourists reported the production of 89 dyes using DMOB as an intermediate in 1971. About 30 percent of DMOB is used as a chemical intermediate in the production of o-dianisidine diisocyanate (3,3'-dimethoxy-4,4'-diisocyanate-biphenyl) that is used in adhesive systems and also as a component of polyurethane elastomers and resins. DMOB is used as a dye itself for leather, paper, plastics, rubber, and textiles. DMOB has also been used in the detection of metals, thiocyanates, and nitrites.

DMOB has been produced commercially for at least 50 years. Current production figures are not available. In 1979, only one company produced DMOB, and production statistics were confidential. In 1978, the U.S. International Trade Commission (USITC) reported 3.9 million lb of DMOB produced and 86,000 lb imported. In 1979, USITC reported 77,000 lb of DMOB and 615,000 lb of DMOB dihydrochloride imported. Production of DMOB was not reported to the USITC in 1980; however, production of the hydrochloride salt was indicated in 1979 by two producers, which implied an annual production of more than 10,000 lb. Imports of DMOB through principal U.S. customs districts in 1980 were 20,000 lb; imports of DMOB hydrochloride were 642,000 lb.

MONS 222790

Human exposure to DMOB is possible through inhalation of dye particles from equipment vent systems and through skin absorption from the finished dye product, textile processing, mixing operations, or packaging processes. Workers potentially exposed to DMOB are dye makers and o-dianisidine diisocyanate production workers. However, current dye production processes for DMOB and dyes made from DMOB are generally closed systems with minimal risk to workers. The National Occupational Hazard Survey in 1974 estimated that 200 workers were potentially exposed to DMOB.

DMOB-based dyes and pigments are metabolized to DMOB. The CPSC staff is concerned that dyes and pigments based on DMOB contain residual levels or trace impurities of DMOB in the parts-per-million range and that traces may be present in the final consumer product. At present, no data exist on the actual quantities present in the final consumer product. A study is now in progress on the dermal penetration of DMOB and DMOB dyes.

In late 1980, CPSC instructed its staff to collect data in order to propose a ban on the use of DMOB-based dyes in mass-merchandised consumer dye products. EPA regulates DMOB under the Resource Conservation and Recovery Act. EPA has also proposed regulation under the Toxic Substances Control Act, 8(a), reporting rule that would provide detailed production and marketing data.

3,3'-Dimethoxybenzidine

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comment	Citation of Regulation
A study is in progress on the dermal penetration of DMOB and DMOB dyes. (CPSC)		
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity of the chemical. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)

MONS 222791

4-DIMETHYLAMINOAZOBENZENE

There is sufficient evidence of carcinogenicity of 4-dimethylaminoazobenzene (DAB) in experimental animals.[1] DAB was carcinogenic in rats, producing liver tumors after administration by several routes (subcutaneous injection, diet, gavage), and in dogs, producing bladder tumors when administered in the diet.[2]

DAB has also been tested by subcutaneous injection in mice, and the results are suggestive of local and hepatic carcinogenicity. Treatment of newborn animals produced liver tumors and lung adenomas in mice. Skin-painting with DAB produced epidermal tumors in rats but not in mice.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 8. Lyon, France: IARC, 1975, pp. 125-46.

4-Dimethylaminoazobenzene (DAB), an aromatic azo compound, is insoluble in water and soluble in strong mineral acids and oils.

DAB is used for coloring polishes and other wax products, polystyrene, soap, and as a chemical indicator.

No current production or import data on DAB are available. Large-scale production in the United States was first reported in 1914. DAB was one of a group of at least 20 colors for which individual production data were not available, but whose U.S. production as a group totaled 1 million lb in 1974

Human exposure to DAB can occur either through inhalation or through skin absorption. OSHA has estimated that 2500 workers were exposed to DAB.

EPA regulates DAB under the Resource Conservation and Recovery Act, and has proposed a reporting rule requiring process and use data under TSCA, 8(a). In 1974, OSHA promulgated standards for DAB based on its carcinogenicity. The standards require protective clothing and hygiene procedures for workers and engineering control measures for the manufacturing and processing of the chemical.

MONS 222792

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Toxicologic and economic assessment in FY82. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates DAB as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 5/29/80.		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-Acetylaminofluorene. (EPA)		
5/11/71: Emergency Temporary Standard: Protective clothing, respirator, hygiene, training, and medical surveillance requirements for workers; exhaust fan requirements; open-vessel operations prohibited; contamination control requirements for regulated areas; labeling requirements for containers. (OSHA)	Regulatory History: 5/11/74: Final Standard--current regulations effective. (OSHA)	29 CFR 1910.1015 (OSHA)

MONS 222793

The available test results are considered to provide sufficient evidence for the carcinogenicity of 3,3'-dimethylbenzidine in experimental animals.[1] Commercial 3,3'-dimethylbenzidine (o-tolidine) when given to the rat by subcutaneous injection caused mainly Zymbal's gland carcinomas, but mammary and forestomach tumors, and miscellaneous tumors at other sites were also present. A gastric intubation experiment with rats produced mammary carcinomas, but the result is of doubtful significance because of the small number of animals involved. In feeding experiments, the commercial product did not produce tumors in hamsters. Other experiments verified 3,3'-dimethylbenzidine as a systemic carcinogen producing multiple site tumors when given subcutaneously to the rat.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 1. Lyon, France: IARC, 1972, pp. 87-91.

3,3'-Dimethylbenzidine (DMB) (o-tolidine), an aromatic amine, is a white to reddish crystalline powder that is slightly soluble in water and highly soluble in ethanol, ethyl ether, and dilute acids.

Over 75 percent of DMB is used as a dye and as an intermediate in the production of dyestuffs and pigments. According to the Society of Dyers and Colourists, more than 95 dyes are derived from DMB. Approximately 20 percent of DMB is used in the production of polyurethane-based high-strength elastomers, coatings, and rigid plastics. DMB has also been used in small quantities in chlorine test kits by water companies and swimming pool owners and in test tapes in clinical laboratories.

The major company producing DMB ceased production in 1978; its annual production average was approximately 200,000 lb. EPA reported five producers and importers during the 1975-1977 period (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). Imports appear to be the only source of DMB at present. The U.S. International Trade Commission (USITC) reported that approximately 3.5 million lb of DMB and 240,000 lb of its hydrochloride were imported during 1979. In 1980, more than 5000 lb of DMB hydrochloride were reported to the USITC (NCI).

MONS 222794

Workers potentially exposed to DMB include dye makers, repackagers of DMB and dyes, workers in toluene-diisocyanate production, and clinical and analytical chemistry laboratory personnel. Workers in a variety of occupations may be exposed to small quantities of DMB used for analytical purposes, among them water and sewage plant attendants, chemical test tape or kit makers, and swimming pool service representatives. NIOSH in 1978 estimated that fewer than 100 employees were exposed to large quantities of DMB in the United States, but as many as 200,000 may be exposed to small quantities. The National Occupational Hazard Survey in 1974 estimated that 420 workers were potentially exposed to DMB.

DMB-based dyes and pigments are metabolized to DMB in vivo. Residual levels of DMB may also be present in DMB-based dyes and pigments and in the final consumer products. Available data indicate that such contaminants occur in the parts-per-million range. The Consumer Product Safety Commission (CPSC) has instructed its staff to collect additional data to propose a ban on the use of DMB-based dyes in mass-merchandised consumer dye products. DMB is present in swimming pool water test kits. Each kit contains 0.5-1 percent DMB. Exposure is through dermal absorption or through ingestion if the test solutions are emptied back into the pool.

DMB used in swimming pool test kits is currently being evaluated by CPSC. Data are being collected on the dermal absorption of DMB and on DMB-based dyes. EPA regulates DMB under the Resource Conservation and Recovery Act.

3,3'-Dimethylbenzidine

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Use in swimming pool test kits is currently being evaluated. (CPSC)		
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates chemical or a hazardous constituent of waste. Promulgated 5/19/80. (EPA)	Regulation based on chronic toxicity of chemical. Fosters greater care in handling of chemical wastes. (EPA)	40 CFR 261.11, 261.33 (EPA)

MONS 222795

There is sufficient evidence for the carcinogenicity of dimethylcarbamoyl chloride in experimental animals.[1] Dimethylcarbamoyl chloride is carcinogenic in mice, producing local carcinomas after application to the skin and local sarcomas after subcutaneous or intraperitoneal injection.[2]

A study of humans exposed to dimethylcarbamoyl chloride is considered inadequate.[1]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 12. Lyon, France: IARC, 1976, pp. 77-84.

Dimethylcarbamoyl chloride (DMCC) is a colorless liquid that rapidly hydrolyzes in water.

DMCC is used as a chemical intermediate in the production of pharmaceuticals, pesticides, rocket fuel, and in dye synthesis. The pharmaceuticals (neostigmine bromide, neostigmine methylsulfate, and pyridostigmine bromide) are used in the treatment of myasthenia gravis. The three U.S. registered pesticides derived from DMCC are known by the trade names, Tandex^{R}, Dimetilan^{R}, and Pirimor^{R}.

Production data are limited; however, the Toxic Substances Control Act (TSCA), Chemical Substance Inventory (1979) reported that there were four producers in 1977 (no production data on public record) and approximately 400 lb imported annually.

Limited human exposure is restricted to chemical workers, pesticide formulators, dye makers, and pharmaceutical workers. OSHA estimated that 200 workers are exposed to DMCC, primarily through inhalation. DMCC has been found at levels up to 6 ppm during the production of phthaloyl chlorides. It is possible that levels of exposure might be higher in facilities in which the chemical is used for further synthesis. When DMCC is used as a dye intermediate, exposure can occur from residue in the product and the migration of the chemical from the product.

The Consumer Product Safety Commission staff stated that residual levels or trace impurities of DMCC might be present in the final consumer product. The presence of this potential carcinogen, even as a trace contaminant, is cause for concern. However, data describing the actual levels of impurities in the final product and the potential for consumer exposure and uptake are currently lacking. The EPA has regulated DMCC as a carcinogen under the Resource Conservation and Recovery Act and has proposed a reporting rule under the TSCA, 8(a).

MONS 222796

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004. Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates dimethylcarbamoyl chloride as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 222797

DIMETHYL SULFATE

There is sufficient evidence for the carcinogenicity of dimethyl sulfate in experimental animals, but the evidence in humans is considered as inadequate.[1]

Dimethyl sulfate was carcinogenic in BD rats after inhalation or subcutaneous injection, producing mainly local tumors, and after prenatal exposure, producing tumors of the nervous system.[2]

Four cases of bronchial carcinomas have been reported in men occupationally exposed to dimethyl sulfate.[2] One case of pulmonary carcinoma in a man exposed to dimethyl sulfate and other chemicals, and one case of choroidal melanoma in a man exposed six years to dimethyl sulfate have also been reported.[1]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 4. Lyon, France: IARC, 1974, pp. 271-76.

Dimethyl sulfate is an industrial chemical that is soluble in water. It is used mainly as an alkylating agent for converting compounds such as phenols, amines, and thiols to the corresponding methyl derivatives. It is also used as a component of polyurethane base adhesives.

Dimethyl sulfate was first produced commercially in the United States in 1928. There are 12 producers and importers with a combined domestic production of approximately 48 million lb/yr. No data on imports or exports are available.

Human exposure occurs by inhalation of the vapors or by skin absorption of the liquid at the sites where the chemical is produced or where its derivatives are formulated. NIOSH has reported that 1250 workers are potentially exposed to dimethyl sulfate. OSHA estimated 3900 workers are potentially exposed.

Environmental sources of dimethyl sulfate are primarily from the production losses to air and water. The chemical has been found in the wastewater streams and air emissions from plants where it was made or used. The hydrolysis of dimethyl sulfate in water is rapid; its transfer from water to air is not likely to occur.

MONS 222798

The EPA's Carcinogen Assessment Group has included this chemical on its list of carcinogens. The EPA regulates dimethyl sulfate under the Resource Conservation and Recovery Act and proposes to require reporting under the Toxic Substances Control Act. The FDA regulates this substance under the Food, Drug, and Cosmetic Act as an optional component of polyurethane base adhesives. There is no expected migration of this chemical to food under conditions of use specified in the adhesive regulation. OSHA has adopted limits for the concentration of dimethyl sulfate in the workplace as 1 ppm (5 mg/m^3) in an 8-hour time-weighted average. This standard was adopted by OSHA for toxic effects other than cancer.

Dimethyl Sulfate

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Designates dimethyl sulfate as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 251.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 7/29/80.		45 FR 42, p. 13644 (EPA)
See the Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Regulatory Authority: FD&CA; FR 11/10/77. (FDA)		21 CFR 175.105 (FDA)
PEL: 1 ppm (5 mg/m^3) 8-hour TWA. Potential for skin absorption noted. (Standard assists for toxic effects other than cancer.) (OSHA)	Regulatory History: 1974: Walsh-Healy; 1 ppm maximum allowable concentration. 8/27/71): OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 222799

There is sufficient evidence for the carcinogenicity of 1,4-dioxane in experimental animals.[1] 1,4-Dioxane administered in drinking water is carcinogenic in rats and guinea pigs. It produced malignant tumors of the nasal cavity and liver in rats and tumors of the liver and gall bladder in guinea pigs. It was also active as a promoter in a two-stage skin carcinogenesis study in mice.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 11. Lyon, France: IARC, 1976, pp. 247-56.

1,4-Dioxane is a highly volatile liquid that is flammable and moderately explosive.

1,4-Dioxane is used as a stabilizer for chlorinated degreasing solvents and as a solvent for lacquers, plastics, varnishes, paints, dyes, fats, greases, waxes, and resins. The chemical can occur as a contaminant in certain consumer products, and as a byproduct of reactions based on condensing ethylene oxide (EtO) or ethylene glycol.

The first commercial production of dioxane in the United States occurred in 1951. The EPA reported that 13 producers and importers account for 7.7 million lb of domestic production and approximately 800,000 lb of imports. No significant change in the estimated trends for U.S. production and sales of dioxane is forecast.

Exposure to dioxane is primarily through inhalation of the vapors, but the chemical is also readily absorbed through the skin. Exposure in industry occurs when dioxane vapors are released from degreasing operations and from spent solvents. Additional workers involved with shipping operations, primarily by rail and truck, may be exposed to dioxane through leakage from bulk loading lines.

According to the Consumer Product Safety Commission (CPSC), consumers may be exposed to residual levels of 1,4-dioxane formed during the manufacture of detergents, shampoos, surfactants, and certain pharmaceuticals. CPSC has stated that the presence of 1,4-dioxane even as a trace contaminant is cause for concern. However, no data are available on the actual levels of impurities in final products or on the potential for consumer exposure and uptake.

MONS 222800

The National Occupational Hazard Survey in 1974 estimated that 334,000 workers were potentially exposed to dioxane, 100,000 of whom were exposed as a result of dioxane contamination of 1,1,1-trichloroethane. Estimates from OSHA, however, indicated that 466,000 workers were potentially exposed.

Because dioxane is volatile and infinitely soluble in water, there is a large potential for its presence in the environment. Emissions to the atmosphere can occur where it is manufactured and used, and improperly disposed spent solvents can contaminate ground and surface waters.

The EPA regulates dioxane through the Resource Conservation and Recovery Act. The FDA has undertaken a survey of 1,4-dioxane contamination of raw materials and products. OSHA has adopted a permissible exposure limit of 100 ppm or 360 mg/m^3 as an 8-hour time-weighted average in the workplace for dioxane. This standard was adopted by OSHA for toxic effects other than cancer.

1,4-Dioxane

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
FDA Bureau of Foods, FD&CA: Proposed action pending; may propose to minimize its exposure.		21 CFR 175.105 (FDA)
Regulatory Authority: FD&CA 601(a). (FDA)	Survey of raw materials and product contamination under way. (FDA)	
PEL: 100 ppm (360 mg/m^3) 8-hr TWA. Potential for skin absorption noted. [Standard adopted for toxic effects other than cancer.] (OSHA)	Regulatory History: 1972. Walsh-Healy, 100 ppm maximum allowable concentration. 8/27/71: OSHA Takeover Standard-currently last effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 222801

DIRECT BLACK 38

There is sufficient evidence that commercial Direct Black 38 is carcinogenic to experimental animals.[1] In a thirteen-week feeding study Direct Black 38 (technical grade) was carcinogenic in male and female Fischer 344 rats, inducing hepatocellular carcinomas and neoplastic nodules in the liver. The test dye was not carcinogenic to B6C3F1 mice under the same test conditions.[2]

In a recent occupational hazard review,[3] it was concluded that all benzidine-based dyes, including Direct Black 38, regardless of their physical state or proportion in the mixture, should be recognized as potential human carcinogens.

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France. IARC, 1982.

[2]National Cancer Institute. Thirteen-Week Subchronic Toxicity Studies of Direct Blue 6, Direct Black 38, and Direct Brown 95 Dyes. Technical Report Series No. 108. DHEW Publication No. (NIH) 78-1358. Bethesda, Maryland, 1978.

[3]National Institute of Occupational Safety and Health. Special Occupational Hazard Review for Benzidine-Based Dyes. Washington, D.C.: U.S. Government Printing Office, 1980.

Direct Black 38 is a water-soluble azo dye derived from benzidine. It is usually sold as a dry powder.

Direct Black 38 is possibly being used to dye fabric, leather, cotton, cellulosic materials, and paper; these are then used in consumer products. The chemical may be used by artists (CPSC, EPA). The FDA has indicated that although Direct Black 38 is identified in the literature as a hair-dye component, it is currently not used by the cosmetic industry.

U.S. manufacturers of consumer dye products stated that they have discontinued the use of benzidine-based dyes. EPA reported six producers and importers of Direct Black 38 in one region, with domestic production of 4 million lb and imports of 370,000 lb (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). U.S. production of Direct Black 38 was reported to the U.S. International Trade Commission for 1980 as greater than 5000 lb.

MONS 222802

In view of a health hazard alert issued in December 1980 by OSHA, which cautioned workers and employers of the carcinogenic effect of benzidine-derived Direct Black 38, new nonbenzidine Direct Black dyes have been developed and used successfully in commercial applications by the paper and leather industry during the past year. These nonbenzidine dyes were developed with the hope of replacing benzidine-based dyes throughout industry.

Human exposure to Direct Black 38 may occur through inhalation, skin absorption, and unintentional ingestion. Consumer exposure to Direct Black 38 depends upon the ability of the dye to migrate out of consumer products and either penetrate the skin or degrade prior to penetrating the skin. No additional data quantifying the rate of migration or degradation of this dye are currently available. In the general population, unspecified exposure levels to Direct Black 38 are thought to occur through the use of textile dyed products and retail packaged dyes for home dyeing and school use. The National Occupational Hazard Survey in 1974 estimated that approximately 16,000 workers were potentially exposed to Direct Black 38. The population exposed consisted of dyers of leather, plastics, cotton, wool, and silks, along with makers of aqueous inks, biological stains, typewriter ribbons, and wood stains.

In late 1980, CPSC directed its staff to collect additional scientific and economic data in order to propose a ban on the use of all benzidine congener dyes in consumer dye products. Currently CPSC is studying the skin penetration of benzidine congener dyes and the presence of these dyes in textile, leather, and paper consumer products. EPA is currently proposing regulation of Direct Black 38 under the TSCA, 8(a), reporting rule that would provide detailed production and marketing data. FDA does not regulate the cosmetic use of Direct Black 38, but was petitioned to approve Direct Black 38 for use as indirect food additives, i.e., as dyes for paper and paperboard products. In 1979, the petition was withdrawn. NIOSH reported that Direct Black 38 was the subject of a November 1979 Special Hazard Review and recommended stringent work practices, material replacement, and other measures applied to carcinogens. The Special Hazard Review was based on an April 1978 joint NCI/NIOSH recommendation.

MONS 222803

REGULATIONS

Regulations and Other Actions	Effect of Regulations: Other Comments	Citation of Regulation
CPSC is currently studying the skin penetration of benzidine congener dyes and the presence of these dyes in textile, leather, and paper consumer products. (CPSC)		
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)
NIOSH recommended stringent work practices, material replacement, and use of other protective measures applicable to carcinogens. (NIOSH)		Special Hazard Review, 1978 (NIOSH)

MONS 222804

There is sufficient evidence for the carcinogenicity of Direct Blue 6 (technical grade) in experimental animals.[1] In a thirteen-week feeding study Direct Blue 6 dye (technical grade) was carcinogenic to male and female Fischer 344 rats, inducing hepatocellular carcinomas and neoplastic nodules in the liver. The test dye was not carcinogenic to B6C3F1 mice under the same test conditions.[2]

In a recent occupational hazard review,[3] it was concluded that all benzidine-based dyes, including Direct Blue 6, regardless of their physical state or proportion in the mixture should be recognized as potential human carcinogens.

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]National Cancer Institute. Thirteen-Week Subchronic Toxicity Studies of Direct Blue 6, Direct Black 38, and Direct Brown 95 Dyes. Technical Report Series No. 108. DHEW Publication No. (NIH) 78-1358. Bethesda, Maryland, 1979.
[3]National Institute of Occupational Safety and Health. Special Occupational Hazard Review for Benzidine-Based Dyes. Washington, D.C.: U.S. Government Printing Office, 1980.

Direct Blue 6 is a water-soluble azo dye derived from benzidine. It is sold as a dry powder for commercial use and as a component in retail packaged dyes.

Direct Blue 6 may still be used by artists. It is potentially used to dye fabric, leather, cotton, cellulosic materials, and paper; these are then used in consumer products (CPSC, EPA). The FDA has indicated that although Direct Blue 6 has been identified in the literature as a hair dye component, it is not presently used by the cosmetic industry.

In 1978, 61,000 lb of Direct Blue 6 were produced in the United States and 220 lb were imported.

All three manufacturers of consumer dye products stated that they have discontinued the use of benzidine-based dyes (CPSC). In their initial inventory of domestic producers and users of chemicals, EPA reported five producers and importers of Direct Blue 6 in one region, with a total domestic production of 75,000 lb and imports of 4000 lb (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). Production of Direct Blue 6 was not reported to the U.S. International Trade Commission in 1980; however,

MONS 222805

production was reported in 1979 by one producer, which implied an annual production of more than 5000 lb. The producer currently produces direct dyes, but it is unknown whether the company actually ceased the production of this particular direct dye or simply did not produce it in 1980.

Human exposure to Direct Blue 6 may occur through inhalation, skin absorption, and to a lesser extent, unintentional ingestion, when the dye is in the press cake or dry powder form. The primary source for exposure to Direct Blue 6 is at the production site. The initial production step is in a closed system. However, other production operations, such as filter press, drying, and blending, may be performed in the open and, therefore may afford a greater potential for worker exposure. The general population may be exposed to Direct Blue 6 through the use of retail packaged dyes containing this benzidine-based dye.

Consumer exposure to Direct Blue 6 depends upon the ability of the dye to migrate out of the consumer product and either penetrate the skin or break down prior to penetrating the skin. No additional data are currently available. The National Occupational Hazard Survey in 1974 estimated that 1300 workers were potentially at risk of exposure to Direct Blue 6.

In the late 1980s, the CPSC directed the staff to collect additional scientific and economic data in order to propose a ban on the use of all benzidine congener dyes in consumer products. CPSC is now studying the skin penetration of benzidine dyes and the presence of these dyes in textile, leather, and paper consumer products. EPA is currently proposing a reporting rule for Direct Blue 6 under TSCA, 8(a). FDA, which does not regulate the cosmetic use of Direct Blue 6, was petitioned to approve this chemical, among others, for use as an indirect food additive, i.e., as a dye for paper and paperboard products. In 1979, the petition was withdrawn. NIOSH has reported that Direct Blue 6 was the subject of a November 1979 Special Hazard Review. NIOSH recommended stringent work practices, material replacement, and treatment of these substances as carcinogens. The Special Hazard Review was based on an April 1978 joint NCI/NIOSH recommendation.

Direct Blue 6

REGULATION

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
CPSC is currently studying the skin penetration of benzidine congener dyes and the presence of these dyes in textile, leather, and paper consumer products. (CPSC)		
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)
NIOSH recommended stringent work practices, material replacement, and other protective measures applicable to carcinogens. (NIOSH)		Special Hazard Review, 1979 (NIOSH)

MONS 222806

ETHYLENE THIOUREA

There is sufficient evidence for the carcinogenicity of ethylene thiourea (ETU) in experimental animals.[1] ETU given in the diet to rats produced thyroid carcinomas.[2,3] Increased incidence of liver-cell tumors was reported in two strains of mice following oral administration of ETU (gavage initially, then diet).[4]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]Graham, S.L., W.H. Hansen, K.J. Davis, and C.H. Perry. Effects of One-Year Administration of Ethylene Thiourea Upon the Thyroid of the Rat. J. Agric. Food Chem. Vol. 21, 1973, pp. 324-29

[3]Gak, J.C., C. Graillot, O. Fournier, R. Truhaut, and B. Radenen. Differences in Susceptibility of Hamsters and Rats to the Effects of Long-Term Administration of Ethylene Thiourea. Eur. J. Toxicol. Environ. Hyg. Vol. 9, 1976, pp. 303-12.

[4]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 7. Lyon, France: IARC, 1974, pp. 45-52.

Ethylene thiourea is a water soluble chemical, available in the United States as a solid powder and as an oil dispersion.

ETU has been widely used in the United States since 1948 as an accelerator in the vulcanization of various elastomers, including neoprene (polychloroprene) and polyacrylate rubber. Although the curing of these rubbers converts most of the ETU to other compounds, trace amounts are still present in the cured products. Neoprene is used almost exclusively in industrial applications such as automotive parts, wire and cable production, construction, and adhesives. Consumer products containing neoprene include shoes and closures for containers (e.g., aerosol dispensers). The EPA has reported additional uses of ETU as an intermediate in the manufacture of antioxidants, insecticides, fungicides, dyes, pharmaceuticals, and synthetic resins, and as a constituent of electroplating baths.

ETU is a manufacturing, processing, and metabolic product of the ethylenebisdithiocarbamate group of fungicides such as maneb, mancozeb, metiram, and zineb. ETU appears as a stable residue on fruit and vegetable crops that have been treated with ethylenebisdithiocarbamate fungicides. Studies have revealed that ETU is present in 28 different ethylenebisdithiocarbamate commercial products.

MONS 222807

Commercial production was first reported in the United States in 1951. Domestic production reported by EPA (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record) was 375,000 lb by seven producers in four regions. U.S. production greater than 1000 lb was reported to the U.S. International Trade Commission in 1980 (NCI). ETU is distributed and available from most major chemical companies in small as well as bulk quantities. No data are available on current levels of imports or exports.

The National Occupational Hazard Survey in 1974 estimated that 68,000 workers were potentially exposed to ETU. The major routes of exposure are skin contact and inhalation. NIOSH estimated that 3500 workers are exposed to ETU in the manufacture of fabricated rubber products.

In October 1978, ETU was the subject of a NIOSH Special Hazard Review. NIOSH considered carcinogenic and teratogenic effects in recommending that worker exposure be minimized by using an encapsulated form of the substance in the workplace.

EPA currently regulates ETU under the Resource Conservation and Recovery Act and is proposing regulation under the TSCA, 8(a), reporting rule. FDA has prohibited the use of ETU in food.

Ethylene thiourea

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Under evaluation. (CPSC)		
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261.33
TSCA, 8(a). Reporting rule requiring process and use data, proposed 2/28/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)
FDA has prohibited the use of ethylene thiourea in food. (FDA)		21 CFR 189 (FDA)
NIOSH considered carcinogenic and teratogenic effects in recommending that worker exposure be minimized by using an encapsulated form of the substance in the workplace. (NIOSH)		Special Hazard Review, 1978 (NIOSH)

MONS 222808

FORMALDEHYDE

There is sufficient evidence for the carcinogenicity of formaldehyde in experimental animals.[1]

Formaldehyde was tested for carcinogenicity by inhalation exposure in two strains of rats and one strain of mice. A significant incidence of squamous-cell carcinomas of the nasal cavity was induced in both strains of rats but not in mice. Another study in mice and one in hamsters by inhalation exposure, one in rats by subcutaneous administration, and one in rabbits by exposure of the oral mucosa were considered inadequate for evaluation. Levels of formaldehyde that caused nasal tumors also caused acute degeneration, necrosis, inflammation and increased cell replication in the nasal mucosa of rats and mice following inhalation exposure.[1,2]

The available epidemiological studies do not provide adequate evidence for assessing the carcinogenicity of formaldehyde in man.[1,2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 29. Lyon, France: IARC, 1982, pp. 345-89.

Formaldehyde (HCHO) is a colorless, pungent irritant gas that is water soluble and most frequently marketed as 37-56 percent aqueous solutions, commonly known as formalin. The solutions are usually stabilized with 10-15 percent methanol to prevent polymerization.

HCHO is a high-volume chemical of which 65-70 percent is used for the production of phenolic, urea, melamine, and acetal resins with wide usage in the construction, automotive, and appliance industries. HCHO also has many uses in products such as textiles, embalming fluids, fungicides, bactericides, air fresheners, cosmetics, medicinals, and toothpastes.

Sixteen companies currently produce HCHO at 53 plants in the United States. Production levels for 1980 have been estimated as 6 billion lb, while 1979 estimates were 6.5 billion lb. Imports and exports in 1980 were reported as 10.2 million and 15.6 million lb, respectively. In 1978, market analysts forecasted an average growth rate of 0-3 percent through the early 1980s; however, some analysts predict production decreases of 5-30 percent.

MONS 222809

Human exposure to HCHO is principally through inhalation and skin absorption or less frequently by ingestion. Most of the HCHO production in the United States is from methanol in closed automated process systems. The exposure potential during transportation and storage is likely to be minimal. Estimated emission levels from production plants range from 0.0004 to 2500 ug/m^3, with a median exposure of 0.01 ug/m^3. EPA estimates that 27.7 million people living within 12.5 miles of point sources may be exposed to low levels. NIOSH estimates that 8000 workers are potentially exposed to HCHO during direct production. In addition, pathologists and histology technicians represent a high exposure group. In 1974, the National Occupational Hazard Survey estimated that 57,000 full-time and 1.7 million part-time employees may have been exposed to HCHO, and OSHA estimated the number of workers exposed as 2.6 million.

Most consumers are exposed to formaldehyde through its use in construction materials, wood products, textiles, home furnishings, paper, cosmetics, and pharmaceuticals. The ambient air levels in the United States, ranging from about 0.001 ppm to 0.030 ppm, expose the entire population of 230 million. Two subpopulations have been identified as having particularly high potential for HCHO exposure: 2.2 million residents of mobile homes containing particle board and plywood have an average exposure of 0.4 ppm HCHO, and 1.7 million persons living in conventional homes insulated with urea-formaldehyde foam have a potential average exposure of 0.12 ppm. Inadvertant production of formaldehyde from combustion sources also may contribute to these exposures. An estimated 159 million persons are potentially exposed to ambient air concentrations at maximum levels of 0.25 ug/m^3 of HCHO. Automobiles alone emit 610 million lb of HCHO each year. HCHO has a short half-life in air because it is degraded by photochemical processes. HCHO is also unstable in water, and no effluent data are available.

The Consumer Product Safety Commission (CPSC) requires labeling, to warn that formaldehyde is a strong sensitizer, on household products containing 1 percent or more of formaldehyde. Under the authority of Section 8 of the Consumer Product Safety Act, the CPSC banned the use of urea-formaldehyde foam insulation in residences and schools (16 CFR Part 1304, Vol. 47 #64, April 2, 1982, pp. 14366-421). The Commission is currently studying the off-gassing of formaldehyde from other products, the bioavailability and dermal penetration of formaldehyde from textiles, and the sensitizing capability of formaldehyde. EPA also regulates HCHO under the Clean Water Act, the Resource Conservation and Recovery Act (RCRA), and the Clean Air Act. The RCRA regulations are not based on carcinogenicity; however, they encourage greater care in handling and shipping of HCHO and should result in a reduction of accidental exposures. OSHA adopted permissible exposure levels of 3 ppm as an 8-hour time-weighted average, 5 ppm ceiling, and 10 ppm maximum peak concentration for 30 minutes in an 8-hour period. This standard was adopted by OSHA for toxic effects other than cancer.

Actions initiated by FDA and EPA are presently under assessment to determine what additional regulatory course, if any, should be taken.

MONS 222810

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Regulatory Authority CPSA/FHSA FHSA Any product containing 1 percent formaldehyde has to be labeled as a strong sensitizer		1600 CFR 1500.13(d)
Final ban on the use of urea-formaldehyde foam insulation in schools and residences. (CPSC)	An increased risk of cancer of up to 1 e additional cases from every 10,000 additional homes insulated with urea-formaldehyde will be eliminated. (CPSC)	16 CFR Part 1209, Vol. 47 #84, pp 14366-14421, 4/2/82 (CPSC)
CWA 311 Hazardous spill regulation designating reportable quantity (1000 lb. 454 kg) and imposing reporting requirements. Promulgated 6/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping of chemicals, and should result in reduction of accidental exposures. (EPA)	40 CFR 117.3, 117.13
RCRA, 3001-3004 Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designated as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
CAA: Assessment of sources and exposures completed 4/80. Continuing assessment to determine regulatory course, if any. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		OAQPS, personal communication, 9/80 (EPA)
Regulatory Authority: FD&CA 601(a).	Coordinating effort through IRLG. (FDA)	21 CFR 175.105, 602.99, 173.340, 176.210, 176.3120, 175.210, 175.300, 175.320, 175.390 176.170, 177.1210, 176.180, 177.2410, 177.2800, 573.460
In March 1982 the FDA announced the availability of safety and effectiveness data that could be used to support a new drug application in aquaculture. (FDA)		47 FR 15611, 4/9/82 (FDA)
PEL: 3 ppm 8-hr TWA, 5 ppm ceiling, 10 ppm maximum peak, 30 min in an 8-hr period. [Standard adopted for toxic effects other than cancer.] (OSHA)	Regulatory History: 1971: Walsh-Healy, 3 ppm maximum allowable concentration. 8/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 222811

HEMATITE UNDERGROUND MINING

There is sufficient evidence for the carcinogenicity to humans of underground hematite mining (with exposure to radon).[1]

No carcinogenic effects were observed in mice, hamsters, or guinea-pigs given ferric oxide intratracheally.[2]

Underground hematite miners have a high incidence of lung cancer, whereas surface hematite miners do not. It is not known whether this excess risk may be due to hematite; to radon (a known lung carcinogen); to inhalation of ferric oxide or silica; or to a combination of these or other factors. Some studies of metal workers exposed to ferric oxide dusts have shown an increased incidence of lung cancer, while other studies have not.[1,2] The influence of factors in the workplace other than ferric oxide cannot be eliminated.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 1. Lyon, France: IARC, 1972, pp. 29-39.

Human exposure to hematite from underground hematite mining is principally through inhalation and/or ingestion of dust. No estimates are available concerning the number of underground miners exposed.

The EPA views hematite mining as being primarily within the jurisdiction of the Mine Safety and Health Administration of the U.S. Department of Labor. Some EPA guidelines address the ferric ore mining, milling, and refining categories but do not specifically address underground hematite mining. It is unlikely that EPA will assume further jurisdiction.

Hematite Underground Mining

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Hematite mining is viewed by EPA as primarily within the jurisdiction of MSHA (extraction and milling) or OSHA (iron production). Some effluent guidelines address the ferric ore mining, milling, and refining but do not address hematite mining per se. In view of the indication that the primary cancer risk is to workers, it is unlikely that EPA will assume further jurisdiction. (EPA)		

MONS 222812

HEXACHLOROBENZENE

There is sufficient evidence for the carcinogenicity of hexachlorobenzene in experimental animals.[1] Hexachlorobenzene (HCB) was tested by dietary administration in mice, hamsters and rats (one experiment with each species). In Swiss mice, HCB produced liver-cell tumors in animals of both sexes. In Syrian golden hamsters, HCB produced hepatoma., liver hemangioendotheliomas and thyroid adenomas in both sexes.[2] Female Agus and MRC Wistar rats fed hexachlorobenzene in their diet developed liver-cell tumors.[3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 155-78.

[3]Smith, A.G., and J.R. Cabral. Liver-Cell Tumors in Rats Fed Hexachlorobenzene. Cancer Lett. Vol. 11, 1980, pp. 169-72.

Hexachlorobenzene (HCB) is an industrial chemical and a byproduct from many chemical and pesticide manufacturing processes. HCB technical-grade formulations include wettable powders, liquids, and dust.

HCB's principal use in the United States has been as a fungicide to control wheat bunt and smut fungi on other grains. HCB has also been used as a chemical intermediate in dye manufacture and synthesis of other organic chemicals and as a wood preservative.

HCB is formed as an impurity during the synthesis of several herbicides and pesticides, including the herbicide dimethyltetrachloroterephthalic acid (DCPA), which may contain 10-14 percent HCB, and the pesticide pentachloronitrobanzene (PCNB), which may contain 1-6 percent HCB. HCB is used as an intermediate in the production of pentachlorophenol (PCP), a widely used herbicide and fungicide. PCP may contain up to 13 percent impurities, part of which consist of residual HCB.

Commercial production of HCB in the United States was first reported in 1933. Production of HCB in the United States ended in 1976. In the period between 1975 and 1977, there were three producers and importers in three regions, with a domestic production of 3.7 million lb and imports of 3800 lb (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). NCI reported that HCB is not now imported or produced commercially in the United States. Approximately 8.5 million lb of HCB wastes are produced annually by 14 industries surveyed as sources of HCB wastes.

MONS 222813

The production and use of HCB as a fungicide over the past several decades, and its occurrence as a byproduct in the manufacture of other chemicals, indicate that widespread human exposure occurs in both occupational and nonoccupational settings. Exposure to HCB may occur as a result of its presence in wastes from pesticide manufacture. Contamination of the ground and of grazing cattle around dumps and along roads where the waste is trucked has occurred. The National Occupational Hazard Survey in 1974 estimated that 4400 workers were potentially exposed to HCB. Occupations where the potential for human exposure exists include fungicide workers, organic chemical synthesizers, synthetic rubber producers, seed disinfecters, pesticide producers, and wood preservers. The EPA's monitoring of human adipose tissue collected across the United States has shown that approximately 95 percent of the population has trace residues of HCB.

HCB residues have been detected in soil, wildlife, fish, and food samples collected worldwide. In the Total Diet Program of the FDA, HCB was detected in food composites in 30 cities at levels of 0.006 to 0.040 mg/kg. The average daily intake of humans in 1973 and 1974 has been calculated to be 0.04 ug/day and 0.07 ug/day, respectively.

HCB was detected in most river water residues (2 ng/l to 90 ng/l) and soil residues ranging from traces to 1700 ug/kg near industrialized regions of the United States. HCB is a toxicological and environmental concern due to its bioaccumulation and persistence. HCB is insoluble in water and under most environmental conditions has a very low rate of degradation.

EPA has recommended an upper limit of 0.5 ppm HCB in fatty tissues of cattle, pigs, and sheep, but has not promulgated a tolerance. EPA regulates HCB under the Clean Water Act, 304 and 311, and the Resource Conservation and Recovery Act. In addition, a reporting regulation is proposed under TSCA, 8(a).

MONS 222814

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
In current action; under evaluation, CPSC)		
CWA, 304: Water quality criteria published in final form, 11/28/80.		45 FR, p. 79318
CWA 311: Hazardous spill regulation establishes reportable quantity [illegible] and imposes reporting requirement. Promulgated 3/29/79.	Regulation based on aquatic toxicity. Fosters greater care in handling and shipping of chemicals.	40 CFR 117.3, 117.11
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 100 kg to handling and report/record keeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity of chemical. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)

MONS 222815

HYDRAZINE AND HYDRAZINE SULFATE

There is sufficient evidence for the carcinogenicity of hydrazine in experimental animals.[1] Hydrazine administered by gavage, mainly as hydrazine sulfate, produced a high incidence of multiple pulmonary adenomas and adenocarcinomas, and hepatomas and hepatocarcinomas in mice of several strains. Low-level inhalation exposure to hydrazine produced lung tumors in mice, albeit in a small number of animals.[2] Intraperitoneal injection to several strains of mice of hydrazine in physiological saline produced sarcomas of the mediastinum, leukemias and lung tumors. Administration of hydrazine sulfate by gavage to Cb/Se rats caused lung adenomas and adenocarcinomas, liver adenocarcinomas and mammary fibroadenomas.[3]

Two reports on cancer mortality of workers exposed to hydrazine have been published some years ago but the evidence provided is considered as inadequate.[3]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] McEwen, J.D., E.E. McConnel, and K.C. Back. The Effect of a Six Month Chronic Level Inhalation Exposure to Hydrazine on Animals. L-Medical Research Laboratory, Wright-Patterson Air Force Base, Ohio. AMRL-TR-74-125, Paper No. 16. Distributed by National Technical Information Service. U.S. Department of Commerce, Springfield, Virginia. AD-A-011865. 1974.

[3] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 4. Lyon, France: IARC, 1974, pp. 127-36.

Hydrazine and hydrazine sulfate are both highly soluble in water.

Hydrazine is used primarily as a chemical intermediate and as a rocket fuel. The chemical has been used commercially as an oxygen scavenger in water boiler and heating systems. Hydrazine is used as an intermediate in the production of agricultural chemicals, spandex fibers, and antioxidants; as a polymerization catalyst; as a blowing agent; as a scavenger for gases; for plating metals on glass and plastics; and in fuel cells, solder fluxes, and photographic developers. Hydrazine sulfate is used in refining rare metals, as an antioxidant in soldering flux for light metals, in analytical tests for blood, as a biocide for fungi and molds, and in the preparation of hydrazine hydrate.

MONS 222816

Hydrazine is a suspect contaminant of liquid formulations of isoniazide, a drug used in treating tuberculosis. FDA is investigating the magnitude of the problem to ensure that the contamination of isoniazide is kept to the lowest detectable limit. Hydrazine sulfate has been investigated as an adjunct to antineoplastic drug treatment, although extensive use is not foreseeable. Its carcinogenic potential does not necessarily preclude use for this purpose; many antineoplastic agents are carcinogenic.

EPA has estimated 17 producers and importers of hydrazine in four regions, with domestic production of 7.' million lb and imports of 444,000 lb. Ten producers and importers of hydrazine sulfate were listed in the Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record; domestic production was reported as 562,000 lb; imports were not reported. Production of hydrazine was not reported to the U.S. International Trade Commission in 1979-1980. The 1982 Directory of Chemical Producers, however, indicates that three U.S. companies now produce hydrazine in commercial quantities.

The National Occupational Hazard Survey in 1974 estimated that about 11,600 workers were potentially exposed to hydrazine.

The environmental fate of hydrazine and its derivatives is largely unknown. All the simple hydrazine derivatives are polar, nonvolatile, and soluble in water. The use of hydrazine in boiler water treatment might result in its occurrence in discharged waste, but it would rapidly react with oxygen.

There is no known presence of hydrazine in consumer products. The possible route of human exposure to hydrazine is ingestion of trace residues in processed foods. Steam in contact with food must contain no hydrazine (21 CFR 173.310 (d)). In 1979, FDA proposed to revoke the use of hydrazine as a boiler water additive for boilers in contact with food. Final action is pending. The EPA regulates hydrazine under the Resource Conservation and Recovery Act. Hydrazine was the subject of a June 1978 NIOSH Criteria Document that considered a variety of serious health effects and recommended a reduction of the OSHA permissible exposure limit from 1 ppm (1.3 mg/m^3) time-weighted average to 0.04 mg/m^3 ceiling.

MONS 222817

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80. (EPA)	Regulation based on chronic toxicity of chemical. Fosters greater care in handling of chemical wastes. (EPA)	40 CFR 261.11, 261.33 (EPA)
Regulated as a secondary direct food additive for use in boiler water. Use is limited to zero content in steam in contact with food. (FDA)		21 CFR 173.310 21 CFR 173.310(d) (FDA)
PEL: 1 ppm (1.3 mg/m^3). potential for skin absorption noted. [Standard accepted for toxic effects other than cancer.] (OSHA)	Regulatory History: 1980: Walsh-Healy, 1 ppm (1.3 mg/m^3) TWA. (OSHA)	29 CFR 1910.1000 (OSHA)
NIOSH recommended a reduction of the OSHA PEL from 1.3 mg/m^3 TWA to 0.04 mg/m^3 ceiling. (NIOSH)		Criteria Document, 1978 (NIOSH)

MONS 222818

The evidence for the carcinogenicity in experimental animals can be considered sufficient for hydrazobenzene.[1,2] When administered in the feed, hydrazobenzene was carcinogenic to Fischer 344 rats of both sexes, causing increased incidences of hepatocellular carcinoma and Zymbal's gland squamous-cell neoplasms in male rats; and neoplastic nodules of the liver, and mammary adenocarcinomas in female rats. Hydrazobenzene was also carcinogenic to female B6C3F1 mice, causing an increased incidence of hepatocellular carcinomas. The compound was not carcinogenic to male mice.[1]

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[1]National Cancer Institute. Bioassay of Hydrazobenzene for Possible Carcinogenicity. Technical Report Series No. 92. DHHS Publication No. (NIH) 78-1342. Bethesda, Maryland, 1978.

[2]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis, eds. Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

Hydrazobenzene is insoluble in water but soluble in ethanol and ethers. The chemical name for hydrazobenzene is 1,2-diphenylhydrazine.

Hydrazobenzene finds its major use in the dye manufacturing industry as the precursor of the important dye intermediate benzidine, a potent carcinogen. The chemical is also used as an intermediate in the production of phenylbutazone, which is used in the treatment of rheumatoid arthritis and related conditions.

There are seven producers and importers of this chemical, with an annual domestic production of 373,000 lb and an annual import of 135,000 lb. Additional unknown quantities are produced at dye manufacturing facilities by the reduction of nitrobenzene to hydrazobenzene, prior to its rearrangement to benzidine.

The potential for exposure to hydrazobenzene is greatest for workers in the dye industry, although workers in the pharmaceutical industry may also be exposed. The primary route of exposure is through ingestion or inhalation of the chemical. There are no data for the numbers of persons exposed or possible levels of exposure, because there are no reliable estimates for its occurrence as an intermediate in the production of benzidine. Because of the importance of benzidine, the potential for exposure to its precursor, hydrazobenzene, probably involves many workers.

MONS 222819

The EPA has published a water quality criteria document for the protection of human health and has proposed a rule under the Toxic Substances Control Act that would require the reporting of data concerning the processing and use of hydrazobenzene. Hydrazobenzene is regulated under the Resource Conservation and Recovery Act, based on chronic toxicity.

Hydrazobenzene

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
No current action. (CPSC)		
CWA 311: Hazardous spill regulation designating reportable quantity as 100 lb (45.4 kg), proposed 7/9/80. Isomer of diphenylhydrazine not specified.	Based on carcinogenicity.	45 FR 133, p. 46094
CWA, 304(a): Water quality crite.. a published in final form, 11/28/80.		45 FR 231, p. 79318
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to Handling and report/recordkeeping requirements. Promulgated 5/19/80.	Based on chronic toxicity. Fosters greater care in handling of chemical wastes. (EPA)	40 CFR Pt.11, 261.33
TSCA, 8(a). Reporting rule requiring process and use data, proposed 2/29/80. (EPA)		45 FR 42, p. 13644 (EPA)

MONS 222820

INDENO(1,2,3-cd)PYRENE

There is sufficient evidence of the carcinogenicity of this compound in experimental animals. Indeno(1,2,3-cd)pyrene (IP) was shown to be a complete carcinogen and an initiator of skin carcinogenesis in the mouse (Swiss-albino HA/ICR/Mil). It produced local sarcomas in XVIInc/Z male mice after subcutaneous injection. It seems to be of lower potency as a skin carcinogen than benzo(a)pyrene.[1,2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 3. Lyon, France: IARC, 1973, pp. 229-37.

IP is a polycyclic aromatic hydrocarbon (PAH). Although reported for the Toxic Substances Control Act Inventory, IP is not commercially manufactured, and no use data are available. This compound is widely found as a byproduct of poorly controlled combustion that occurs in refuse burning, coal furnaces, diesel-powered vehicles, forest fires, and coke ovens. IP has been measured in soot at 15 ng/kg, in coal tar pitch at 7300-8300 ng/kg, and in petroleum asphalt at 1 ng/kg. It has also been isolated in smoke from cigarettes at concentrations ranging from 0.4 ug to 2.0 ug/cigarette. Fresh sausages contained 0.3 ug/kg, and low levels (0.9-1.6 ug/kg) have been detected in edible oils.

The 1974 National Occupational Hazard Survey has estimated that about 210,000 workers were exposed to PAHs found in asphalt, coal-tar and pitch volatiles, and coke oven emissions, all of which contain IP. An unspecified number of workers may be exposed to IP in the byproducts of combustion from fuel oil, diesel fuel, kerosene, and wood.

The EPA has included IP on the Carcinogen Assessment Group list of carcinogens. EPA regulates IP under the Resource Conservation and Recovery Act. Under the Toxic Substances Control Act, 8(a), EPA is proposing the reporting of process and use data, and under the Clean Water Act the Agency published a water quality criteria for the protection of human health.

MONS 222821

Indeno(1,2,3-cd)pyrene

REGULATIONS

Regulations and Other Actions	Effect of Regulation, Other Comments	Citation of Regulation
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 100 kg to handling and report/recordkeeping requirements. Also designates this compound as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	42 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring process and use data published 2/29/80.	Would, if promulgated, permit a basis for estimating exposure.	45 FR 42, p. 13644
See Carcinogen Assessment Group statement under 2-acetylaminofluorene.		
CWA, 304(a): Water quality criteria published in Final Form, 11/28/80. (EPA)		45 FR 231, p. 79318 (EPA)

MONS 222822

IRON DEXTRAN COMPLEX

There is sufficient evidence for the carcinogenicity of iron dextran complex in experimental animals; the evidence of carcinogenicity in humans is inadequate.[1]

Iron dextran complex was carcinogenic to mice and rats after subcutaneous or intramuscular injection, producing local tumors.[2]

There have been case reports of sarcomas in human subjects associated with injections of iron dextran. The tumors appeared at the probable site of injections, and the similarity of the local effect in humans and animals was noted.[1]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 2. Lyon, France: IARC, 1973, pp. 161-78.

Iron dextran is a complex of ferric hydroxide with dextran. Dextrans are polysaccharides produced by bacterial action on sucrose.

Iron dextran complex is used for parenteral treatment of iron-deficiency anemia in humans and baby pigs. The product for human use is a sterile, dark-brown colloidal solution in saline. The products designed for animal use are more concentrated.

The iron dextran complex was introduced in the United States in 1957. There is no record of current U.S. production, although it is known to be produced by two manufacturers. Iron dextran is available as two prescription items, Chromagen-D and Imferon. In 1980, 30,000 prescriptions were dispensed by pharmacies. The therapeutic dose for humans is 1-5 ml (50-250 mg iron) daily by deep intramuscular injection. Use is advised solely for those patients who have not responded to oral administration of iron. Clear warning of potential injection-site sarcoma is included with the physician's package insert.

The EPA has classified iron dextran as a hazardous waste constituent and regulates environmental release under the Resource Conservation and Recovery Act. The FDA approved iron dextran in 1974 and regulates this substance as a drug under the Federal Food, Drug, and Cosmetic Act.

MONS 222823

Iron Dextran Complex

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
no current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also design ted as a hazardous constituent of waste. Wastes known to contain iron dextran are subject to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
Regulatory Authority: FD&CA. Bureau of Drugs and Bureau of Veterinary Medicine regulated as an approved prescription drug. (FDA)	Use limited to iron deficiency that does not respond to oral treatments. Clear warning of potential injection-site sarcoma is included in physician package insert. (FDA)	40 FR, p. 13958 41 FR, p. 6065 42 FR, p. 53955 21 CFR 522.1182, 522 1183 (FDA)

MONS 222824

ISOPROPYL ALCOHOL MANUFACTURING (STRONG ACID PROCESS)

There is sufficient evidence that the manufacture of isopropyl alcohol (strong acid process) is carcinogenic in humans.[1] An increased incidence of cancer of the paranasal sinuses was observed in workers in factories manufacturing isopropyl alcohol by the strong-acid process. The risk of laryngeal cancer may also have been elevated. It is not clear which substances are responsible (diisopropyl sulfate, isopropyl oils, or other chemicals).[1,2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 15. Lyon, France: IARC, 1977, pp. 223-43.

Commercial isopropyl alcohol, a water-soluble alcohol, has been produced in the United States since 1921.

There are several industrial processes for the manufacture of isopropyl alcohol. One process using strong sulfuric acid leaves a residue composed of a mixture of many organic chemicals including isopropyl oils. No figures are available on the quantities of isopropyl oils formed during the manufacture of isopropyl alcohol through the strong acid process; newer processes have been replacing the strong acid method. The EPA reports annual production of isopropyl alcohol to be approximately 750 million lb. The amount of isopropyl oils produced is unknown. Diethyl sulfate, as well as isopropyl oils, have been suggested as a potential causative agent for the increased incidence of cancer in workers manufacturing isopropyl alcohol by the strong acid process.

Approximately 50 percent of the isopropyl alcohol is used in acetone production. Additional commercial uses are as a solvent, as a chemical intermediate, and in pharmaceutical and cosmetic formulations.

Human exposure is primarily through inhalation during the manufacture of isopropyl alcohol. NIOSH estimates that about 141,000 employees may be exposed to isopropyl alcohol in the United States. The EPA has no data to indicate that isopropyl oils are present in effluents, emissions, or wastes from production facilities.

MCNS 222825

Isopropyl Alcohol Manufacturing (Strong Acid Process)

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
The particular hazard cited is associated with the workplace. It is indicative that the process in which isopropyl oils are produced as by-products is decreasing. In addition, there is no indication that isopropyl oils are found in the effluents, emissions, or wastes of isopropyl alcohol manufacturers. (EPA)		

MONS 222826

KEPONE^{R} (CHLORDECONE)

There is sufficient evidence that chlordecone is carcinogenic in experimental animals.[1,2] After administration of chlordecone in the feed, a significant increase was found in the incidence of hepatocellular carcinomas in Osborne-Mendel rats and B6C3F1 mice. In addition, the time to detection of the first hepatocellular carcinoma observed at death was shorter for treated than control mice, and in both sexes and both species, it appeared inversely related to the dose.[3] In an earlier experiment in which rats, of unspecified strain, were exposed to chlordecone in the diet, hepatocellular carcinomas were seen in both sexes.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 67-81.

[3]National Cancer Institute. Bioassay of Chlordecone (Kepone) for Possible Carcinogenicity. DHHS Publication No. (NIH) 76-1278. Bethesda, Maryland, 1976.

Chlordecone is the common name for a synthetic chlorinated organic compound, which was commercially available under the trade name of Kepone^{R}.

Kepone^{R}, first introduced in 1958, has been used as an insecticide for leaf-eating insects, ants, and cockroaches, and as a larvicide for flies.

Kepone^{R} is not manufactured or used in the United States. In July 1975, the Virginia State Health Department ordered termination of production by the sole manufacturer of Kepone^{R} when a number of workers were found to have serious neurological disorders. Before the shutdown, the average annual production was estimated as 882,000 lb. More than 99 percent of the production was exported, and only 0.8 percent was available for domestic use, mainly as bait in ant traps.

Chlordecone is a degradation product of the insecticide mirex. This compound has been detected in soil at a level of 0.02 ug/g of soil 12 years after application of 1 ug/g mirex. In the United States, detectable levels of Kepone^{R} have been found in 400 samples of air, drinking water, plant and aquatic life, and municipal waste where Kepone^{R} was manufactured.

MONS 222827

Human exposure to chlordecone can occur by inhalation, ingestion, and skin absorption. There are many reports of its occurrence in human body fluids. In 1976, NIOSH had identified 50 establishments processing or formulating pesticides using Kepone® (chlordecone), and had estimated that about 600 workers were potentially exposed.

In 1977, formulators of Kepone® voluntarily canceled production. EPA canceled the registration of Kepone® under its Federal Insecticide, Fungicide, and Rodenticide mandate. All registered products containing Kepone® were effectively canceled by May 1, 1978. Distribution, sale, and use of Kepone® products formulated prior to May 1, 1978, were permitted until such stocks were exhausted. EPA has also regulated this compound under the Clean Water Act and the Resource Conservation and Recovery Act. On January 27, 1976, NIOSH recommended that the workplace level for Kepone® be limited to 1 $\mu g/m^3$ as a time-weighted average concentration for up to 10 hours/workday, 40 hours/workweek.

Kepone® (Chlordecone)

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
CWA, 311: Hazardous spill regulation establishing reportable quantity (1 lb, 0.454 kg) and imposing reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity, although the quantity triggering reporting requirements is most stringent under this rule	40 CFR 117 J, 117.13
FIFRA, 6: Voluntary cancellations of registrations (7/27/77) effectively removing product from market. Notice of intent to cancel published 4/11/77, not challenged as foregoing entry indicates.	Registrants were permitted to sell 500 lb of active ingredients after a determination that any additional risk of cancer would be very low. (EPA)	42 FR, p. 36 05 42 FR 59, p. 18695
RCRA, 3001-3006: subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates Kepone® as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR [illegible] (EPA)
Recommended workplace standard for Kepone®, 1 ug/m^3 TWA for 10 hr/day, 40 hr/workweek. (NIOSH)		

MONS 222828

LEAD ACETATE AND LEAD PHOSPHATE

There is sufficient evidence for the carcinogenicity of lead acetate and lead phosphate in experimental animals.[1] Lead acetate and lead phosphate are carcinogenic to rats, producing benign and malignant tumors of the kidney when administered in the diet or parenterally. Gliomas occurred in rats given lead acetate in the diet.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Suoplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 23. Lyon, France: IARC, 1980, pp. 325-415.

Lead acetate is water soluble. Lead phosphate is a white powder insoluble in water. Lead acetate is usually available commercially as hydrate (lead acetate trihydrate).

Lead acetate is used as a mordant in cotton dyes; in lead coating of metals; as a drier in paints, varnishes, and pigment inks; and in medicinals such as astringents. Concentrations up to 0.6 percent (weight to volume) are limited for use as color additives in hair dyes. For 1978, sales of lead acetate hair dyes exceeded 1 million bottles. Lead phosphate is used as a stebilizer in styrene and casein plastics.

In 1980, seven producers in three EPA regions reported domestic production levels of lead acetate to be approximately 407,000 lb. U.S. imports of lead acetate in 1978 were estimated at 250 lb. Imports in 1975 were approximately 6000 lb. No production figures were reported for lead phosphate, but the Toxic Substances Control Act, Chemical Substance Inventory, 1979 (public record), lists two producers.

Human exposure to lead acetate and lead phosphate occurs through ingestion, inhalation, and skin absorption. Lead acetate is absorbed at about 1.5 times the rate of other lead compounds. The National Occupational Hazard Survey (NOHS) in 1974 has estimated that 132,000 and 18,000 workers may have been exposed to lead acetate and lead phosphate, respectively. OSHA has estimated that 223,000 workers may be exposed to lead acetate, with 28,000 and 27,000 workers exposed to lead phosphate dibasic and lead phosphate tribasic, respectively. NOHS and OSHA numbers vary due to the difference in methodology used for estimating exposure.

NOHS 222829

The Consumer Product Safety Commission (CPSC) has banned paint and similar surface-coating materials for use in consumer products that contain lead or lead compounds in which the lead content is in excess of 0.06 percent of the weight of the product. This ban excludes artists' paints and related materials. CPSC staff evaluated consumer exposure to lead inks in printed consumer products. No lead was found in printed matter intended for children. Although lead was found in some inks used in printed products, the levels in the final products did not warrant further action. The CPSC staff indicated that there was little lead found in other printed consumer products. FDA regulates the use of lead acetate in hair dyes under the Food, Drug, and Cosmetic Act.

EPA regulates lead and certain lead compounds under the Resource Conservation and Recovery Act (RCRA), the Clean Water Act (CWA), and the Safe Drinking Water Act (SDWA). The dissociated lead addressed in these regulations would provide a degree of control over many lead compounds, including lead acetate and lead phosphate. CWA has published a water quality criteria document for the protection of human health. Under RCRA, the EPA established a maximum concentration of 50 ug/l in wastes for the protection of health. Under SDWA, a primary drinking water standard of 0.05 mg/l was published December 24, 1975. This standard was not based on carcinogenicity. OSHA has established permissible exposure levels of 50 ug/m^3 as an 8-hour time-weighted average and 60 ug/100 g as the maximum permissible blood lead level. In addition, the standard requires personal protective equipment, engineering and work practice controls, and medical surveillance with provisions for medical removal. OSHA regulates lead on the basis of acute and chronic toxicity for several organ systems, but not on the basis of carcinogenicity.

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REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
In 1972 the Lead Based Poison Prevention Act set a 0.5 percent limit for lead in paints. In 1976, the Act was amended to set the standard at 0.06 percent, this limit became effective in February 1978. 1982: No current action. (CPSC)	Exposure has been reduced, based on the lower limits allowed in paints. Use of lead acetate in inks is scheduled for screening. (CPSC)	16 CFR 1307 (CPSC)
SDWA: Dissociated Lead Primary standard of 0.05 mg/l, promulgated 12/24/75.	Not based on carcinogenicity. Major sources of lead in drinking water appears to be pipes, solder, and fixtures in the distribution system.	40 CFR 141.11
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates both as hazardous constituents of wastes. Promulgated 5/19/80.		40 CFR 261.11, 261.33
Designated as a toxic waste. Requires testing to determine if total lead exceeds that concentration. Promulgated 5/19/80.	Establishes a maximum concentration of 50 ug/l in wastes as criterion for health (based on general toxicity).	40 CFR 261.24
CWA, 304(a): Water quality criteria published in final form, 11/28/80.	Because lead dissociates in water, any any standard would afford some control over the named chemical.	45 FR 231, p. 79318
CWA, 311: Hazardous spill regulation establishing reportable quantity for lead acetate (5000 lb) and imposing reporting requirements. Promulgated 8/29/79.	Fosters greater care in handling and shipping of chemicals. Based on aquatic toxicity. (EPA)	40 CFR 117.3, 117.3
FIFRA, 4 Lead acetate was reviewed for possible regulation under FIFRA. In April 1978, jurisdiction was passed to FDA under an agreement that the questioned use was as a veterinary drug. (EPA)		OPP, Status Reports (EPA)
FDA Bureau of Drugs, FD&CA: Limits lead acetate in hair dyes to 0.6 percent (weight to volume), 10/31.80		45 FR, p. 72112
FDA listed lead acetate permanently for use in hair dyes, 3.8/81. (FDA)		21 CFR 731.2396 (FDA)
PEL: 50 ug/m³ 8-hr TWA, 50 ug/100 g maximum blood lead level. Protective clothing, hygiene, training, and medical surveillance requirements for workers; respirator requirements where engineering and work practice controls not sufficient or feasible, sign requirements for regulated areas; medical removal; income protection (for lead). (OSHA)	Regulatory History: 8/27/71: OSHA Takeover Standard--200 ug/m³ 8-hr TWA. 2/1/79: Final Standard--current regulations effective (for lead). (OSHA)	29 CFR 1910.1025 (OSHA)

MONS 222831

LINDANE AND OTHER HEXACHLOROCYCLOHEXANE ISOMERS

The evidence for the carcinogenicity of lindane and other hexachlorocyclohexane isomers in experimental animals was judged as limited by a recent IARC working group.[1] Another working group considered that there was sufficient evidence that α-HCH, lindane, and technical HCH are carcinogenic in mice, but the evidence for the carcinogenicity of β-HCH was evaluated as limited.[2] Technical α- and β-hexachlorocyclohexane and lindane, the γ-isomer, were carcinogenic in mice when administered in the diet, producing liver tumors. The technical-grade hexachlorocyclohexane also produced neoplasms. Studies in rats and dogs were considered to be inadequate, and so were tests by skin application of technical hexachlorocyclohexane and lindane. Hexachlorocyclohexane increased the incidence of liver neoplasms in rats previously treated with N-nitrosodiethylamine.[1,2]

The evidence for the carcinogenicity of lindane and other hexachlorocyclohexane isomers in humans was judged as inadequate.[1]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 195-239.

Lindane is the common name for the gamma isomer of hexachlorocyclohexane (HCH). Technical-grade HCH is a mixture of different isomers. Lindane is a colorless crystalline solid with a solubility of 10 mg/l in water.

Approximately 95 percent of the lindane and its isomers used in 1974 was in agriculture with the remainder used by industry. The major uses of lindane are for insecticidal treatment of hardwood logs and lumber, seed grains, and livestock; the minor uses are as an insecticide on several dozen fruit and vegetable crops and for personal hygiene (as a scabicide and pediculocide) in the form of lotion, cream, or shampoo.

Commercial production of lindane began in the United States in 1945 and ceased in 1976. Since 1976 lindane has been imported in an undisclosed amount. Production of lindane peaked in the 1950s when 15 million lb were manufactured. The chemical is not reported to the Toxic Substances Control Act, Chemical Substance Inventory, 1979 (public record); however, EPA in 1980 estimated that 1 million lb of lindane were used annually.

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Approximately 480,000 workers were occupationally exposed to these substances prior to Agency regulations (1977), which imposed limitations on uses. Workplace and residence use sites were primarily of concern as sources of exposure. Pesticide applicators were at highest risk of exposure to lindane.

The general population is at risk of exposure through the consumption of contaminated foodstuff. Major dietary sources include milk, eggs, dairy products, and, to a lesser extent, seafood. The dietary intake of lindane and its isomers by the U.S. population has been estimated to be in trace quantities with a significant, steady decline.

EPA has regulatory authority over the use of lindane and its isomers. EPA has proposed to limit exposure to lindane by canceling registration for all uses except on ornamentals, pineapples, livestock, and logs. The proposed action is scheduled to result in approximately an 80 percent reduction of the total estimated annual usage of 1 million lb. Continued use for the few permissible registrations would be restricted to certified personnel wearing appropriate protective clothing. EPA designated hexachlorocyclohexane as a toxic waste constituent. The Agency established a maximum concentration of 0.4 mg/l in wastes. During 1975, EPA promulgated drinking water standards limiting maximum contaminant levels to 0.004 mg/l. OSHA adopted a permissible exposure limit for lindane of 0.5 mg/m^3 as an 8-hour time-weighted average. This standard was adopted by OSHA for toxic effects other than cancer and noted lindane's potential for skin absorption.

MONS 222833

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
No current action No known presence in consumer products under CPSC jurisdiction (CPSC)		
FIFRA, 6 NPAR issued 2/14/77.	Agreement by producers to discontinue use of manganese isomers (mostly α and β). Based in part on recognition of inefficacy of manganese isomers.	42 FR, p. 9816
Proposed determination published 7/3/80.	Proposed immediate cancellation of registrations for most uses. Proposed 2-year phase-out of use on logs and acreages.	45 FR (30, p. 45362
RCRA, 3001-3004 Requires testing to determine if lindane exceeds stated concentration. Promulgated 5/19/80.	Designates lindane as a toxic waste. [Established a maximum concentration of 0.4 mg/l of lindane in wastes as a criterion for toxicity.	40 CFR 261.24
Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg of hexachlorocyclohexane (unspecified isomers) to handling and reports, recordkeeping requirements. Also designates hexachlorocyclohexane as a hazardous constituent of wastes. Promulgated 5/19/80.		40 CFR 261.11, 261.33
FIFRA, 6: Voluntary cancellation of registrations for all products using manganese isomers of HCH. 7/21/78. 319-84-6 α - HCH 319-85-7 β - HCH (Action applies to both).	Unreasonable risk and general ineffectiveness of ingredients.	43 FR, p. 31432
CWA, 304(a): Water quality criteria published in final, 11 28/80. Addresses α, β, and γ isomers, and technical grade products.		45 FR 231, p. 79318
CWA, 311 Hazardous spill regulation establishes reportable quant [illegible] lbs, 2.184 kg) for [illegible] imposes reporting requirement, 8/29/79.	Aquatic toxicity. Most stringent level, however, Fosters greater care in handling and shipping of chemicals.	40 CFR 117.3, 117.3
CWA, 311. Hazardous spill regulation designating reportable quantity, proposed, 7/9.80 (hexachloran,cyclohexane (other than lindane).	based on carcinogenicity.	45 FR 133, p. 46094
SDWA, 1412: Primary drinking water standard. Promulgated 12/24/75.	Maximum contaminant level of 0.00[illegible] mg/l established.	40 CFR 141.12
SDWA, 1412: Revision of primary or standards in development. (EPA)	Chronic toxicity is being considered. Target for proposal 8/83. (EPA)	SDW, memorandum, 3/81 (EPA)
PEL: 0.5 mg/m³ 8-hr TWA; potential for skin absorption notes (lindane). (Standard or rates for toxic effects other than cancer.) (OSHA)	6/21/71 OSHA "crossover standards"-- current limit effective. (OSHA)	29 CFR 1910,.000 (OSHA)

MONS 222834

MELPHALAN

There is sufficient evidence for the carcinogenicity of melphalan in humans and in experimental animals.[1] Melphalan is carcinogenic in mice and rats following intraperitoneal injection, producing lymphosarcomas, a dose-related increase in lung tumors in mice, and peritoneal sarcomas in rats.[2]

Case reports of second primary malignancies (mainly acute leukemia) in patients treated with melphalan have been published. Epidemiological studies showed substantially increased rates of leukemia in patients treated with melphalan for multiple myeloma and ovarian cancer. Some of these patients were also treated with other alkylating agents and ionizing radiation; however, sufficient numbers of patients were treated with melphalan alone to implicate it as the causal factor. Additionally, the incidence of acute leukemia in patients with multiple myeloma has increased since the introduction of melphalan therapy.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 9. Lyon, France: IARC, 1975, pp. 167-80.

Melphalan is a nitrogen mustard that is practically insoluble in water.

This drug is used in the treatment of multiple myeloma and cancer of the ovary. It is also used in investigation on other types of cancer and as an antineoplastic in animals.

Melphalan is not produced in the United States, although one marketer in the United States has been reported. In 1979, 3000 lb were imported.

Human exposure to melphalan occurs principally during its use in cancer treatment. FDA estimates that 30,000 to 50,000 patients may be treated each year. Melphalan is administered orally or intravenously. Adult dose rate is 6 mg per day, 5 days per month.

Melphalan has been approved by the FDA for treatment of myeloma and epithelial ovarian cancer. For certain other cancers, it has been approved for investigational use only. As with other potent antineoplastic agents, the likelihood of these drugs being carcinogenic is not surprising, and its clinical use recognizes that risk by its restrictive approved clinical indications. EPA regulates melphalan under the Resource Conservation and Recovery Act.

MONS 222835

Melphalan

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and reporting/recordkeeping requirements. Also designates melphalan as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.(I, 261.33) (EPA)
FDA Bureau of Drugs, FD&CA: Approved drug for treatment of myeloma and epithelial ovarian cancer. Investigational use only for certain other cancers. (FDA)	Use restricted to Bureau of Drugs-approved treatments. As with other potent antineoplastic agents, the restricted use limits potential risk to the patient. (FDA)	CFR 21, Subchapter D (FDA)

MONS 222836

4,4'-METHYLENEBIS(2-CHLOROANILINE) (MOCA)

There is sufficient evidence for the carcinogenicity of 4,4'-methylenebis(2-chloroaniline) in experimental animals.[1] 4,4'-Methylenebis(2-chloroaniline) was carcinogenic in mice and rats (several strains) after dietary administration, producing vascular, liver and lung tumors. It also produced distant tumors (liver cell carcinomas and primary lung carcinomas) in Wistar rats after subcutaneous injection.[2]

There are no conclusive epidemiological studies on which the evaluation of human carcinogenic risk could be based. In a study of 31 men, whose exposure to MOCA ranged from 6 months to 16 years, no cytological evidence was found of bladder cancer. In addition, 178 other MOCA workers with unstated duration of exposure were also examined cytologically more than 10 years after exposure had ceased, and no cases of bladder cancer were found.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 4. Lyon, France: IARC, 1974, pp. 65-71.

4,4'-Methylenebis(2-chloroaniline), an aromatic amine, is commonly referred to as MOCA. It is only slightly soluble in water, but soluble in most organic solvents and lipids. MOCA is commercially available in pellet, liquid, and granular form, and as a premixed compound with polyhydric alcohols.

MOCA has been used as a curing agent in urethane and epoxy resin systems containing isocyanates, which are utilized in the manufacture of certain products, particularly integral-skin polyurethane semirigid foam for crash padding, and solid urethane rubber moldings, such as gear blanks and industrial tires. It is also consumed in the manufacture of gun mounts, jet engine turbine blades, radar systems, and home appliances. In the laboratory, MOCA has been regarded as a model compound in the study of carcinogens.

Production of MOCA was first reported to the U.S. Tariff Commission in 1950. EPA estimated five producers and importers of MOCA in two regions, with a domestic production of 369,000 lb; no imports were reported (Toxic Substances Control Act (TSCA) Inventory, 1977, public record). MOCA was not reported to the U.S. International Trade Commission in 1980; however,

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production of MOCA was indicated in 1979 by two producers, which implied an annual production of more than 10,000 lb. The 1982 Directory of Chemical Producers indicates that one U.S. company now produces MOCA. CPSC indicated only one U.S. manufacturer of MOCA as of 1981.

The CPSC staff stated that residual levels of MOCA may be present in the final product. However, data describing the actual levels of impurities and the potential for consumer exposure are currently lacking. The National Occupational Hazard Survey in 1974 estimated that 33,000 workers were potentially exposed to MOCA.

When used as a curing agent, MOCA is melted before mixing into elastomer formulations and could possibly be volatilized and emitted into waste gases and wastewater from plants where it is being used. In 1971, MOCA was detected in all samples of soil that were obtained within a three-quarters mile radius of a chemical plant in Adrian, Michigan. Some samples taken from soil on public roads in the area contained more than 500 ppm MOCA. Sludge from the Adrian wastewater treatment plant contained as much as 86 ppm MOCA, whereas samples of sludge obtained from the industrial lagoon contained 2000 ppm. Urine from workers at the plant contained levels as high as 49 ppm of MOCA per liter of urine.

Currently MOCA is regulated by EPA under the Resource Conservation and Recovery Act, and regulation is proposed under TSCA, 8(a), that would provide detailed production and marketing data. NIOSH issued a Special Hazard Review on MOCA in 1978, recommending a standard of 3 ug/m^3 time-weighted average The OSHA standard for MOCA was suspended by court action in 1974.

MONS 222838

4,4'-Methylenebis(2-chloroaniline) (MOCA)

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity of chemical. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13645 (EPA)
Substance prohibited from use in human food. (FDA)		21 CFR 189 (FDA)
	Regulatory History: 5/3/73: Emergency Temporary Standard--protective clothing and hygiene requirements for workers, restrictions on open-vessel operations, engineering requirements. 1/29/74: Revised standard promulgated. 12/7/74: U.S. Court of Appeals remanded standard. (OSHA)	
NIOSH recommended a standard of 3 mg/m^3 TWA. (NIOSH)		Special Hazard Review, 1978 (NIOSH)

MONS 222839

4,4'-METHYLENEBIS(N,N-DIMETHYL)BENZENAMINE

4,4'-Methylenebis(N,N-dimethyl)benzenamine, administered in the feed, was carcinogenic in male and female Fischer 344 rats, inducing thyroid follicular-cell carcinomas, and in female B6C3F1 mice, causing a combination of hepatocellular carcinomas and hepatocellular adenomas. There was no conclusive evidence that 4,4'-methylenebis(N,N-dimethyl)benzenamine was carcinogenic in male B6C3F1 mice.[1] An IARC working group considered that there was limited evidence for the carcinogenicity of this substance in experimental animals.[2] In view of another evaluation the evidence can be regarded as sufficient.[3]

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[1]National Cancer Institute. Bioassay of 4,4'-Methylenebis(N,N-dimethyl)benzenamine for Possible Carcinogenicity. Technical Report Series No. 186. DHEW Publication No. (NIH) 78-1742. Bethesda, Maryland, 1979.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 27. Lyon, France: IARC, 1982, pp. 119-24.

[3]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis (eds.). Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

4,4'-Methylenebis(N,N-dimethyl)benzenamine, commonly referred to as Michler's base, is an aromatic amine. It is insoluble in water and soluble in benzene, acids, diethyl ether, and carbon disulfide.

Michler's base is used as an intermediate in dye manufacture and as an analytical reagent in the determination of lead.

The Society of Dyers and Colourists reported that six dyes and one pigment can be prepared from the chemical. In 1979, only one of the dyes, Basic Yellow 2, was being produced commercially by two companies.

Michler's base has been commercially produced in the United States since at least 1921. EPA estimated five producers and importers in two regions, with domestic production reported as 370,000 lb, and no imports (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). U.S. production of Michler's base was reported to the U.S. International Trade Commission as greater than 10,000 lb in 1980.

MONS 222840

According to the CPSC staff, it is possible that residual levels of Michler's base may be present in the final consumer product. Exposure even to trace amounts may be a cause for concern. This concern is based on experience with other dyes derived from aromatic amines. However, data describing the actual levels of impurities in the final product are currently not available. The potential for exposure is greatest among workers in the dye and chemical manufacturing industries. In 1974, the National Occupational Hazard Survey estimated that 1600 workers were potentially exposed to Michler's base.

EPA is proposing a reporting rule for Michler's base under TSCA, 8(a).

4,4'-Methylenebis(N,N-dimethylbenzenamine

REGULATIONS		
Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
No current action. (CPSC)		
TSCA, 8(a): Reporting rule requiring process and use data, proposed 3/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action (EPA)	45 FR, p. 13648 (EPA)

MONS 222841

MICHLER'S KETONE

Michler's Ketone, administered in the feed, was carcinogenic in male and female Fischer 344 rats and female B6C3F1 mice, causing hepatocellular carcinomas; in male B6C3F1 mice it produced hemangiosarcomas.[1] These results can be considered as providing sufficient evidence for the carcinogenicity of Michler's Ketone in experimental animals.[2]

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[1]National Cancer Institute. Bioassay of Michler's Ketone for Possible Carcinogenicity. Technical Report Series No. 181. DHEW Publication No. (NIH) 78-1737. Bethesda, Maryland, 1979.

[2]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: U. Montesano, H. Bartsch, and L. Tomatis (eds.). Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

Michler's ketone, a derivative of dimethylaniline, is an aromatic amine, which is practically insoluble in water.

Michler's ketone is used as a chemical intermediate in the synthesis of at least 13 dyes and pigments, especially auramine derivatives.

EPA reported 10 producers and importers in three regions, with a domestic production of 37,000 lb and imports of 37,000 lb (Toxic Substances Control Act (TSCA), Chemical Substances Inventory, 1979, public record). One domestic producer manufactured a quantity insufficient for reporting to the U.S. International Trade Commission in 1979-1980, but imports of Michler's ketone amounted to 40,000 lb in 1980.

Human exposure to Michler's ketone may occur through inhalation and skin absorption. Occupational exposure is greatest for workers in facilities that manufacture the compound or any of the dyestuffs for which Michler's ketone is an intermediate. In 1974, the National Occupational Hazard Survey made no estimate on potential worker exposure to Michler's ketone (NIOSH). Residual levels or trace impurities of Michler's ketone may possibly be present in some dyes based on this chemical and in the final consumer product. Exposure even to trace amounts may be a cause for concern. This concern is based on the experience with other dyes derived from aromatic amines. Data are inadequate to describe the actual levels of impurities in the final product, the potential for consumer exposure, and the uptake.

EPA now regulates Michler's ketone under the Resource Conservation and Recovery Act and has proposed regulation under the Toxic Substances Control Act, 8(a).

MONS 222842

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
No current action. (CPSC)		
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)

MONS 222843

There is sufficient evidence that mirex is carcinogenic in experimental animals.[1] Mirex has been tested in two strains of mice by gavage and by administration in the diet and in rats by administration in the diet. It has also been tested in two strains of mice by subcutaneous injection of single doses. In the studies using oral administration, it produced benign and malignant liver tumors in mice and rats of both sexes. An excess of liver tumors was also found in males of one of the two strains of mice following a single subcutaneous injection; this experiment also suggested that it produced reticulum-cell sarcomas in males of both strains.[2]

[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 283-301.

Mirex, a chlorinated cyclic hydrocarbon, is practically insoluble in water. Mirex was used extensively in the southeastern United States for control of the fire ant. From 1962 to 1978, about 132 million acres in 10 states were treated with mirex bait (consisting of 497,000 lb of mirex). The bait was aerially applied in most cases. Mirex was also used to treat other species of ants and yellow jackets, but it was most effective as a species-specific pesticide. One company has marketed mirex as a fire-retardant additive.

Mirex first became commercially available in the United States in 1958. There is no current production of mirex because its registrations for technical products were canceled as of December 1977. Prior to this action, it was manufactured by two U.S. producers in significant amounts and some quantities were imported; no specific data were available.

According to the 1974 National Occupational Hazard Survey, an estimated 1000 workers were potentially exposed to mirex. Because insecticidal use of mirex has been discontinued, direct human exposure is small. However, residues have been detected in water, soil, food and beverages, and human tissues for as long as 12 years after exposure. These residues may result in general population exposure. Mirex is known to degrade in soil to yield Kepone®.

In December 1976, EPA, under the Federal Insecticide, Fungicide, and Rodenticide Act, canceled the registrations of pesticides containing mirex, effective December 1, 1977, with specified termination of uses of existing stock. The State of Mississippi received an emergency exemption from EPA for specific uses effective through June 1979.

MONS 222844

Mirex

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
FIFRA, 6: Registrations for technical products canceled, 12/76; effective 12/77. All products and uses were included. (EPA)	Remaining stocks could be used before 12/31/77. Emergency use permits were granted in 1977-78, but have been denied since that time. (EPA)	41 FR, p. 1670] (EPA)

MONS 222845

MUSTARD GAS

The evidence of carcinogenicity of mustard gas in humans is sufficient; the evidence in experimental animals is limited.[1] Mustard gas is carcinogenic in mice, the only species tested, after inhalation or intravenous injection producing lung tumors, and after subcutaneous injection producing local sarcomas.[2]

Several studies have shown an increased mortality from respiratory tract cancer among individuals exposed to mustard gas. This mortality was greater in those with chronic occupational exposure than in those with sporadic exposure.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 9. Lyon, France: IARC, 1975, pp. 181-92.

Mustard gas is a colorless, oily liquid that is sparingly soluble in water.

Mustard gas was used in chemical warfare primarily during World War I. Mustard gas has been tested as an antineoplastic agent, but its clinical use as a tumor inhibitor has been minimal. It is used as a model compound in biological studies of alkylating agents.

Mustard gas is not in the Toxic Substances Control Act, Chemical Substance Inventory (1979) of commercial chemicals nor is there any indication that there is any manufacture or use in the United States at the present time. Production and stockpiling of this chemical took place during World War II, and stocks may have existed in the United States as recently as 1974.

If production of mustard gas as a chemical warfare agent were to be resumed, it would probably be excluded from regulation under the National Security Clause. However, the Resource Conservation and Recovery Act designates mustard gas as a hazardous constituent of waste, should it be produced again.

MONS 222846

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
RCRA, 3001-3004: Designates mustard gas as a hazardous constituent of waste, and subject wastes known to contain it to handling and report/recordkeeping requirements. Promulgated 5/19/80. If production of mustard gas as a chemical warfare agent were to be resumed, it would probably be excluded from regulation under the National Security Clause contained in each authority. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261 11 (EPA)

MONS 222847

2-NAPHTHYLAMINE

There is sufficient evidence for the carcinogenicity of 2-naphthylamine both in humans and in experimental animals.[1] 2-Naphthylamine was carcinogenic, producing urinary bladder carcinomas in hamsters, dogs, and non-human primates, and hepatomas in mice, after oral administration (by stomach tube or in the diet).[1,2]

Epidemiological studies have shown that occupational exposure to 2-naphthylamine, either alone or when present as an impurity in other compounds, is causally associated with bladder cancer.[1,2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 1. Lyon, France: IARC, 1979, p. 38.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 4. Lyon, France: IARC, 1974, pp. 97-111.

2-Naphthylamine, an industrial chemical, is soluble in hot water, alcohol, and many organic solvents.

2-Naphthylamine has been used principally as an intermediate in the manufacture of dyes and as an antioxidant in the rubber industry. In recent years, other chemicals have been substituted for 2-naphthylamine, and it is now used for research purposes only.

2-Naphthylamine has not been produced or imported in the United States since January 1, 1975. However, it had been produced commercially in substantial amounts for nearly 50 years. United States imports amounted to 38,000 lb in 1967. The company that had reported 2-naphthylamine for the Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, withdrew their report in 1980 (CPSC). The Federal Register notice of this amendment was published in 1981 (CPSC, EPA).

Human exposure to 2-naphthylamine is primarily through inhalation. Prior to the discontinuation of domestic production and use in the dye and rubber industries, an estimated 1000 workers were potentially exposed. 2-Naphthylamine has been reported in coal tar, cigarette smoke (0.02 ug/cigarette), and as an impurity in commercial 1-naphthylamine (0.5 percent or less).

The EPA regulates 2-naphthylamine under the Resource Conservation and Recovery Act and under the TSCA. The OSHA standard for 2-naphthylamine, promulgated in 1974, includes protective clothing, engineering controls, and medical surveillance requirements.

MONS 222848

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products. (CPSC)		
RCRA, 3001-3004 Subjects waste products, off-specification discards, and spill residues in excess of 1000 kg to handling and report/race keeping requirements. Also designates 2-naphthylamine as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
EPA has removed 2-naphthylamine from the TSCA inventory and reported in June 1981, that there was no current manufacture, importation, or processing of 2-naphthylamine. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		46 FR 30560 (EPA)
Protective clothing, respiratory, hygiene training, and medical surveillance requirements for workers, exhaust fan requirements; open-vessel operations prohibited; contamination control requirements; signs requirements for area, labeling requirements for containers. (OSHA)	Regulatory History: 5/10/73: Emergency Temporary Standard--protective clothing and hygiene requirements for workers, open-vessel operations restricted, engineering requirements. 2/11/74: Final Standard--current regulations effective (OSHA)	29 CFR 1910.1009 (OSHA)

MONS 222849

NICKEL REFINING, NICKEL, AND CERTAIN NICKEL COMPOUNDS

There is sufficient evidence that nickel refining is carcinogenic to humans.[1] Epidemiological studies have demonstrated increased incidences of cancer of the nasal cavity, lung, and possibly larynx in workers in nickel refineries. It is not possible, however, to specify which specific nickel compounds are carcinogenic for humans.[2]

The evidence of carcinogenicity of nickel and certain nickel compounds in experimental animals is sufficient.[1] Nickel subsulfide is carcinogenic in rats by inhalation, producing lung cancer. Nickel compounds (nickel powder, subsulfide, oxide, carbonate, and nickelocene) produced local sarcomas in mice, rats and hamsters when given intramuscularly. Inhalation of nickel carbonyl produced a low incidence of lung tumors in rats.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 11. Lyon, France: IARC, 1976, pp. 75-112.

Nickel is a metallic element used in steel and other alloy manufacturing and in electroplating. Nickel is also used to make coins, as a chemical catalyst, in ceramics, in storage batteries, electric circuits, coloring glass, petroleum refining, and in the hardening of edible oils.

The combined annual domestic production of nickel and 14 nickel compounds is 121 million lb, and imports total approximately 330 million lb.

Human exposure to nickel and nickel compounds is through ingestion, inhalation, and skin absorption. These exposures can occur from the presence of nickel in air, water, soil, food, and consumer products. OSHA estimates that 709,000 workers are potentially exposed to nickel and its compounds. EPA estimates that nearly 720,000 people living within 12.5 miles (20 km) of primary sources may be exposed to nickel at concentrations up to 15.8 ug/m^3 (median, 0.2 ug/m^3). As many as 160 million people live within 12.5 miles of all sources of nickel and nickel compounds, and they may be exposed to median concentrations of 0.05 ug/m^3. The entire population may be exposed to low levels of nickel (300-600 ug/day) in food and water. Nickel levels in U.S. drinking water are estimated as less than 10 ug/l. Food processing methods can increase dietary nickel levels by means of leaching from nickel-containing alloys.

MONS 222850

Environmental sources of nickel include emissions from coal- and oil-fired boilers, coke ovens, diesel-fuel burning, and gray iron foundries. Total annual emissions from these types of sources were estimated at 22.4 million lb. Soils normally contain nickel in the range of 5-500 ppm, and soils from serpentine rock may contain as much as 5000 ppm.

The EPA regulates nickel and nickel compounds under the Clean Water Act and the Resource Conservation and Recovery Act. Certain nickel compounds have been proposed for regulation under the Toxic Substances Control Act. FDA does not regulate nickel as a food additive. OSHA has adopted permissible exposure levels of 0.007 mg/m^3 as an 8-hour time-weighted average for nickel carbonyl and 1 mg/m^3 as an 8-hour time-weighted average for metal and soluble compounds. This standard was adopted by OSHA for toxic effects other than cancer.

The Consumer Product Safety Commission (CPSC) staff preliminarily determined in 1980 that nickel carbonyl was not present in consumer products under CPSC jurisdiction. The Commission subsequently requested (45 FR 16344) public comment to verify the accuracy of its information. No comments were received on this chemical. Pending the receipt of new information, the Commission plans no action on nickel carbonyl.

MONS 222851

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Nickel: No current action. No known presence in consumer products (CPSC)		45 FR, p 16344 (CPSC)
CWA, 301 Effluent guidelines for certain industrial categories address nickel. Promulgated 3.12/74, 4/24/75 with subsequent revisions.	Control established through NPDES permits. Carcinogenicity was not considered in developing these guidelines. Repromulgation for some will occur in mid-1981.	40 CFR 413, 415 (portions)
CWA, 304(a) Water quality criteria published in final form, 11/28/80.	Protection of human health (general toxicity) 13.4 ug/l.	45 FR 231, p 79318
RCRA, 3001-3004 Nickel and nickel compounds not otherwise specified are listed as hazardous constituents of waste. Wastes known to contain nickel are subject to handling and report/recordkeeping requirements Promulgated 5/19/80.		40 CFR 261.11
RCRA, 4004. Land application of sludges containing nickel under assessment, pending formulation of an EPA policy on sludge.		OSW, personal communication, 4/82
CWA, 405: Limitation on concentration of nickel and other toxics in sludges intended for use as soil conditioners under study.	Development or hold pending formulation of an EPA policy on sludge. (EPA)	OSW, personal communication, 4/82
TAA: Assessment of sources and exposures completed 5/80. Under continuing assessment to determine if risks warrant regulation. Determination anticipated late 1981 or early 1982.		OAQPS, personal communication, 10/80 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene (EPA)		
FDA Bureau of Foods, Bureau of Medical Devices, FD&CA Not regulated as a "food additive" No regulation on nickel present in implants		
No action has been taken on nickel as a carcinogen because the data available are not adequate to assess its carcinogenicity through dietary exposure (FDA)		
PEL 15 mg Ni/m³ (8-hr TWA Recommended standard for inorganic nickel (1977) containing recommendations for medical surveillance, labeling and posting, personal protective clothing and equipment, work practices, monitoring of workplace air, employee education. (NIOSH)		
PEL 0.001 ppm (0.007 mg/m³) 8-hr TWA (nickel carbonyl), 1 mg/m³ 8-hr TWA (as Ni metal and soluble Ni compounds) (Standard adopted for toxic effects other than cancer.) (OSHA)	Regulatory History. 1952: Walsh-Healy, 1 ppm (nickel carbonyl) maximum allowable concentration. 8/27/71, OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

(Continued)

MONS 222852

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Nickel Acetate (Basic Nickel Acetate)		
TSCA, 8(a): Reporting rule requiring process and use data proposed, 2/29/80.		45 FR 42, p. 13646
RCRA, 3001-3004: Nickel and nickel compounds not otherwise specified are designated as hazardous constituents of waste, and wastes known to contain them are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.33 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Nickel Ammonium Sulfate:		
CWA, 311: Hazardous spill regulation establishing reportable quantity 15000 lb, 2270 kg) and targeting reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures. (EPA)	40 CFR 117.3, 117.33
RCRA, 3001-3004: Nickel and nickel compounds not elsewhere specified are designated as hazardous constituents of waste, and wastes known to contain them are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)		45 FR 42, p. 13646 (EPA)
See Nickel. (NIOSH)		
See regulation for nickel. (OSHA)		29 CFR 1910.1000 (OSHA)
Nickel Carbonate		
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80.		45 FR 42, p. 13646
RCRA, 3001-3004: Nickel and nickel compounds not otherwise specified are designated as hazardous constituents of waste, and wastes known to contain them are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.33 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

(Continued)

MONS 222853

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Nickel Carbonyl		
No current action - no known presence in consumer products (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1 lb to handling and report/recordkeeping requirements. Also designates nickel carbonyl as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 6/(illegible)/80.		40 CFR 261.11, 261.33
TSCA, 8(a). Reporting rule requiring process and use data, proposed 2/29/80. (EPA)		45 FR 42, p. 13646 (EPA)
PEL: 7 mg/m^3 (1 ppb) 8-hr TWA. Special Hazard Review containing recommendations for medical surveillance, sanitation engineering, signs for regulated areas, personal protective clothing and equipment, recordkeeping requirements. (NIOSH)		
PEL: 7 mg/m^3 (1 ppb) 8-hr TWA. (OSHA)		29 CFR 1910.1000 (OSHA)
Nickel Chloride:		
CWA, 311: Hazardous spill regulation, establishing reportable quantity (1000 lb, 2270 kg) and imposing reporting requirements. Promulgated 6/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures. (EPA)	40 CFR 117.3, 117.11
RCRA, 3001-3004: Nickel and nickel compounds not otherwise specified are designated as hazardous constituents of waste, and wastes known to contain them are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.11
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80 (EPA)		45 FR 42, p. 13646 (EPA)
See nickel. (NIOSH)		
See nickel regulation (OSHA)		29 CFR 1910.1000 (OSHA)
Nickel Hydroxide:		
CWA, 311: Hazardous spill regulation establishing reportable quantity (1000 lb, 454 kg) and imposing reporting requirements. Promulgated 6/29/79.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures. (EPA)	40 CFR 117.3, 117.11
RCRA, 3001-3004: Nickel and nickel compounds not otherwise specified are designated as hazardous constituents of wastes. Wastes known to contain any of them are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80. (EPA)		40 CFR 261.11 (EPA)

(Continued)

MONS 222854

REGULATIONS		
Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Nickel Oxide		
RCRA, 3001-3004 Designates nickel compounds not otherwise specified as hazardous constituents of waste, and subjects wastes known to contain them to handling and report/recordkeeping requirements. Promulgated 5/19/81.		50 CFR 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)		46 FR 41, p. 13646 (EPA)
Nickel Subsulfide:		
RCRA, 3001-3004. Designates nickel compounds not otherwise specified as hazardous constituents of waste, and subjects wastes known to contain them to handling and report/recordkeeping requirements. Promulgated 5/19/81.		40 CFR 261.33
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80. (EPA)		46 FR 42, p. 13646 (EPA)
Nickel Sulfate		
CWA, 311: Hazardous spill regulation, establishing reportable quantity (5000 lb, 2270 kg) and imposing reporting requirements. Promulgated 8/29/78.	Not based on carcinogenicity. Encourages greater care in handling and shipping chemicals and should result in reduction of accidental exposures. (EPA)	40 CFR 117.3, 117.11
RCRA, 3001-3004 Nickel and nickel compounds not otherwise specified are designated as hazardous constituents of wastes, and wastes known to contain them are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80 (EPA)		40 CFR 261.11 (EPA)
See nickel (NIOSH)		
See regulation for nickel. (OSHA)		29 CFR 1910.1000 (OSHA)
Nickelocene		
RCRA, 3001-3004 Nickel and nickel compounds not otherwise specified are designated as hazardous constituents of wastes, and wastes known to contain them are subject to handling and report/recordkeeping requirements. Promulgated 5/19/80. (EPA)		40 CFR 261.33 (EPA)

MONS 222855

NITRILOTRIACETIC ACID

Long-term feeding studies to test the monohydrate of the trisodium salt of nitrilotriacetic acid ($Na_3NTA \cdot H_2O$) for carcinogenicity were conducted using Fischer 344 rats; and both Fischer 344 rats and B6C3F1 mice. Similar bioassays, using rats and mice, were conducted with the free nitrilotriacetic acid (NTA). NTA and $Na_3NTA \cdot H_2O$ were shown to be carcinogenic to the urinary tract and kidneys of both rats and mice.[1] Trisodium nitrilotriacetic acid was found to be carcinogenic in the kidney when administered in drinking water to male albino rats (Crl/COBS CD (SD) BR).[2]

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[1]National Cancer Institute. Bioassay of Nitrilotriacetic Acid (NTA) and Nitrilotriacetic Acid, Trisodium Salt, Monohydrate ($Na_3NTA \cdot H_2O$) for Possible Carcinogenicity. Technical Report Series No. 6. DHEW Publication No. (NIH) 77-806. Bethesda, Maryland, 1977.

[2]Goyer, R.A., H.L. Falk, M. Hogan, D.D. Feldman, and W. Richter. Renal Tumors in Rats Given Trisodium Nitrilotriacetic Acid in Drinking Water for Two Years. J. Nat. Cancer Inst. Vol. 66, 1981, pp. 869-80.

Nitrilotriacetic acid (NTA) is a chelating agent that is insoluble in water and most organic solvents; however, it can form mono-, di-, and tri-basic salts that are soluble in water.

EPA reported that NTA replaced phosphates as a detergent builder in the late 1960s. In 1971, the use of NTA was discontinued. The possibility of resumed use arose in 1980. The Consumer Product Safety Commission (CPSC) stated that NTA is now used in laundry detergents in two states where phosphates are banned. FDA reported that NTA is also used as a boiler feedwater additive at a maximum use level of 5 ppm of trisodium salt. Currently, the remaining nondetergent uses of NTA are for water treatment, textile treatment, metal plating and cleaning, and pulp and paper processing.

EPA reported that the domestic production for 1979 was 70-75 million lb, with 50-65 million lb exported. Estimates indicate that reintroduction would increase production to 250 million lb immediately and to 1 billion lb in the near future, with most of this amount used domestically. The EPA (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record) estimated three producers and importers in three regions. Domestic production data were not available, but imports were 37,500 lb. Production reported to the U.S. International Trade Commission for 1980 was more than 5000 lb of NTA and more than 15,000 lb of its trisodium salt.

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The route of human exposure is ingestion of trace residues that possibly remain in processed foods. In 1974, the National Occupational Hazard Survey estimated that 14,600 workers were potentially exposed to NTA, and 46,000 workers were exposed to NTA trisodium salt. NTA levels in the U.S drinking water prior to NTA's discontinued use in detergents was estimated by EPA to have ranged from 0.20-24.5 ug/l. NTA is rapidly degraded under aerobic conditions at temperatures above 5° C, and biodegradation does not lead to the formation of persistent intermediates.

Until the spring of 1980, industry voluntarily abstained from using NTA in detergents in the United States. At that time, EPA released a risk assessment on the use of NTA in laundry detergents. In response to a request by one manufacturer to resume use of NTA, it was stated that "...projected levels of exposure from the use of this substance in laundry detergents are generally low, and therefore the associated risks would also be low." EPA decided not to take regulatory action against the use of this substance for laundry detergent, but cautioned against its use in shampoos, foods, hand dishwashing detergents, and other products designed to give direct oral or dermal exposure.

EPA has determined that the exposure to NTA is low (1 ug/kg/day/adult), but has included some caveats as recommendations to manufacturers and processors (March 1980). The recommendations were given under TSCA. FDA regulates NTA as a secondary direct food additive, i.e., as a substance added to food during preparation or handling, and subsequently removed before the food is ready for consumption. FDA limits the nitrilotriacetate added to boiler feedwater to 5 ppm. FDA is currently reviewing the carcinogenicity data on NTA for possible future regulatory actions.

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REGULATIONS

Regulations and Other Actions	Effect of Regulations· Other Comments	Citation of Regulation
No current action. (CPSC)		
TSCA, S, 5--Recommendations: - Manufacturers and processors should employ strict controls to limit occupational exposure. - Should not be used in consumer products designed to have direct oral or dermal exposure. - Manufacturers should conduct monitoring and environmental studies to confirm projections of low environmental levels; EPA to participate in design. - Manufacturers and processors should maintain record of reports of ingestion of NTA-containing detergents. (EPA)	Animal carcinogenicity is established, but the compound does not appear to be a mutagen or teratogen. Exposure projected to be low (1 ug/kg/day/adult). (EPA)	Letter from S.B. Jellinek, to Procter & Gamble and Monsanto, 6/27/80. Testimony to Investigations and Oversight Subcommittee, Interstate and Foreign Commerce Committee, House of Representatives, 6/2/80. Five other companies notified prior to 7/29/80. (EPA)
Nitrilotriacetate added to boiler feedwater is limited to 5 ppm. (FDA)		21 CFR 173.310(d) (FDA)

MONS 222858

5-NITRO-o-ANISIDINE

5-Nitro-o-anisidine, administered in the feed, was carcinogenic in Fischer 344 rats, causing tumors of the integumentary system in males and females, and tumors of the clitoral gland in females. The compound was also carcinogenic in female B6C3F1 mice, causing hepatocellular carcinomas.[1] This evidence of carcinogenicity in experimental animals was considered as limited by an IARC working group.[2] In view of another evaluation it can be regarded as sufficient.[3]

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[1]National Cancer Institute. Bioassay of 5-Nitro-o-anisidine for Possible Carcinogenicity. Technical Report Series No. 127. DHEW Publication No. (NIH) 78-1382. Bethesda, Maryland, 1978.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 27. Lyon, France: IARC, 1982, pp. 133-39.

[3]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis (eds.). Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

5-Nitro-o-anisidine is a trisubstituted benzene derivative used primarily as an intermediate in the synthesis of dyes. 5-Nitro-o-anisidine is an orange-reddish crystalline solid, highly soluble in alcohol, acetone, acetic acid, and benzene, but only slightly soluble in water.

5-Nitro-o-anisidine is used in the production of C.I. Pigment Red 23; this pigment is used in printing inks, interior latex paints, lacquers, rubber, plastics, floor coverings, paper coatings, and textiles. 5-Nitro-o-anisidine can also be used with various coupling components to produce certain red, brown, yellow, and violet dyes for cotton, silk, acetate, and nylon. The chemical has been used in a formulation tested for pesticidal properties and in a formulation used to color keratin fibers, especially human hair.

5-Nitro-o-anisidine has been produced in this country since 1937. Two companies--both listed in Synthetic Organic Chemicals, U.S. Production and Sales, 1980--reported production or sales of this compound's stabilized diazonium salt, Azoic Diazo Component 13. According to Imports of Benzenoid Chemicals and Products, 63,720 lb of Azoic Diazo Component 13 base were imported into the United States in 1980. In addition, 23,000 lb of 5-nitro-o-anisidine were imported into the United States in 1980. According to the

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Consumer Product Safety Commission (CPSC) imports have significantly and steadily decreased since 1974. EPA estimated six producers and importers in four regions. Domestic production was reported as 37,000 lb, and no import data were available (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). In 1979, 332,000 lb of Pigment Red, produced from the diazonium salt of 5-nitro-o-anisidine, were produced by 11 companies in the United States. U.S. production of 5-nitro-o-anisidine was reported to the U.S. International Trade Commission for 1980 as greater than 15,000 lb.

Human exposure to 5-nitro-o-anisidine is principally through inhalation and skin absorption. The potential for exposure to this compound is greatest for workers who manufacture, handle, or use the dyes and pigments derived from 5-nitro-o-anisidine. The CPSC staff indicated that residual levels or trace impurities of 5-nitro-o-anisidine may possibly be present in some dyes based on this chemical and in the final consumer product. Exposure even to trace amounts may be a cause for concern. This concern is based on the experience with other dyes derived from aromatic amines. However, data describing the actual levels of impurities in the final product, the potential for consumer exposure, and the uptake are currently lacking. The 1974 National Occupational Hazard Survey made no estimate of the number of workers potentially at risk of exposure to the chemical.

5-Nitro-o-anisidine is currently proposed for regulation by EPA under the TSCA, 8(a), reporting rule.

5-Nitro-o-Anisidine

REGULATIONS		
Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
No current action. (CPSC)		
TSCA, 8(a)* Reporting rule requiring process and use data, proposed 2/29/80 (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action (EPA)	45 FR, p 13646 (EPA)

MONS 222860

NITROFEN

Nitrofen (technical grade)--a substituted diphenyl ether--administered in the feed, was carcinogenic to B6C3F1 mice, causing hepatocellular carcinomas in both sexes. There was no evidence of carcinogenicity in Fischer 344 rats.[1] In another bioassay, nitrofen (technical grade) administered in the feed was found to induce hepatocellular carcinomas in B6C3F1 mice of both sexes, and hemangiosarcomas of the liver in male B6C3F1 mice. In addition, adenocarcinomas of the pancreas were induced in female Osborne-Mendel rats.[2] These results can be considered as providing sufficient evidence for the carcinogenicity of nitrofen in experimental animals.[3]

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[1]National Cancer Institute. Bioassay of Nitrofen for Possible Carcinogenicity. Technical Report Series No. 184. DHEW Publication No. (NIH) 79-1740. Bethesda, Maryland, 1979.

[2]National Cancer Institute. Bioassay of Nitrofen for Possible Carcinogenicity. Technical Report Series No. 26. DHEW Publication No. (NIH) 78-826. Bethesda, Maryland, 1978.

[3]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis (eds.). Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

Nitrofen, the trade name for 2,4-dichlorophenyl-p-nitrophenyl ether, is commonly referred to as TOK. Nitrofen is practically insoluble in acetone, methanol, and xylene.

Nitrofen is a contact herbicide used for pre- and postemergence control of annual grasses and broadleaf weeds on a variety of food and ornamental crops. Nitrofen has been applied in approximately 25 states by growers of rice, broccoli, cauliflower, cabbage, brussel sprouts, onions, garlic, and celery. Nitrofen has also been used in nurseries growing roses and chrysanthemums and on rights-of-way. The direct crop use of nitrofen for 1980 was estimated as 682,000 pounds. Nitrofen has not been used around homes and gardens.

According to EPA, nitrofen is produced by one company in one region (Toxic Substances Control Act (TSCA), Chemical Substances Inventory, 1979, public record). More than 5,000 lb were produced in 1980, according to NCI.

MONS 222861

In August 1980, the sole manufacturer of nitrofen (TOK-E-25 and TOK-WP-50) began recalling all existing stocks of the herbicide from dealers, distributors, and users.

Human exposure to nitrofen occurs through inhalation, skin absorption, and ingestion. Occupational exposure to nitrofen, primarily through inhalation and dermal contact, may occur among workers at production facilities. Field handlers of the herbicide are subject to inhalation exposure during application procedures. The 1974 National Occupational Hazard Survey made no estimate of the number of workers potentially exposed to nitrofen.

EPA has established tolerances for nitrofen residues on a variety of raw agricultural commodities, dairy products, and meat products.

Nitrofen

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Tolerances have been established for nitrofen residues on a variety of raw agricultural commodities and on a variety of dairy and meat products (11/25/71; 2/15/74; 8/6/74). (EPA)	Based on adverse effects of the chemical use patterns and detection limits. Enforcement vested in FDA and USDA. (EPA)	40 CFR 180.223 (EPA)

MONS 222862

N-NITROSODI-n-BUTYLAMINE

There is sufficient evidence that N-nitrosodi-n-butylamine (DBN) is carcinogenic in experimental animals.[1] DBN was carcinogenic in all animal species tested: mice, rats, Syrian golden, Chinese and European hamsters, rabbits and guinea pigs, after oral (diet, drinking water and/or gastric intubation), subcutaneous, intraperitoneal or intravenous administration. It produces benign and malignant tumors in the urinary bladder, esophagus, liver, respiratory tract, stomach and intestine, and also leukemia; it is particularly effective as a bladder carcinogen. It was carcinogenic if administered prenatally (subcutaneous injection to mothers) and in single doses.[2]

The two metabolites, N-nitroso-n-butyl-N-(4-hydroxybutyl)amine and N-nitroso-n-butyl-N-(3-carboxypropyl)amine, were also carcinogenic, the first in mice, rats, hamsters and dogs and the second in rats. When given in drinking water to mice, N-nitroso-n-butyl-N-(4-hydroxybutyl)amine produced carcinomas of the urinary bladder; when given in drinking water or intravesicularly to rats, it produced papillomas and carcinomas of the urinary bladder; when given subcutaneously to hamsters, it produced tumors of the urinary bladder and respiratory tract and cholangiocellular tumors; and when given subcutaneously to dogs, it produced urinary bladder tumors. N-Nitroso-n-butyl-N-(3-carboxypropyl)amine produced tumors of the urinary bladder in rats after administration in drinking water or intravesicular instillation.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 51-75.

DBN, a yellow oil that is soluble in water, is used primarily as a research chemical and may have limited use as an intermediate in the organic synthesis of di-n-butylhydrazine. DBN has also been tested for fungistatic activity.

Annual production of DBN is approximately 725 lb; no imports or exports have been reported. DBN is prepared in a closed, pressurized process system.

MONS 222863

The extent of human exposure to DBN during commercial production and use is unknown. Persons at risk are researchers engaged in the study of DBN's biological effects and workers exposed to DBN as a contaminant. DBN may be formed from ingested secondary or tertiary n-butyl amines and quarternary ammonium salts by reaction with nitrites. The degree of this exposure in the general population is not known, but it is assumed to be sporadic and at low levels.

N-nitrosamines are frequently produced during rubber processing and may be present as a contaminant in the final rubber product. Exposure is dependent on the ability of the nitrosamine to migrate out of the product and enter the body. CPSC has a project under way that is examining children's rubber pacifiers. The study will determine the presence of specific nitrosamines and the amounts released under normal exposure conditions.

The most probable source of environmental nitrosamines is nitrosation of amines, which are ubiquitous in the environment. It has been estimated that air, diet, and smoking contribute to human exposure at levels of a few micrograms per day. Microgram quantities of DBN have been detected in tobacco smoke, the effluents from a coke plant, a variety of cooked meat products, animal feeds, and soybean oil.

EPA regulates DBN under the Resource Conservation and Recovery Act as a constituent of hazardous waste. The water quality criteria document for nitrosamines (Clean Water Act) published November 28, 1980, also includes this compound. DBN is regulated under the Clean Water Act hazardous spill regulation, and is proposed for regulation under the Toxic Substances Control Act reporting rule.

MONS 222864

REGULATIONS		
Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Nitrosamines in pacifiers project in progress. Laboratory studies are measuring the amounts of nitrosamine released from pacifiers. (CPSC)		
CWA, 304(a): Water quality criteria for nitrosamines published in final form, 1/28/80 (addresses N-nitrosodi-n-butylamine).		45 FR 231, p. 79318
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to be handling and report/recordkeeping requirements. Also designates N-nitrosodi-n-butylamine as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring use data, published 2/29/80.		45 FR 82, p. 13646
CWA, 311: Hazardous spill regulation establishing reportable quantity (1 lb, @ 454 kg), proposed 7/9/80.	Based on carcinogen ally (EPA)	45 FR 133, p. 46096 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene (EPA)		

MONS 222865

N-NITROSODIETHANOLAMINE

There is sufficient evidence for the carcinogenicity of N-nitrosodiethanolamine (NDELA) in experimental animals.[1] NDELA was carcinogenic in rats after administration in drinking water and in hamsters after subcutaneous injection. It produced hepatocellular carcinomas and renal adenomas in rats, and adenocarcinomas of the nasal cavity, papillary tumors of the trachea, hepatocellular adenomas and local fibrosarcomas in hamsters.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 77-82.

NDELA is a yellow, viscous liquid miscible with water in all proportions. NDELA belongs to the group of N-nitroso compounds, which are widely distributed in the environment.

No evidence of commercial production or use has been found; however, the EPA has reported production of 350 lb annually by one producer.

Human exposure to NDELA is possible by ingestion, skin absorption, and to a lesser extent by inhalation. It is a known contaminant of various cosmetics, cutting fluids, certain pesticides, and tobacco. The concentrations of NDELA range from 1 ppb to 49,000 ppb. As of June 1980, FDA has analyzed 335 cosmetic products for NDELA, and 42 percent were found to be contaminated with this compound. Cutting fluids have been reported to contain up to 5 percent NDELA. Atrazine, a pesticide, contained 0.5 mg/kg of NDELA. Maleic hydrazide, a pesticide commonly applied to tobacco, has been reported to contribute to the formation of NDELA in tobacco at concentrations up to 173 ug/kg. The number of persons exposed to NDELA is not known.

The Consumer Product Safety Commission (CPSC) staff preliminarily determined in 1980 that NDELA was not present in consumer products under CPSC jurisdiction. The Commission subsequently requested (45 FR 61344) public comment to verify the accuracy of this information. No comments were received. Pending the receipt of new information, the Commission plans no action on NDELA. Currently, this compound is regulated by EPA under the Resource Conservation and Recovery Act as a constituent of hazardous waste. FDA has alerted the cosmetic industry to the presence of this compound in a number of products; FDA is also conducting a survey for product contamination.

MONS 222866

REGULATIONS		
Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004. Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and reporting/recordkeeping requirements. Also designates this compound as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80 See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11 261.33 (EPA)
FD&CA, 501(a). (FDA)	Survey for product contaminants and contract research under way. Industry alerted to problem by 44 FR 21365 notice. (FDA)	

MONS 222867

N-NITROSODIETHYLAMINE

There is sufficient evidence for the carcinogenicity of N-nitrosodiethylamine (NDEA) in experimental animals.[1] NDEA was carcinogenic in all animal species tested: mice, rats, Syrian golden, Chinese and European hamsters, guinea pigs, rabbits, dogs, gerbils, pigs, monkeys, hedgehogs, various fish, frogs and birds. It induced benign and malignant tumors after administration by various routes, including ingestion, parenteral injection, inhalation and rectal instillation. The major target organs were the liver, respiratory and upper digestive tracts and the kidney. It was carcinogenic when administered prenatally (subcutaneous injection to mothers) and in single doses. In several studies, dose-response relationships were established.[2]

N-Nitroso-N-ethyl-N-(2-hydroxyethyl)amine, a metabolite of N-nitroso-diethylamine, produced mainly liver tumors when given orally to BD rats.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 77-82.

NDEA is a yellow, volatile liquid that decomposes in the presence of sunlight and is soluble in water and organic solvents.

NDEA is predominantly used as a research chemical; minor applications include the use in plastics, as a lubricant additive, and as an antioxidant.

Two producers are listed in the EPA public records, which show a domestic production of 725 lb annually. Human exposure is possible in laboratory, copolymer, lubricant, and pesticide workers. There is no estimate of the number of people exposed.

The general public may be potentially exposed to unknown quantities of NDEA because it occurs in the environment and is present in food and beverages. The concentration of NDEA in the air of a major U.S. city was estimated as 200 ng/m^3. Wastewater from chemical plants contained up to 0.24 ug/l, and high nitrate well water used for drinking contained 0.01 ug/l; however, it does not persist in environments exposed to sunlight. Various kinds of fish, treated or untreated meats, cheeses, and vegetable products such as soybean oil contain NDEA in the microgram per kilogram range. Similar concentrations have been found in alcoholic beverages and in tobacco smoke condensates. For example, up to 0.008 ug/cigarette was found in mainstream smoke and about 10 times more in sidestream smoke.

MONS 222868

N-nitrosamines are frequently produced during rubber processing and may be present as a contaminant in the final rubber product. Exposure is dependent on the ability of the nitrosamine to migrate out of the product and enter the body. CPSC has a project under way that is examining children's rubber pacifiers. The study will determine the presence of specific nitrosamines and the amounts released under normal exposure conditions.

EPA issued a notice in September 1977 requiring all registrants of pesticides potentially contaminated with nitroso compounds to analyze and document the levels by specified analytical procedures. The compound is regulated under the Clean Water Act and the Resource Conservation and Recovery Act as a hazardous waste constituent. A water quality criteria document for the protection of human health has been issued.

N-Nitrosodiethylamine

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Nitrosamines in pacifiers project in progress. Laboratory studies are measuring the amounts of nitrosamine releases from pacifiers. (CPSC)		
CWA, 304(a): Water quality criteria for nitrosamines published in final form, 11/28/80. Addresses N-nitrosodiethylamine.		45 FR 231, p. 79318
CWA, 311: Hazardous spill regulation establishing reportable quantity (1 lb, 0.454 kg), proposed 7/9/80.		45 FR 133, p. 45094
RCRA, 3001-3004. Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates N-nitrosodiethylamine as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 C.F.R 261.11, 261.33
TSCA, 8(d): Proposed reporting rule requiring use data, published 2/19/80.		45 FR 42, p. 13644 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 222869

N-NITROSODIMETHYLAMINE

There is sufficient evidence for the carcinogenicity of N-nitrosodimethylamine (DMNA) in experimental animals.[1] DMNA was carcinogenic in all animal species tested: mice, rats, Syrian golden, Chinese and European hamsters, guinea-pigs, rabbits, ducks, mastomys, various fish, newts and frogs. It induced benign and malignant tumors when administered by various routes, including ingestion and inhalation, in various organs and in various species. It produced tumors, mainly of the liver, kidney and respiratory tract. It was carcinogenic when administered prenatally (injection to mothers) and in single doses. In several studies dose-response relationships were established.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 125-75.

DMNA is a yellowish oily liquid that is very soluble in water.

Prior to April 1, 1976, DMNA was used in the United States as an intermediate in the production of 1,1-dimethylhydrazine, a storable liquid rocket fuel that contained approximately 0.1 percent DMNA as an impurity. In addition, DMNA was used as a solvent in the fiber and plastics industry, as an antioxidant, as a softener of copolymers, and as an additive to lubricants. No evidence has been found that DMNA is used at present except as a test chemical for research purposes.

DMNA came into industrial use in the United States in the manufacture of 1,1-dimethylhydrazine in the mid-1950s. DMNA is currently not produced in commercial quantities. The EPA public records indicate previous annual domestic production at 750 lb. In 1976, the last commercial plant making DMNA was closed.

Human exposure to DMNA can be by inhalation and ingestion. The exposure potential to N-nitroso compounds is believed to be widespread. Precursors of N-nitroso compounds, such as nitrates, nitrites, and amines, are naturally occurring substances, and N-nitroso compounds, including DMNA, may be found in soil, water, air, food, and the gastrointestinal tract of humans and animals.

MONS 222870

Workers in dimethylamine and dimethylhydrazine manufacturing plants, leather workers, oil and gas extraction workers, pesticide workers, and research workers may have been occupationally exposed to DMNA. Formulations of the pesticide 2,3,6-trichlorobenzoic acid with dimethylamine contain DMNA as a contaminant in concentrations up to 640 µg/l.

N-nitrosamines are frequently produced during rubber processing and may be present as a contaminant in the final rubber product. Exposure is dependent on the ability of the nitrosamine to migrate out of the product and enter the body. CPSC has a project under way that is examining children's rubber pacifiers. The study will determine the presence of specific nitrosamines and the amounts released under normal exposure conditions.

In September 1977, EPA issued a notice requiring all registrants of pesticide products potentially contaminated with N-nitroso compounds to analyze for the compounds by specified analytical methods to document the levels from potential sources. The compound has been regulated under the Resource Conservation and Recovery Act and the Clean Water Act. A water quality criteria document for the protection of human health is available. FDA has established action levels of 5 ppb DMNA in malt beverages and 10 ppb in barley malt. This is expected to reduce or eliminate exposure to DMNA from these sources. In February 1974, OSHA promulgated a standard for DMNA, which included protective clothing, respirators, medical surveillance requirements, and engineering controls.

MONS 222871

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Nitrosamines in pacifiers project in progress. Laboratory studies are measuring the amounts of nitrosamine released from pacifiers. (CPSC)		
CWA, 304(a): Water quality criteria for nitrosamines published in final form, 2/28/80 (separates N-Nitrosodiethylamine).		45 FR 231, p. 79318
CWA, 311: Hazardous spill regulation establishing reportable quantity (1 lb, 0.454 kg), proposed 7/9/80	Based on carcinogenicity. (EPA)	45 FR 133, p. 46904
RCRA, 3001-3004: Subject waste products, off-specification batches, and spill residue in excess of 1 kg to handling and report/recordkeeping requirements. Also designates N-nitrosodimethylamine as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring use data, published 2/19/80.		45 FR 42, p. 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Protective clothing, retention, hygiene training, and medical surveillance requirements for workers; exhaust fan requirements; open-vessel operations prohibited, containation control requirements, sign requirements for areas, labeling requirements for containers. (OSHA)	Regulatory History: 5/10/73: Emergency Temporary Standard--protective clothing and hygiene requirements for workers, open-vessel operations restricted, engineering requirements. 2/13/74: Final Standard--current regulations effective. (OSHA)	29 CFR 1910.1016 (OSHA)
FDA Bureau of Foods, FD&C. (FDA)	The FDA has established action levels of 5 ppb DMNA in malt beverages and 10 ppb in barley malt. (FDA)	

MONS 222872

p-NITROSODIPHENYLAMINE

p-Nitrosodiphenylamine, administered in the feed, was carcinogenic in male B6C3F1 mice, causing hepatocellular carcinomas. The chemical was also carcinogenic in male Fischer 344 rats, causing liver neoplasms. There was no evidence for the carcinogenicity of p-nitrosodiphenylamine in female B6C3F1 mice or in female Fischer 344 rats.[1] These results were considered as providing limited evidence of carcinogenicity in experimental animals,[2] but in view of another evaluation, they can be regarded to provide sufficient evidence.[3]

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[1]National Cancer Institute. Bioassay of p-Nitrosodiphenylamine for Possible Carcinogenicity. Technical Report Series No. 190. DHEW Publication No. (NIH) 79-1746. Bethesda, Maryland, 1979.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 27. Lyon, France: IARC, 1982, pp. 213-25.

[3]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis (eds.). Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

p-Nitrosodiphenylamine (4-nitroso-N-phenylbenzenamine) is an industrial chemical that is slightly soluble in water and petroleum ether and soluble in alcohol and benzene.

p-Nitrosodiphenylamine is used as a chemical intermediate for dyes and pharmaceuticals and as a polymerization inhibitor during the manufacture of vinyl monomers. Use of p-nitrosodiphenylamine as a chemical intermediate is believed to be limited primarily to the production of N-phenyl-p-phenylenediamine and its derivatives. p-Nitrosodiphenylamine has also been used as an accelerator in the vulcanization of rubber.

Commercial production of p-nitrosodiphenylamine in the United States was first reported to the U.S. International Trade Commission (USITC) by one company in 1975, although it is believed to have been produced since 1970. EPA estimated one producer in one region. Domestic production was reported as 369,000 lb; imports were not reported (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). The U.S. production of p-nitrosodiphenylamine was reported to the USITC as greater than 5000 lb for 1980.

MONS 222873

The potential for exposure to p-nitrosodiphenylamine is greatest for workers in elastomer, dye, pharmaceutical, and vinyl monomer manufacturing facilities. The 1974 National Occupational Hazard Survey made no estimate of the number of workers potentially exposed to p-nitrosodiphenylamine.

p-Nitrosodiphenylamine is proposed for regulation by EPA under the TSCA, 8(a), reporting rule.

p-Nitrosodiphenylamine

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
T.CA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80 (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)

MONS 222874

N-NITROSODI-n-PROPYLAMINE

There is sufficient evidence for the carcinogenicity of N-nitrosodi-n-propylamine (NDPA) in experimental animals.[1] NDPA was carcinogenic in rats after administration in drinking water and in rats and hamsters after subcutaneous injection. It produced benign and malignant tumors of the liver, kidney, esophagus and respiratory tract. The metabolite N-nitroso-N-(2-hydroxy-n-propyl)-n-propylamine was also carcinogenic in rats and hamsters: it produced benign and malignant tumors of the respiratory tract and liver after subcutaneous injection.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 177-89.

NDPA is a yellow liquid that has been found as a contaminant in microgram quantities in wastewater from chemical factories, in cheese, in brandy and liquors, and in pesticides such as Treflan and Isopropalin.

Under the Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979 (public record), EPA reported two U.S. producers with an estimated domestic NDPA production of 350 lb.

The general population may be exposed sporadically to low levels of NDPA. However, no exposed group suitable for an epidemiological investigation has been identified. The potential population at risk includes pesticide workers and research personnel. There are no data available on the number of people exposed.

EPA regulates NDPA under the Resource Conservation and Recovery Act. The proposed reporting rule under TSCA would require the reporting of process and use information. In 1980, EPA published water quality criteria for the protection of human health. However, the document addressed nitrosamines as a class, rather than NDPA as a specific chemical.

MONS 222875

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates NDPA as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring process and use data, published 2/29/80.		45 FR 42, p. 13846 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 222876

N-NITROSO-N-ETHYLUREA

There is sufficient evidence for the carcinogenicity of N-nitroso-N-ethylurea (ENU) in experimental animals.[1] ENU was carcinogenic in all animal species tested: mice, rats, Syrian golden hamsters, rabbits, opossums, pigs and monkeys. It produced benign and malignant tumors following administration by different routes, including single oral doses; the main target organ appeared to vary with the route of administration. Prenatal exposure to the substance was shown to be particularly effective in producing tumors of the nervous system. In several studies, dose-response relationships were established.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 191-205.

ENU is a water-soluble crystalline solid. ENU belongs to a group of chemicals that are widely distributed in the environment as contaminants. This compound has been used for the laboratory synthesis of diazoethane.

ENU is produced in small quantities for research purposes. However, the Toxic Substances Control Act, Chemical Substance Inventory, 1979 (public record), reports approximately 360 lb of ENU were produced domestically by one producer.

Data on human exposure to ENU are not available, although laboratory personnel may be exposed to this compound.

The EPA proposes to regulate ENU under the Safe Drinking Water Act and has regulated it under the Resource Conservation and Recovery Act as a hazardous waste constituent.

MONS 222877

N-Nitroso-N-ethylurea

REGULATIONS		
Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
SDWA Primary drinking water standards in progress, 8/82.		SDW memorandum, 8/80
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to be manifesting and record/recordkeeping requirements. Also designates EHW at a hazardous constituent of waste, and subjects vessel known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, Sec: Proposed reporting rule requiring use data, published 2/29/80.		45 FR 42, p. 13644 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 222878

N-NITROSO-N-METHYLUREA

There is sufficient evidence for the carcinogenicity of N-nitroso-N-methylurea (NMU) in experimental animals.[1] NMU was carcinogenic in all animal species tested: mice, rats, Syrian golden, Chinese and European hamsters, guinea-pigs, rabbits, gerbils, pigs, dogs and monkeys. It induced benign and malignant tumors following administration by different routes, including ingestion. It produced tumors at different sites, including the nervous tissue, stomach, esophagus, pancreas, respiratory tract, intestine, lymphoreticular tissues, skin and the kidney. It is carcinogenic following its administration prenatally by injection to mothers and in single doses.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 227-55.

NMU is soluble in water and polar organic solvents. NMU is used for laboratory synthesis of diazomethane, but it has been largely replaced by other reagents. It has also been studied as a cancer chemotherapeutic agent, either alone, or in combination with cyclophosphamide.

There is no evidence of any commercial production or use of NMU; any production would be for research purposes. The EPA listed one producer, and the Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, reported production of 350 lb (public record).

Few workers are exposed during the production of this compound, and only a limited number of research laboratory workers are potentially exposed. The only direct exposure would be to cancer patients through the administration of NMU as a chemotherapeutic agent but there are no reliable data for the frequency or extent of this use.

Under the TSCA, 8(a), EPA has proposed a reporting rule requiring NMU use data. The EPA regulates this compound under the Resource Conservation and Recovery Act.

MONS 222879

N-Nitroso-N-methylurea

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/record-keeping requirements. Also designated as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring process and use data, published 1/29/80.		45 FR 42 p. 13645 (EPA)
See Carcinogen Assessment Group statement under 2-Acetylaminofluorene. (EPA)		

MONS 222880

N-NITROSOMETHYLVINYLAMINE

There is sufficient evidence for the carcinogenicity of N-nitrosomethylvinylamine (NMVA) in experimental animals.[1] NMVA was carcinogenic in rats, the only species tested. It produced carcinomas of the esophagus, tongue and pharynx after continuous administration in drinking water and carcinomas of the nasal cavities after inhalation exposure.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 257-61.

NMVA is a pale yellow liquid that is very volatile and photolabile. NMVA is soluble in water, organic solvents, and lipids. It is relatively unstable in aqueous solutions.

The only known use for NMVA is limited to laboratory research. NMVA has reportedly been found as a contaminant in apple brandy.

There is no evidence that this chemical has ever been produced commercially. The small number of researchers using NMVA could be exposed to it, and consumers of contaminated apple brandy might be directly exposed.

The EPA has included NMVA on its list of carcinogens and regulates it under the Resource Conservation and Recovery Act.

N-Nitrosomethylvinylamine

REGULATIONS		
Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
ACGIH, 1981-1982: Subjects waste products, off-specification batches, and spill residues in excess of 1 kg to handling and reporting, recordkeeping requirements. Also designates this compound as a hazardous constituent of waste and subjects waste known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR [illegible] §261.33 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 222681

N-NITROSOMORPHOLINE

There is sufficient evidence for the carcinogenicity of N-nitrosomorpholine (NMOR) in experimental animals.[1] NMOR was carcinogenic in various fish, mice, rats, and hamsters (Syrian golden, Chinese and European). When administered in drinking water, it produced benign and malignant tumors of the liver and lung in mice, and of the liver, kidney and blood vessels in rats. After subcutaneous injection it produced tumors of the upper digestive and respiratory tracts in hamsters; it was carcinogenic after administration in single doses. It produced liver tumors in rats following intravenous injection. When dissolved in tank water, it produced liver tumors in various fish. A study in hamsters has been reported in which a dose-response relationship was established.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 263-80.

NMOR is a yellow crystalline solid that is water soluble. NMOR belongs to the chemical group of N-nitroso compounds, which are widely distributed in the environment and can also be formed in the human body.

NMOR is neither commercially produced nor used in the United States, although patents have been issued for its use as a solvent for polyacrylonitrile, an intermediate in the production of N-aminomorpholine, and for application as an antimicrobial agent. NMOR has been detected as a contaminant in analytical grade dichloromethane and chloroform, in morpholine (0.8 ug/g), and in a rubber cross-linked accelerator (0.4-0.7 ug/g).

Human exposure to NMOR may occur by inhalation and less frequently through ingestion and skin absorption. Workers in chemical research laboratories and in the rubber and tire manufacturing industry may be exposed to the chemical. An average worker in a rubber or tire factory may be exposed to amounts in the range of 9-130 ug NMOR/day. Wastewater from these factories contained NMOR at levels of 0.003 ug/g. Dirt scrapings from a staircase in one of the factories revealed an NMOR level of 730 ug/g. A soil sample taken outside the same chemical plant contained NMOR at 4.4 ug/g.

MONS 222882

N-nitrosamines are frequently produced during rubber processing and may be present as a contaminant in the final rubber product. Exposure is dependent on the ability of the nitrosamine to migrate out of the product and enter the body. CPSC has a project under way that is examining children's rubber pacifiers. The study will determine the presence of specific nitrosamines and the amounts released under normal exposure conditions.

The EPA regulates NMOR under the Resource Conservation and Recovery Act.

N-Nitrosomorpholine

REGULATIONS		
Regulation and Other Action	Effect of Regulations; Other Comments	Citation of Regulation
Nitrosamine in pacifiers project in progress. Laboratory studies are measuring the amounts of nitrosamine released from pacifiers. (CPSC)		
ECRA, 3001-3004; Designates this compound as a hazardous constituent of waste, and subjects wastes known to contain it to handling and report/recordkeeping requirements. Promulgated 8/18/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.33 (EPA)

MONS 222883

N-NITROSONORNICOTINE

There is sufficient evidence that N-nitrosonornicotine (NNN) is carcinogenic in experimental animals.[1] NNN was carcinogenic in rats, mice and Syrian golden hamsters. Following oral administration to rats, it produced carcinomas of the upper digestive tract, mainly the esophagus, and of the nasal cavities. In hamsters, subcutaneous injections produced mainly tracheal tumors. In mice, intraperitoneal injections produced lung tumors.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 281-86.

NNN is a yellow oil that is insoluble in water. NNN reportedly does not have a commercial use, but it may be synthesized for research purposes. No evidence was found that NNN has been manufactured commercially in the United States.

Cigarette smokers, tobacco chewers, cancer researchers, and organic chemists are at greatest risk of exposure to NNN. Cigarette workers and tobacco farmers have low exposure to NNN because the compound is released during curing. Smokers and persons breathing tobacco smoke may inhale a significant amount of NNN. The amount of the substance in commercial U.S. tobacco products varies from 1.9 to 88.6 ppm; this is one of the highest values of an environmental nitroso compound reported in the literature. Approximately half of the NNN originates in the unburnt tobacco, whereas the remainder is formed during burning. The Office on Smoking and Health has estimated that there are currently 54 million smokers in the United States.

The EPA has placed NNN on its Carcinogen Assessment Group list of carcinogens and has regulated it under the Resource Conservation and Recovery Act.

N-Nitrosonornicotine

REGULATIONS		
Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
RCRA, 3000-3004: Designates this compound as a hazardous constituent of waste, and subjects wastes known to contain it to handling and report/recordkeeping requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.33 (EPA)

MONS 222884

N-NITROSOPIPERIDINE

There is sufficient evidence for the carcinogenicity of N-nitrosopiperidine (NPIP) in experimental animals.[1] NPIP was carcinogenic in mice, rats, hamsters (Syrian golden, European and Chinese), and monkeys when administered by several routes. It produced benign and malignant tumors of the liver, lung, forestomach and esophagus in mice, of the liver, esophagus and respiratory system in rats, and of the upper digestive tract, respiratory system and liver in hamsters; it also produced hepatocellular carcinomas in monkeys. It was carcinogenic in mice and hamsters when administered in single doses.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 287-301.

NPIP belongs to the group of compounds known as nitrosamines. NPIP has been used in the production of epoxy resin for electrical leads and for cardiovascular implants.

NPIP is not manufactured on an industrial scale but is produced by one company specializing in laboratory chemicals and sold in 25 g quantities. Because of the small quantities produced, exposure during production is limited. Nitrosamines are rapidly decomposed by sunlight and therefore do not persist in ambient air or water.

The general population may be sporadically exposed to low concentrations of NPIP from cigarette smoke and certain foods. Several scientists have reported trace amounts of NPIP in cigarettes; however, these observations have not been confirmed in all brands of cigarettes tested. There is evidence that NPIP is present in processed and preserved meats. Concentrations ranging up to 60 ug/kg have been detected in meat and fish products such as bacon, bologna, wieners, and smoked cod. FDA published a regulation on November 16, 1972, which requires separate packaging of spices from sodium nitrite in dry, premixed cures; this dramatically lowered NPIP in dry mixes. The presence of NPIP in meat, cheese, and spices results from the use of the nitrite as a preservative. FDA has estimated that between 10,000 and 100,000 patients may be exposed to NPIP by medical implants. The FDA Bureau of Medical Devices has not taken regulatory action at this time. Occupations with the highest probability of exposure to NPIP are cancer researchers, organic chemists, and workers engaged in the manufacture of pacemakers.

MONS 222885

N-nitrosamines are frequently produced during rubber processing and may be present as a contaminant in the final rubber product. Exposure is dependent on the ability of the nitrosamine to migrate out of the product and enter the body. CPSC has a project under way that is examining children's rubber pacifiers. The study will determine the presence of specific nitrosamines and the amounts released under normal exposure conditions.

NPIP has been included in the list of chemicals assessed as carcinogens by the EPA Carcinogen Assessment Group and is regulated under the Resource Conservation and Recovery Act. The FDA regulates NPIP under the Food, Drug, and Cosmetic Act.

N-nitrosopiperidine

REGULATIONS		
Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Nitrosamines in pacifiers project in progress. Laboratory studies are measuring the amounts of nitrosamine released from pacifiers. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designated as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring process and use data. published 2/29/80.		45 FR 42, p. 13546 (EPA)
·See Carcinogen Assessment Group statement presented under 2-acetylaminefluorene. (EPA)		
FDA Bureau of Foods, FD&CA. (FDA)	Enforcement of regulations precludes the formation of nitrosamines in meat-curing preparations. (FDA)	FR notice, 11/16/73, p. 31679-80 CFR 21, 170.40 (FDA)

MONS 222886

N-NITROSOPYRROLIDINE

There is sufficient evidence for the carcinogenicity of N-nitrosopyrrolidine (NPYR) in experimental animals.[1] NPYR was carcinogenic in rats after administration in drinking water. It produced hepatocellular carcinomas. It also increased the incidence of lung adenomas in mice when given in drinking water. A study in rats was reported in which a dose-response relationship was established.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 313-26.

N-Nitrosopyrrolidine (NPYR) is a water-soluble liquid. NPYR belongs to the group of chemicals called N-nitroso compounds, which are widely distributed in the environment and can also be formed in the human body.

There is currently no evidence of commercial use of NPYR, although it was reported by one producer for the Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979 (public record). Exposure to NPYR can occur by inhalation and by ingestion of nitrite-treated meats (e.g., bacon, sausage, and ham), condiments, tobacco, curing spices, and animal feed. Heating nitrite-treated foodstuffs may result in formation of NPYR. The recent trend to decrease the concentration of sodium nitrite in food and use ascorbic acid as a substitute preservative has decreased exposure to NPYR. For example, bacon contained an average of 67 ug/kg of NPYR in 1971-74; but by 1975-76, it contained only 17 ug/kg. When bacon is fried, an average of 50 percent of the NPYR normally present in bacon is found in the vapor. NPYR has also been found in tobacco smoke in amounts up to 0.113 ug/cigarette. The residue in pipe bowls has been found to contain 1.6 mg of NPYR/kg of residue.

In 1978, NPYR production and manufacturing facilities were reported as having 0.09-0.20 ug/l NPYR in their effluents. Dry premixed cures containing spices and sodium nitrite have been found to contain 40 ug/kg NPYR. In spices, NPYR increased to 520 ug/kg during 6 months of storage. NPYR has been found in 50 percent of certain animal feeds at levels of 1-26 ug/kg.

There are no available estimates of the extent of human exposure to NPYR; but it should be assumed that exposure is probable when nitrite-preserved foods, especially fatty foods, are heat-prepared and ingested.

MONS 222887

N-nitrosamines are frequently produced during rubber processing and may be present as a contaminant in the final rubber product. Exposure is dependent on the ability of the nitrosamine to migrate out of the product and enter the body. CPSC has a project under way that is examining children's rubber pacifiers. The study will determine the presence of specific nitrosamines and the amounts released under normal exposure conditions.

Currently, the EPA regulates NPYR under the Clean Water Act (CWA), the Resource Conservation and Recovery Act (RCRA), and the TSCA. Under the CWA, the EPA has published a water quality criteria document for nitrosamines; the document addresses NPYR. The RCRA subjects spill residues in excess of 2200 lb to handling and report/recordkeeping requirements. The TSCA reporting rule requires use and process data to be published.

N-nitrosopyrrolidine

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Nitrosamines in pacifiers project in progress. Laboratory studies are measuring the amounts of nitrosamine released from pacifiers. (CPSC)		
CWA, 304(a): water quality criteria for nitrosamines published in final form, 11/28/80. Addresses N-nitrosopyrrolidine.		45 FR 231, p. 79318
RCRA, 3001-3004. Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates N-nitrosopyrrolidine as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring process and use data, published 2/29/80.		45 FR 82, p. 13645 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 222888

N-NITROSOSARCOSINE

There is sufficient evidence for the carcinogenicity of N-nitrososarcosine (NSAR) in experimental animals.[1] NSAR was carcinogenic in mice and rats. It produced carcinomas of the nasal cavities in mice and esophageal carcinomas in rats after administration in feed or drinking water, and liver-cell carcinomas in newborn mice after intraperitoneal injection.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 327-35.

NSAR is a pale yellow crystalline solid that is soluble in water and in polar organic solvents.

NSAR is neither produced nor used commercially in the United States. It is, however, produced by various chemical reactions in air, water, soil, food, and animal systems. This compound has been detected in foodstuffs, particularly meat, in concentrations of 2-56 µg/kg of sample. The general population may be exposed to NSAR by dietary intake or through its presence in the environment.

NSAR has been included in the list of carcinogens prepared by the EPA Carcinogen Assessment Group. EPA regulates NSAR under the Resource Conservation and Recovery Act.

N-Nitrososarcosine

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
RCRA, 3001-3004 Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designated as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

MONS 222889

Ten cases of liver-cell tumors have been reported in patients with blood disorders treated for long periods with oxymetholone alone or in combination with other androgenic drugs; however, a causal relationship cannot be established. The increased risk of liver-cell tumors could be related to hepatic damage known to be caused by oxymetholone. Alternatively, patients with congenital anemias may be at higher risk of developing these tumors, and this risk may become manifest during the extended survival resulting from oxymetholone treatment.[1] This is considered to provide limited evidence of carcinogenicity of oxymetholone in humans. No data are available concerning the carcinogenicity of oxymetholone in experimental animals.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 13. Lyon, France: IARC, 1977, pp. 131-39.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

Oxymetholone is a synthetic steroid hormone having actions similar to those of the male hormone, testosterone. As a pure substance, oxymetholone is a crystalline solid that is practically insoluble in water.

Oxymetholone is used for adjuvant therapy for senile and postmenopausal osteoporosis. At one time, a major use was for treatment of anemias. In 1972, the FDA dropped its approval of this use pending further investigation. Oxymetholone is also used as an anabolic steroid for small animals.

No evidence has been found that oxymetholone has ever been commercially produced in the United States. One U.S. distributor has been reported. The U.S. International Trade Commission reported in 1981 that oxymetholone was imported; however, no specific import data are available.

Human exposure to oxymetholone can occur principally during its use as a pharmaceutical. FDA's Bureau of Drugs estimates that 50,000 to 100,000 patients are treated each year with oxymetholone for postmenopausal osteoporosis. The usual adult dose of 5-10 mg/day is administered orally for about 3 weeks, but not exceeding 13 weeks, for a single course of therapy.

FDA reduced the list of approved uses of oxymetholone in 1972. Since 1977, warning labels of possible adverse effects have been required.

MONS 222890

Oxymetholone

REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
As current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
Because oxymetholone is a pharmaceutical, EPA has minimal regulatory interest in it. Because there is no evidence of domestic manufacture, it is unlikely that EPA will investigate sources for possible regulation. (EPA)		
Oxymetholone was indicated only for treatment of anemia caused by deficient red blood cell production and was approved in 1972 for safety and effectiveness. Since 1973, all other indications except 'probably' effective as adjuvant therapy in senile and postmenopausal osteoporosis have been deleted from the labeling pending further investigation of this less than effective indication. (FDA)	In 1972, FDA required a labeling revision in the adverse reaction section that would include a statement on the occurrence of hepatocellular neoplasms and peliosis hepatitis in association with anabolic androgenic therapy. Use restricted to indicated therapy only. (FDA)	CFR 21, Subchapter D (FDA)

MONS 222891

PHENACETIN

There is sufficient evidence that phenacetin is carcinogenic in experimental animals.[1] Rats fed a diet containing phenacetin had an excess of nasal and urinary tract tumors. Phenacetin given in the diet to rats enhanced the urinary bladder carcinogenesis after they had received N-nitrosobutyl-N-(4-hydroxybutyl)-amine in drinking water.[1,2] The evidence for the carcinogenicity of phenacetin in humans is limited.[1,2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 24. Lyon, France: IARC, 1980, pp. 135-61.

Phenacetin is a crystalline powder that is soluble in water.

Phenacetin is used as an analgesic and antipyretic drug. It is used alone or in combination with aspirin and caffeine for the relief of mild to moderate muscle pain. Phenacetin has also been used as a stabilizer for hydrogen peroxide in hair bleaching preparations. In veterinary medicine, it is used as an analgesic and antipyretic.

Phenacetin has been produced commercially in the United States for over 50 years. In 1979, the EPA indicated an annual domestic production of approximately 550,000 lb and imports of 240,000 lb.

Human exposure to phenacetin is primarily through ingestion. The chemical is generally formulated with other pharmaceutical agents and used in over-the-counter (OTC) remedies for pain and fever. A high proportion of the population may be exposed to doses ranging up to 1 g per day. The usual dose is 300 mg taken 4-6 times per day.

The EPA regulates phenacetin under the Resource Conservation and Recovery Act. After an advisory panel determined that phenacetin could not be considered "safe" for OTC use, the FDA held hearings to remove it from OTC products. This action has been challenged by objections concerning the validity of the carcinogenicity data.

MONS 222892

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004 Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates phenacetin as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
FDA Bureau of Drugs, FD&CA: Phenacetin has been reviewed by the Advisory Review Panel on OTC internal analgesic, antipyretic, and antirheumatic products and categorized as an effective OTC analgesic and antipyretic but not safe for OTC use. The FDA has initiated administrative proceedings to accomplish this, but objections have been raised concerning the validity of the carcinogenesis data. The FDA is thus not in a position at this time to call phenacetin a known human carcinogen. It can class it as an animal carcinogen with some human data available but inadequate to permit human carcinogenicity evaluation. (FDA)	The proposed action would remove phenacetin from over-the-counter preparations. (FDA)	Recommendation of OTC Internal Advisory Review Panel for analgesics and antirheumatic products. (FDA)

MONS 222893

PHENAZOPYRIDINE HYDROCHLORIDE

There is sufficient evidence for the carcinogenicity of phenazopyridine hydrochloride in experimental animals.[1] Phenazopyridine hydrochloride was tested in BC3F1 mice and Fischer 344 rats by dietary administration.[2] In female mice, it significantly increased the incidence of hepatocellular adenomas and carcinomas. In male and female rats, it induced tumors of the colon and rectum.[2,3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]National Cancer Institute. Bioassay of Phenazopyridine Hydrochloride for Possible Carcinogenicity. Technical Report Series No. 99, DHEW Publication No. (NIH) 78-1349. Bethesda, Maryland, 1978.

[3]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 24. Lyon, France: IARC, 1980, pp. 163-73.

Phenazopyridine is a heterocyclic organic compound that is slightly soluble in water.

Phenazopyridine hydrochloride has been used for 40 years as an analgesic drug either alone or in combination with other drugs to reduce pain associated with urinary tract infections.

Large-scale production of phenazopyridine hydrochloride began in the United States in 1944. In 1972, two companies reported production, but no data were published. The National Disease and Therapeutic Index reported in 1980 that 21 percent of this chemical was used in hospitals. Data from the National Prescription Audit reported that retail pharmacies dispensed 4.4 million prescriptions in 1980. The average adult dose rate is 200 mg three times daily.

Exposure to phenazopyridine hydrochloride occurs during manufacture and formulation. The 1974 National Occupational Hazard Survey estimated a potential occupational exposure for 2800 persons.

The FDA has approved the use of phenazopyridine hydrochloride for symptomatic relief of pain and other discomforts arising from irritation of the lower urinary tract.

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REGULATIONS		
Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
As a pharmaceutical, EPA has minimal regulatory authority over phenazopyridine hydrochloride. (EPA)		
FDA Bureau of Drugs, FD&CA: Approved for prescription use only. FDA is considering the inclusion of statements about carcinogenicity and dose duration limitations on the labels of this urinary analgesic. (FDA)	Use limited to short-term symptomatic relief of pain, burning, urgency, frequency, and other discomforts associated with lower urinary tract infection. Future labeling will reflect current toxicological data. (FDA)	21 CFR, Subchapter D (FDA)

MONS 222895

PHENYTOIN

The evidence of carcinogenicity of phenytoin in human subjects and in experimental animals is considered as limited.[1] Phenytoin was shown to be carcinogenic in mice after administration in a liquid diet or by intraperitoneal injection, producing lymphomas and leukemias. Studies performed with rats were considered inadequate.[2,3]

There are case reports and epidemiological studies of lymphomas occurring in patients that received phenytoin; however, no excess of lymphomas was reported in a followup study of epilepsy patients, many of whom received phenytoin along with other antiepileptic drugs. Three recent papers report one case of malignant mesenchymoma and two cases of neuroblastoma in children with phenytoin-induced malformations. An epidemiological study looked at the frequency of use of phenytoin and of phenobarbitone in mothers of children with childhood cancers compared with mothers of normal children. While more mothers of cancer cases reported a history of epilepsy, no differences were seen in the proportion of epileptic mothers who took either phenytoin or phenobarbitone. An excess of lymphomas was seen in children of epileptic mothers, but the occurrence of brain tumors was not reported.[2,3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 1. Lyon, France: IARC. 1979.

[3]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 13. Lyon, France: IARC, 1977, pp. 201-25.

Phenytoin is a heterocyclic organic compound used in the treatment of grand mal epilepsy and Parkinson's syndrome and in veterinary medicine.

Commercial production of phenytoin was first reported in the United States in 1946. The EPA indicated that phenytoin was not reported to the Toxic Substances Chemical Inventory (1975-1977). In 1977, IARC reported that U.S. sales of phenytoin for use in human medicine were 171,000 lb annually. Imports for 1974 were approximately 15,000 lb.

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Human exposure to phenytoin occurs principally during its use as a drug. Figures on the number of patients using phenytoin are not available, but phenytoin is given to a major segment of individuals suffering from epilepsy. The oral dose rate, initially 100 mg three times per day, can gradually increase by 100 mg every 2-4 weeks until the desired therapeutic response is obtained. The intravenous dose is 200-350 mg/day. The EPA has not reported any data indicating the presence of phenytoin in effluents, emissions, or wastes from pharmaceutical manufacturers.

The FDA regulates phenytoin as a prescription drug. The Bureau of Drugs is examining the information on potential human hazards from phenytoin; an advisory committee will recommend further regulatory action if required.

Phenytoin

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
Because phenytoin and its monosodium salt are pharmaceuticals, EPA has minimal regulatory interest in them. The Agency has no indication of their presence in effluents, emissions, or wastes from pharmaceutical manufacturers. The fact that the monosodium salt of phenytoin was reported for the TSCA Inventory indicated that there may be other uses that should be investigated for possible control. The small production volume, compared with other chemicals (including carcinogens) of concern, may limit interest for the foreseeable future. (EPA)		
FDA Bureau of Drugs, FD&CA: Regulated as a prescription drug. The Bureau of Drugs points out that the scientific data are not conclusive to call phenytoin a "known human carcinogen." The problem has been sent to an advisory committee and their recommendation will be considered before any statement is issued from FDA. (FDA)	No specific regulatory action will be taken until an advisory opinion has been submitted. (FDA)	CFR 21, Subchapter D (FDA)

MONS 222897

POLYBROMINATED BIPHENYLS (Firemaster FF-1)

Firemaster FF-1 (Firemaster BP-6 containing 2 percent of calcium trisilicate)--a mixture of pentabromobiphenyl, hexabromobiphenyl and heptabromobiphenyl with hexabromobiphenyl being the major component--administered by gavage produced neoplastic nodules and hepatocellular carcinomas in female Sherman strain rats.[1] In another bioassay, Firemaster FF-1--also administered by gavage--was carcinogenic to Fischer 344 rats and B6C3F1 mice of each sex, inducing neoplastic nodules, hepatocellular carcinomas, and cholangiocarcinomas in rats and hepatocellular carcinomas in mice.[2]

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[1]Kimbrough, R.D., D.F. Groce, M.P. Korver, and V.W. Burse. Induction of Liver Tumors in Female Sherman Strain Rats by Polybrominated Biphenyls. J. Nat. Cancer Inst. Vol. 66, No. 3, 1981, pp. 535-42.

[2]National Toxicology Program. NTP Technical Report on the Toxicology and Carcinogenesis Bioassay of Polybrominated Biphenyl Mixture (Firemaster FF-1). Technical Report Series No. 244. NIH Publication No. 82-1800. Research Triangle Park, North Carolina, 1982.

Polybrominated biphenyls (PBBs) were widely used as flame retardant additives in synthetic fibers and in molded plastics. PBBs are solid at room temperature and practically insoluble in water. They are mixtures of compounds containing, on the average, six bromine atoms per molecule.

PBBs have been incorporated into the plastic housing of many commercial products. PBBs have been sold to manufacturers of polycarbonates, polyesters, polyolefins, and polystyrenes. The Consumer Product Safety Commission (CPSC) reported that hexabromobiphenyl (HBB) was the major component in the most widely used PBB mixture, and that PBBs are not presently being used in consumer products.

The commercial production of PBB began in 1970. Approximately 11 million lb of HBB were manufactured by a single U.S. company from 1970 to 1974 and marketed under the trade names Firemaster BP-6 and Firemaster FF-1. CPSC reported that the sole U.S. manufacturer of HBB ceased production in 1974. The remaining stock of this product held by the sole producer was reportedly exhausted in April 1975.

Other PBB production ceased in the late 1970s. EPA reported one U.S. producer (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). The U.S. production of other PBBs (decabromobiphenyl), as reported to the U.S. International Trade Commission, was greater than 10,000 lb for 1980, according to SCI.

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Workers of a chemical company that manufactured PBB were directly exposed to PBB by skin contact, inhalation, and unintentional ingestion. HBB was detected in workers sera at a range of 1.1 to 1729 ppb, and in their adipose tissue at a range of 0.51-581 ppm. Approximately 2000 lb of PBBs were inadvertently mixed into livestock feed in Michigan in 1973. Thousands of animals died or were destroyed. Initially, 8000 to 12,500 Michigan residents were exposed in 1973 and 1974 to meat, milk, and eggs contaminated with PBBs. A general population survey conducted in Michigan revealed that only 10 percent of the population did not have detectable levels of PBB in their blood. Because the PBBs are biologically stable and slowly eliminated, significant body burdens could persist throughout their lifetimes.

In 1974, the National Occupational Hazard Survey estimated that 4900 workers were potentially exposed to PBBs. The sources of PBBs currently appear to be residues remaining in and around plants that at one time manufactured, processed, or produced products using PBBs. FDA stated that a potential for human exposure exists from the ingestion of foods containing residues of these compounds.

EPA is currently proposing a reporting rule for PBBs under the TSCA, 8(a). Under section 406 of the Food, Drug, and Cosmetic (FD&C) Act, FDA regulates PBB compounds as unavoidable environmental contaminants. In cooperation with CDC and the Public Health Department of the State of Michigan, FDA monitors the long-term human health effects from acute exposure to PBBs.

Polybrominated Biphenyl.

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. (CPSC)		
No regulations are directed specifically at this chemical. The PBB's category, containing potentially some 200-300 chemicals, is subject to a special TSCA, 8(a), reporting rule.		
TSCA, 8(a): Requires manufacturers to report intent to resume or initiate manufacture of any PBBs. Manufacture includes import. Promulgated 6/30/81. (EPA)	Regulation based on known hazards including possible carcinogenicity and on indications that these chemicals were not being produced. (EPA)	40 CFR 704.95 (EPA)
Regulated as unavoidable environmental contaminant under Section 406 of the FD&C Act. (FDA)	Action levels for PBB content: Milk, dairy products* 0.3G mg/kg Meat* 0.30 mg/kg Eggs 0.06 mg/kg Animal feeds 0.05 mg/kg * Fat basis. (FDA)	

MONS 222899

POLYCHLORINATED BIPHENYLS

The evidence for carcinogenicity of polychlorinated biphenyls (PCBs) in experimental animals is sufficient, and the evidence in humans is inadequate.[1]

Certain mixtures of PCBs (e.g., Kanechlor 500, Aroclor 1254 and 1260) were carcinogenic in mice and rats after administration in the diet, producing liver tumors.[2]

A slight increase in the incidence of cancer, particularly melanoma of the skin, has been reported in a small group of men exposed occupationally to Aroclor 1254, a mixture of PCBs.[1]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 18. Lyon, France: IARC, 1978, pp. 43-103.

PCBs vary in appearance from mobile, oily liquids to white crystalline solids to hard noncrystalline resins, with all forms insoluble in water.

Before 1972, PCBs were used in transformer cooling liquids, heat transfer and hydraulic fluids, vacuum pump fluids, lubricants, plasticizers, fillers in investment casting waxes, surface coatings and sealants, pesticide extenders, and for copy paper. By 1974, all domestic uses of PCBs were confined to closed systems.

PCBs have been produced in the United States since 1929. Domestic production reached a peak volume of 86 million lb in 1970 and decreased to approximately 41 million lb by 1974. Annual domestic production prior to 1977 was approximately 35 million lb. Except for limited research and development applications, the PCBs are no longer produced in the United States, and no import or export of the compounds has been permitted since July 1979.

The release of PCBs from prior industrial uses and the persistence of the compounds in the environment have resulted in widespread contamination of water and soil, with subsequent exposure of the general public. Routes of exposure include skin absorption and ingestion; a major source of exposure is through the diet. A 1976 report indicated that fish, cheese, eggs, and contaminated animal feed were the major U.S. commodities in which PCBs were found. The percentage of food samples contaminated with PCBs decreased between 1973 and 1975. Residues of PCBs have been detected in human milk and fat samples collected from the general U.S. population. EPA reports that approximately 12 million persons within 12 miles of three existing and nine projected commercial incinerators could be exposed to releases of PCBs.

MONS 222900

In 1970, EPA banned PCBs as a pesticide ingredient and canceled registration of products containing the PCBs. EPA promulgated toxic pollutant effluent standards in 1977 and modified the marking and disposal rule in 1979. This latter regulation has been effective in identifying and eliminating some sources. In 1979, EPA issued a ban on manufacturing, processing, and distributing of PCBs in commerce; most manufacturing had ceased voluntarily before these rules were issued. EPA proposed a water quality criteria document that will protect freshwater, saltwater, and aquatic organisms, as well as human health. Air pollution sources of PCBs were recently assessed by EPA, and the need for regulation of emissions from incinerators, the only source for which controls may be essential, is under consideration. Under the Safe Drinking Water Act, EPA is preparing a report to the Congress concerning the nature and extent of PCB contamination, as well as recommendations for further regulatory action if necessary.

In 1973, FDA established tolerances for PCBs in several foods and in feeds for food-producing animals. In 1979, four of those tolerances were reduced. The current tolerances are 1.5 ppm (fat basis) in milk and manufactured dairy products; 3 ppm (fat basis) in poultry; 0.3 ppm in eggs; 0.2 ppm in finished animal feed; 2 ppm in animal feed components of animal origin; 5 ppm in fish and shellfish (edible portion); and 0.2 ppm in infant and junior foods. FDA is currently considering the lowering of PCB standards in fish and shellfish from 5 ppm to 2 ppm and has established action levels of 3 ppm (fat basis) in red meat and 10 ppm in paper food-packaging material. OSHA has adopted an 8-hour time-weighted average standard of 1 mg/m^3 for PCBs containing 42 percent chlorine, and 0.5 mg/m^3 for PCBs containing 54 percent chlorine. This standard was adopted by OSHA for toxic effects other than cancer.

MONS 222901

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
FIFRA, 6. Banned as active or inert ingredient of pesticides (with polychlorinated terphenyls). Registration of products reformulated, canceled 10/28/76.	Effectively removed pesticides as source of exposure.	PR notice 70-75 sent to all registrants affected.
TSCA, 6: Marking and disposal rule. Promulgated 2/17/78.	Sources have been identified, wastes are being isolated and/or destroyed. Some sources have been eliminated	40 CFR 761.10, 761.20
TSCA, 6: ANPR addressing issues raised by the court order (EDF versus EPA, 79-1162). Published 5/20/81.	Rulemaking slated for proposal by 4/23/82. (Actually published 6/22/82.)	46 FR, p. 27814
Ban on manufacturing, processing, and distribution in commerce (including some modifications to marking and disposal rule). Promulgated 5/31/79.	Most manufacturing had been voluntarily discontinued prior to these rules (except for certain R&D applications).	40 CFR 761
CWA, 304(a): Water quality criteria published in final form, 11/28/80.		45 FR 231, p. 79318
CWA, 307(a): Toxic pollutant effluent standard. Promulgated 8/28/79.		40 CFR 129.104
CWA, 311. Hazardous spill regulation establishing reportable quantity (10 lb, 4.54 kg) and imposing reporting requirements. Promulgated 6/28/79.	Not based on carcinogenicity. Encouraged greater care in handling and shipping of chemicals, and should result in reduction of accidental exposures.	40 CFR 117.3, 117.13
RCRA, 3001-3004: Proposed rule included six Aroclor compounds in list of toxic wastes, 12/18/78.	Final rule did not include these, as the TSCA disposal rule addressed PCBs in a more stringent fashion than had been contemplated.	43 FR 243, p. 58946
Designates PCBs as hazardous constituents of wastes, and subjects them to special handling and report/recordkeeping requirements. Promulgated 5/19/80.		40 CFR 261.11
RCRA, 4004 Prohibition on open burning, use on food, croplands, or open dumping of municipal sludges designated hazardous. Promulgated 9/13/79.	Prohibition on land crop and specifically addresses PCBs.	40 CFR 257
CAA: Assessment of sources completed, 5/80. Under review to determine if regulation is warranted.	Incinerators deemed only source that may require control in view of TSCA bans (EPA)	OAQPS, draft source assessment, 5/80
SDWA: Report to Congress, now in preparation, will document nature and extent of PCB contamination, treatment, and other implications, and establish what, if any, controls may be needed.		ODW, personal communication, 9/80 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		

(Continued)

MONS 222902

Pol/chlorinated Biphenyls (Concluded)

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
FDACA, 406: Tolerances for PCBs as unavoidable contaminants in certain fruits and animal feeds established 7/6/73. Four tolerances revoked 5/29/79.	Holds human exposure to lowest practicable level.	21 CFR 109.30, 509.30
Action level of 3 ppm (fat basis) for red meat established 8/10/80.	Holds human exposure to lowest practicable level. (FDA)	CFR 7:11.02
FDA announced the availability of documents on the permissive low judge's ruling on whether to consider the economic impact of lowering PCB standards in fish and shellfish from 5 ppm to 2 ppm. (FDA)		46 FR, p. 26551 and 47 FR, p. 10079 (FDA)
PEL: 1 mg/m³ 8-hr TWA (42 percent chlorine), 0.5 mg/m³ 8-hr TWA (54 percent chlorine).	Regulatory History: 1972: Walsh-Healy, 1 mg/m³ maximum allowable concentration.	29 CFR 1910.1000 (OSHA)
Potential for skin absorption noted. (Standard adopted for toxic effects other than cancer.) (OSHA)	8/27/74: OSHA Takeover Standard--current limit effective. (OSHA)	

MONS 222903

PROCARBAZINE AND PROCARBAZINE HYDROCHLORIDE

There is sufficient evidence for carcinogenicity in humans of intensive chemotherapeutic regimens that include alkylating agents, vinca alkaloids, procarbazine hydrochloride, and prednisone. There is inadequate evidence for carcinogenicity of procarbazine hydrochloride alone in humans. There is sufficient evidence for the carcinogenicity of procarbazine in experimental animals.[1,2]

Laboratory exposure of animals to procarbazine was studied by intraperitoneal injection. In rats, malignant lymphoma, adenocarcinoma of the mammary gland, and olfactory neuroblastomas were induced in statistically significant numbers. In mice, malignant lymphoma or leukemia, olfactory neuroblastoma, alveolar/bronchiolar adenoma, and adenocarcinoma of the uterus were induced in statistically significant numbers.[2]

Evidence of carcinogenicity was also found in mice and rats following administration by gavage; in rats following intravenous administration, and in one instance following transplacental exposure. Two studies in two species of nonhuman primates suggest that procarbazine hydrochloride may also produce myelogenous leukemia when administered by multiple routes to the same aniral.[1]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 26. Lyon, France: IARC, 1981, pp. 311-39.

[2]National Cancer Institute. Bioassay of Procarbazine for Possible Carcinogenicity. Technical Report Series No. 19, DHHS Publication No. (NIH) 79-819. Bethesda, Maryland, 1979.

Procarbazine, an organic compound, is soluble but unstable in water or aqueous solutions.

Procarbazine hydrochloride is primarily used as an antineoplastic agent in the treatment of advanced Hodgkin's disease and oat-cell carcinoma of the lung. The FDA approved the use of procarbazine hydrochloride in 1969 and indicated that the drug should be used as an adjunct to standard therapy.

Possible exposure occurs during manufacture of the drug, and direct exposure occurs during administration to patients. The National Prescription Audit reported 1.5 million prescriptions dispensed in 1980. Some of the metabolites of procarbazine are both carcinostatic and carcinogenic.

NONS 222904

REGULATIONS		
Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
EPA has minimal interest in regulating procarbazine or its hydrochloride as pharmaceuticals. (EPA)		
FDA, FD&C Approved for prescription use in 1969. (FDA)	Use restricted to palliative management of Hodgkin's disease and for use by patients who are nonresponsive to other forms of cancer treatment. Clear physician warning of secondary onset of leukemia after treatment with procarbazine is present in package insert. (FDA)	CFR 21, § bchapter B (FDA)

MONS 222905

β-PROPIOLACTONE

There is sufficient evidence for the carcinogenicity of β-propiolactone in experimental animals.[1] β-Propiolactone was carcinogenic in the mouse by skin application or subcutaneous injection, and in the rat by subcutaneous injection. Administration by gavage to a small group of female Sprague-Dawley rats gave squamous cell carcinoma of the forestomach.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 4. Lyon, France: IARC, 1974, pp. 259-69.

β-Propiolactone is a water-soluble industrial chemical. More than 85 percent of the β-propiolactone produced in the United States was used in captive consumption for the manufacture of acrylic acid and esters. Less than 15 percent was used as a sterilant of blood plasma; for vaccines, tissue grafts, surgical instruments, and enzymes; and as a vapor-phase disinfectant in enclosed spaces.

β-Propiolactone was first produced commercially in the United States in 1958. The sole U.S. manufacturer reportedly halted production at the end of 1973. However, for the period 1975-1977, EPA reported one producer in one region (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record).

Exposure to β-propiolactone occurred primarily in the occupational setting, notably through skin absorption and by inhalation of vapors. OSHA estimated that 450 persons were occupationally exposed to β-propiolactone. Occupations at greatest risk of exposure included disinfectant workers and makers of viricidal agents, acrylic plastics, and resins. Potential exposure to waste effluents from production and manufacturing plants was minimal because of β-propiolactone's short half-life in water.

OSHA regulates β-propiolactone on the basis of its carcinogenicity in animals. The regulation requires protective clothing, use of respirators, training in hygiene, medical surveillance, engineering controls to limit contamination, sign requirements for posting regulated areas, and labeling requirements for containers.

MONS 222906

p-Prohibitions

REG 'AT'CNS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Protective clothing, respirators, hygiene training, and medical surveillance requirements; open-vessel operations prohibited, contamination control requirements, sign requirements for regulated areas; labeling requirements for containers. (OSHA)	Regulatory History: 4/10/73: Emergency Temporary Standards--protective clothing and hygiene requirements for workers, open-vessel operations restricted, engineering requirements. 2/11/74: Final Standards--current regulations effective. (OSHA)	29 CFR 1910.1001 (OSHA)

MONS 222907

RESERPINE

Reserpine was tested in B6C3F1 mice by administration in the diet; it induced malignant mammary tumors in females and carcinomas of the seminal vesicles in males. When given in the diet to F344 rats it increased the incidence of pheochromocytomas in males.[1] This available evidence is considered as limited by an IARC working group,[2] but in view of another evaluation of NCI results, it can be considered as sufficient.[3]

The 14 epidemiological case-control and 2 cohort studies are not consistent in showing an increase in breast cancer associated with the use of reserpine. The available evidence of carcinogenicity in humans is considered inadequate.[2]

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[1]National Cancer Institute. Bioassay of Reserpine for Possible Carcinogenicity. Technical Report Series No. 193. DHEW Publication No. (NIH) 80-1749. Bethesda, Maryland, 1980.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[3]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis, eds. Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

Reserpine, a pharmaceutical, is a naturally occurring substance that is isolated from the roots of the plant Rauwolfia serpentina. It is marketed under at least 150 trade names.

In humans, medicinal preparations are used for treating hypertension and as a tranquilizer and sedative. Reserpine is also used in veterinary practice as a tranquilizer or sedative. Reserpine preparations are also added to various animal feeds, such as turkey feed, to lessen the incidence of aortic rupture.

Reserpine was produced by at least six manufacturers. EPA reports one producer in one region (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record). The annual U.S. sales of reserpine for use in human medicine were reported to be about 440,000 lb in 1976. Approximately 15.7 million prescriptions were dispensed by retail pharmacies during 1979, and an additional 2.3 million prescriptions were ordered in hospitals. Sales figures dropped 50 percent from 1976-79, indicating a reduction in reserpine use.

MONS 222908

An estimated 1300 to 2700 persons are occupationally exposed to reserpine. Exposure of the general population is unknown but sizable, based on the number of prescriptions. The average therapeutic dose ranges from 0.1 to 1.0 mg/day.

Federal regulations affecting exposure include EPA's hazardous waste rule, which restricts environmental release, and regulations under the Safe Drinking Water Act and the Resource Conservation and Recovery Act. FDA regulates reserpine as a prescription drug. FDA also regulates its use in animal diets, and on February 25, 1980, FDA revoked the use of reserpine as a component of premixed turkey feed.

Reserpine

REGULATIONS

Regulations and Other Actions	Effect of Regulations/ Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3018: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Designated as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11, 261.33 (EPA)
FDA Bureau of Veterinary Medicine, FD&CA: Regulated for use in turkeys to lessen the incidence of aortic rupture. Approval withdrawn at the request of sponsor; 45 FR 33, p. 10.34, 1/15/80.	Reduces to zero the exposure of the public to residues of reserpine in food animals.	21 CFR §558.505, §556.570 (1979) Sec. §60.570 (revoked) 1. Part 556 is amended by revoking Sec. §56.570 reserpine
Zero residue for reserpine and its metabolites. FDA Bureau of Drugs: Approved for prescription use in treatment of hypertension and for treatment of behavioral disorders. (FDA)	Restricted to approved uses. It has been implicated for risk of human mammary cancer without definitive outcome by a NIH ad hoc advisory committee. An NCI recent study showed increased incidence of mammary and adrenal tumors. As with neuroleptic drugs, there has been a correlation suggested between reserpine's prolactin-releasing activity and increased incidence of mammary tumors in rodents, but it is not to be included among the group of neuroleptic drugs which will be required to be relabeled with an appropriate precautionary statement (see 39 FR, 8/8/80, p. 32931-11. A Federal Register statement has been prepared by FDA proposing a labeling change for all reserpine-containing products to include a description of the animal carcinogenicity study results and the ambiguous results from human epidemiology studies. (FDA)	Sec. §58.505 (revoked) 1. Part 558 is amended by revoking Sec. §58.506 reserpine (FDA)

MONS 222909

SACCHARIN

In April 1977, the Commissioner of the Food and Drug Administration proposed to revoke an interim food additive regulation which permitted the use of saccharin and its salts in prepackaged food (e.g., soft drinks) and as a tabletop nonnutritive sweetener.[1] This proposal was based on several U.S. studies[2,4] and one Canadian study[3] showing that saccharin caused bladder cancer in male rats. An analysis published by the Office of Technology Assessment confirmed this conclusion.[4] According to an IARC working group, there was sufficient evidence that saccharin alone, given in high doses, was carcinogenic in male rats and can promote the action of known carcinogens in the bladder of rats of both sexes; and that the evidence of carcinogenicity is limited in mice.[5] Another IARC working group considered the same evidence as being limited both in rats and mice.[6]

The available epidemiological data provide no clear evidence that saccharin alone, or in combination with cyclamates, causes urinary bladder cancer, but a small increase in the risk of urinary bladder cancer in the general population or a larger increase in some individuals consuming very high doses of saccharin and cyclamates cannot be excluded.[4] The existing human evidence has been classified as inadequate.[5]

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[1]Food and Drug Administration. Saccharin and Its Salts. Proposed Rule Making. Federal Register, Vol. 42, No. 73, 1977, pp. 19996-20010.

[2]Food and Drug Administration. Histopathologic Evaluation of Tissues from Rats Following Continuous Dietary Intake of Sodium Saccharin and Calcium Cyclamate for a Maximum Period of Two Years. Final Report. Project P-169-70. Typescript, December 21, 1973

[3]Health Protection Branch, National Health and Welfare Department, Canada. Toxicity and Carcinogenicity Study of Orthotoluensulfonamide and Saccharin. Project [illegible]. General Protocol. Typescript, 1977.

[4]Office of Technology Assessment, Congress of the United States. Cancer Testing Technology and Saccharin. Washington, D.C.: U.S. Government Printing Office, 1977.

[5]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 22. Lyon, France: IARC, 1980, pp. 111-85.

[6]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

MONS 222910

Saccharin is a white crystalline powder that is soluble in water. Saccharin and sodium saccharin have been produced commercially in the United States for over 80 years. Production levels of saccharin in 1977 were estimated at 4.8 million lb. Imports of saccharin were estimated in 1977 at 3 million lb, and 1.3 million lb in 1980. Saccharin and its ammonium and sodium salts were reported for the TSCA Inventory. EPA reported domestic production of 746,000 lb and imports of 4.2 million lb (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record). There is only one reported manufacturing plant in the United States, and no current production figures are available. Approximately 6-8 million lb of saccharin were used among FDA-regulated products in 1976.

Saccharin has been used as a nonnutritive sweetening agent; however, its use substantially increased after cyclamates were banned in food in 1970. The 1976 U.S. consumption pattern for all forms of saccharin has been estimated as 45 percent in soft drinks; 18 percent in tabletop sweeteners; 14 percent in fruits, juices, sweets, chewing gum, and jellies; 10 percent in cosmetics and oral hygiene products; 7 percent in drugs such as coating on pills; 2 percent in tobacco; 2 percent in electroplating; and 2 percent for miscellaneous uses.

Human exposure to saccharin occurs primarily through ingestion from its use in many dietetic foods and drinks and in some personal hygiene products, including toothpastes and mouthwashes. The general public is exposed, especially those persons who have to reduce sugar intake. The National Occupational Hazard Survey and OSHA estimated that approximately 28,000 workers are occupationally exposed.

In compliance with the Delaney clause, FDA proposed to ban saccharin as a food additive in 1977 on the available evidence of carcinogenicity in animals. However, final regulations are pending because of Congressional action in 1977 requiring further study and labeling of saccharin. A joint FDA/NCI group, the Saccharin Working Group, was formed in 1977. A preliminary report of the epidemiological findings has been published, but an analysis of all the information gathered is yet to be completed. EPA regulates saccharin under the Resource Conservation and Recovery Act.

MONS 222911

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
no current action. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and reporting/recordkeeping requirements. Also designated as a hazardous constituent of waste, and subject wastes known to contain saccharin to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)	Based on chronic toxicity. (EPA)	40 CFR 261.11, 261.33 (EPA)
FDA Bureau of Foods, Bureau of Drugs. FD&CA: After receiving data indicating that saccharin caused cancer in experimental animals, the FDA proposed to ban the use of the compound. The Congress overruled the Agency's action, and the compound is now listed on an interim basis awaiting results from studies being presently conducted. (FDA)	No effect because Congress has overruled FDA. (FDA)	21 CFR 180.37 (FDA)

MONS 222912

SAFROLE

There is sufficient evidence for the carcinogenicity of safrole in experimental animals.[1] When given in the diet, safrole produced various liver tumors in several strains of male mice and male and female rats.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 10. Lyon, France: IARC, 1976, pp. 231-44.

Safrole is a colorless liquid that is insoluble in water and very soluble in alcohol.

This compound has been used to flavor beverages and foods and as a pesticide ingredient. It is reported to be used in soap manufacture, perfumery, sleep aids, and sedatives.

EPA indicated that nine companies produced and imported a total of over 2 million lb of the compound in 1977. No production data are available in the trade literature after 1977. However, according to the United States International Trade Commission (1981), approximately 36,000 lb of safrole were imported from Brazil during 1980.

OSHA estimated that 30 workers were potentially exposed. The FDA indicated that exposure to safrole of the general public through food consumption was extremely low since the Agency prohibited its use in food. Minimal exposure may occur through the use of edible spices, including nutmeg and mace, which contain low levels of naturally occurring safrole. The compound does not pose a hazard to the general population through consumption of drinking water because of its insolubility in water.

The EPA and the FDA regulate the use of safrole. During 1977, EPA promulgated standards for voluntary cancellation of safrole in pesticide products. The Agency did, however, permit one registrant to distribute and sell one safrole-containing product until March 11, 1978. Thereafter, no stocks were available for pesticide use. The FDA banned the use of oil of safrole and sassafras bark in food. However, edible spices (nutmeg and mace), which contain very small quantities of naturally occurring safrole, were permitted for use in foods. The Agency has been reviewing the use of safrole in sleeping aids and sedatives.

MONS 222913

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
FIFRA, 6: Voluntary cancellation of all registrations, 6/77.	Removal of restrictions as source of exposure. (EPA)	42 FR, p. 29957 (last notice)
RCRA, 3001-3004 Subjects waste products, off-specification batches, and spill residues in excess of 100L to it Handling and report/recordkeeping requirements. Also designates the compound as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80		40 CFR 261.11, 261.33
TSCA, 8(a): Proposed reporting rule requiring process and use data, published 2/20/80.		45 FR 42, p. 13346 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
FDA Bureau of Foods, FD&CA. Banned for use in foods, oil of sassafras; sassafras bark as source of safrole also banned.	Prohibited use of safrole and oil of sassafras and sassafras bark as sources of safrole in foods. Risk from safrole and these sources of safrole completely eliminated. Safrole-free extract of sassafras permitted under 172.510. Safrole-free extract permitted by both 172.510 and 172.580 (added 1/30/68--30 FR 692). Amended to 189.181 on 5/11/76 (41 FR 19807).	25 FR, p. 12412 (12/3/60) 42 FR, p. 14669 (3/15/77, amended) 42 FR, p. 56729 (10/28/77) (FDA)
FDA Bureau of Foods, FD&CA: Spices (nutmeg and mace) GRAS (182.10). (FDA)	Use of spices in foods permitted. (FDA)	

MONS 222914

SELENIUM SULFIDE

Dermal application of selenium sulfide to ICR Swiss mice was not carcinogenic, but the study was limited to 88 weeks because of test animal deaths from amyloidosis.[1] An NCI skin painting study with ICR Swiss mice using Selsun^{R}, a commercial selenium sulfide formulation, also gave negative results, and was terminated after 88 weeks because of the same amyloidosis problem.[2] In another chronic skin painting study of mice and rabbits, Selsun^{R} was also reported negative.[3] However, selenium sulfide administered by gavage to F344 rats and B6C3F1 mice induced hepatocellular carcinomas in male and female rats and female mice, and alveolar/bronchiolar carcinomas and adenomas in female mice, but it was not carcinogenic to male mice.[4] These results can be regarded as providing sufficient evidence of carcinogenicity in experimental animals.[5]

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[1]National Cancer Institute. Bioassay of Selenium Sulfide for Possible Carcinogenicity (Dermal Study). Technical Report Series No. 197. DHHS Publication No. (NIH) 80-1753. Bethesda, Maryland, 1980.

[2]National Cancer Institute. Bioassay of Selsun^{R} for Possible Carcinogenicity (Skin Painting Study). DHHS Publication No. (NIH) 80-1753. Bethesda, Maryland, 1980.

[3]Stenback, F. Local and Systemic Effects of Commonly Used Cutaneous Agents: Lifetime Studies of 16 Compounds in Mice and Rabbits. Acta Pharmacol. Toxicol. Vol. 41, 1977, pp. 417-31.

[4]National Cancer Institute. Bioassay of Selenium Sulfide for Possible Carcinogenicity (Gavage Study). Technical Report Series No. 199. DHHS Publication No. (NIH) 80-1750. Bethesda, Maryland, 1980.

[5]Griesemer, R.A., and C. Cueto. Toward a Classification Scheme for Degrees of Experimental Evidence for the Carcinogenicity of Chemicals for Animals. In: R. Montesano, H. Bartsch, and L. Tomatis (eds.). Molecular and Cellular Aspects of Carcinogen Screening Tests, IARC Scientific Publications, No. 27. Lyon, France: International Agency for Research on Cancer, 1980, pp. 259-81.

Selenium sulfide, an inorganic compound, is insoluble in water and soluble in alcohol.

EPA reports that selenium sulfide is used for the treatment of seborrhea, especially in shampoos. The chemical is available over the counter as Selsun^{R}, a stabilized buffered suspension. FDA reports that selenium sulfide is an active ingredient in some drug products used for the treatment of dandruff

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and certain types of dermatitis. A dandruff shampoo containing 1 percent selenium sulfide is available without a prescription and is recommended for use once or twice a week. By prescription, selenium sulfide is available in a 2.5 percent shampoo or lotion, with the recommended application limited to 10 minutes for 7 days to avoid the possibility of acute toxic effects. Selenium sulfide is also used topically in veterinary medicine for eczemas and dermatomycoses.

Selenium sulfide was not reported for the Toxic Substances Control Act (TSCA), Chemical Substance Inventory, public record. In 1979, approximately 1800 lb of selenium sulfide were imported. NCI reports that no separate current data on production or imports of selenium sulfide are available. No current U.S. producers were listed in the 1982 Directory of Chemical Producers.

NCI estimates that substantial exposure of the population to selenium sulfide is questionable. Skin absorption has been reported only in patients with open scalp lesions. In 1974, the National Occupational Hazard Survey estimated that 8500 workers were potentially exposed to selenium sulfide.

Selenium is widely distributed throughout the environment, occurring in groundwater, surface water, rocks, and soil. No data on the environmental occurrence of selenium sulfide are available; however, the EPA in 1976 estimated that about 700 lb of selenium sulfide wastes are generated annually by the medicinal industry.

Selenium sulfide is currently regulated by EPA under the Resource Conservation and Recovery Act. OSHA has adopted a permissible exposure level of 0.2 mg/m^3 time-weighted average for selenium compounds.

Selenium Sulfide

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. /Proposed 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes. (EPA)	40 CFR 261.11, 261.33 (EPA)
PEL: 0.2 mg/m^3 TWA (Selenium compounds as Se). (OSHA)	Regulatory History: 1952: Walsh-Healy, 0.1 mg/m^3 maximum allowable concentration. 8/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 222916

SOOTS, TARS, AND MINERAL OILS

There is sufficient evidence that soots, tars, and some mineral oils are carcinogenic both in humans and in experimental animals.[1] Soots, coal tars, creosote oils, shale oils and cutting oils are carcinogenic in experimental animals after skin painting or subcutaneous injection.[1]

Occupational exposure to coal soot, coal tar and pitch, coal tar fumes and some impure mineral oils causes cancer of several sites, including skin, lung, bladder, and gastrointestinal tract. Recent epidemiological data support those conclusions. This effect may be due to the presence of polycyclic aromatic hydrocarbons in these materials.[1]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

Soots, tars, and mineral oils (including creosote, shale, and cutting oils) are largely byproducts, contaminants, or wastes. These substances result from fossil fuel processing technology such as coal carbonization and from incomplete combustion of other carbonaceous materials. Each of these materials is composed of many ingredients.

Although these substances are largely byproducts, contaminants, or wastes, there are commercial uses of these substances. Coal tars have been used to treat skin disorders; however, their commercial importance is based on their use as chemical intermediates for a number of products such as creosote, pitch, timber preservatives, pesticide formulations, benzene, toluene, xylene, and naphthalene. Petrolatum and mineral oils are commercially important because of their use in pharmaceuticals, in protective coatings on fruits and vegetables, and in bakery products.

In 1975, approximately 35 million lb of coal tar and 2 million lb of coal tar neutral oil were manufactured or processed for use. In 1976, about 948 million lb of creosote were produced in the United States.

Human exposure to soots, tars, and oils occurs through inhalation, ingestion, and skin absorption. NIOSH has estimated that 10,000 coal handlers, coke oven workers, and byproduct plant workers are occupationally exposed to coal tar. OSHA has estimated that 121,000 workers are exposed to tars. The environmental contamination by these substances is widespread, and it can be assumed that the entire population is exposed to these substances at some level.

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EPA regulates these substances under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), which restricts use, and under the Resource Conservation and Recovery Act (RCRA), which fosters greater care in handling of chemical wastes. The EPA Carcinogen Assessment Group included soots, coal tars, and creosote in its list of carcinogens; and as a result of this listing, these substances are included in the hazardous waste disposal rule of the RCRA. FDA regulates the use of petrolatum and mineral oil in food and the use of coal tar in drugs. The FDA Advisory Panel on Over the Counter Drug Products has recently determined that coal tar is not safe when used as a topical antifungal agent. Only petrolatum and mineral oil that contain no PAH may be used in coatings for fruits and vegetables and in release agents for bakery products. OSHA adopted a permissible exposure limit for coal tar pitch volatiles of 0.2 mg/m^3 as an 8-hour time-weighted average.

Soots, Tars, and Mineral Oils

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Creosote		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and reporting/recordkeeping requirements. Also designates creosote as a hazardous constituent of waste, 6/19/80. (EPA)	Based on chronic toxicity. Fosters greater care in handling chemical wastes. (EPA)	40 CFR 261.11, 261.33 (EPA)
Coal Tar, Coal Tar Neutral Oil, and Creosote		
FIFRA, 6: Cancellation of registration of products not conforming to provision below. Proposed, 2/19/81.	Possible reduction in use and consequent reduction in exposure.	46 FR, p. 13020
FIFRA, 3: Restricted use for specified wood preservative products. Proposed 2/19/81. (EPA)	By imposing conditions of use, exposure potential is reduced. (EPA)	46 FR, p. 13020 (EPA)
Coal Tar, Soot, and Creosote		
See Carcinogen Assessment Group statement under 2-acetylaminofluorene (EPA)		
Coal Tar		
The FDA Advisory Panel on Over the Counter Drug Products has determined that coal tar is not safe to be used as a topical antifungal agent. (FDA)		47 FR, p. 12518-6 (FDA)
Criteria Document: Coal tar products, NIOSH recommendations; engineering controls, medical surveillance, labeling and posting, respirators, training. Recommended standard for coal tar products [1977]: 0.1 mg/m^3 in cyclohexane extractable fractions. (NIOSH)	Work practices to minimize exposure to emissions. (NIOSH)	
PEL: 0.2 mg/m^3 8-hr TWA (coal tar pitch 29 CFR 1910.1000 volatiles). (OSHA)	6/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	

MONS 222918

STREPTOZOTOCIN

There is sufficient evidence that streptozotocin (STR) is carcinogenic in experimental animals.[1] Strentozotocin is carcinogenic in mice, rats and Chinese hamsters following intravenous or irt.aperitoneal administration. It produced benign and malignant tumors of the liver and kidney and islet-cell tumors of the pancreas. It is carcinogenic after administration in single doses.[2]

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[1]International Agency for Research on Cancer. IAPC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 17. Lyon, France: IARC, 1978, pp. 337-49.

STR, a water-soluble N-nitruso compound, was of interest as a potential antibacterial agent, but the chemical has not been used commercially. STR has been used in studies on diabetes because it has specific toxic action on pancreatic β-cells, including hyperglycemia. It has been shown to have cytotoxic effects, and it could be used as an antineoplastic drug.

STR is produced by the soil microorganism Streptomyces achromogenes. STR production was reported by two manufacturers of research biochemicals (U.S. International Trade Commission Publication 804, 1977), but the amounts were not indicated.

Human exposure to STR could occur primarily through ingestion and less likely through skin absorption and inhalation. Occupational exposure to STR is limited to pharmaceutical workers and researchers.

EPA regulates STR under the Resource Conservation and Recovery Act. The FDA in 1980 reported that STR was submitted for approval as a new drug application, but the application was withdrawn before evaluation was completed.

MONS 222919

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
No current action. No known problems in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004. Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designate streptozotocin as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement for 2-acetylaminofluorene (EPA)		40 CFR 261.11, 261.33 (EPA)
Bureau of Drugs, FD&CA: Request for approval was withdrawn. (FDA)	No approved uses at time. (FDA)	

MONS 222920

SULFALLATE

Sulfallate, a chlorinated dithiocarbamate, administered in the feed, was carcinogenic to Osborne-Mendel rats and to B6C3F1 mice, inducing mammary gland tumors in females of both species, tumors of the forestomach in male rats, and lung tumors in male mice.[1]

[1]National Cancer Institute. Bioassay of Sulfallate for Possible Carcinogenicity. Technical Report Series No. 115. DHEW Publication No. (NIH) 78-1370. Bethesda, Maryland, 1978.

Sulfallate is a trade name for diethyldithiocarbamic acid 2-chloroallyl-ester; it is soluble in water. The chemical is formulated into emulsifiable concentrates, liquids, and granules.

The major use for sulfallate in the United States is as a preemergent selective herbicide to control certain annual grasses and broadleaf weeds around vegetable and fruit crops. Sulfallate has also been used for weed control among shrubbery and ornamental plants.

Sulfallate was introduced as a herbicide in 1954. According to NCI, during 1980, the production was greater than 5000 lb. Sulfallate was not reported for the Toxic Substances Control Act (TSCA), Chemical Substance Inventory (public record).

The 1974 National Occupational Hazard Survey provided no estimate of the number of workers potentially exposed to sulfallate. A potential for exposure exists during the manufacture and application of the herbicide. Agricultural workers have the greatest risk of sulfallate exposure, and rural residents of agricultural communities may be exposed to airborne residues of sulfallate after spraying operations. At commercially recommended rates of 4 lb/gal, the average persistence of sulfallate in soil is 3-6 weeks. The general population may be exposed through ingestion of residues in food crops.

The EPA has established tolerances for sulfallate residues on a variety of raw agricultural commodities. Enforcement is vested in FDA.

Sulfallate

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Tolerances established for pesticide chemicals in or on raw agricultural commodities (11/25/71, 2/7/73). (EPA)	Based on adverse effects of the chemical, use patterns, and detection limits. Enforcement vested in FDA. (EPA)	40 CFR 180.247 (EPA)

MONS 222921

2,3,7,8-TETRACHLORODIBENZO-p-DIOXIN (TCDD)

The evidence for the carcinogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in experimental animals is considered as sufficient.[1] An increased incidence of hepatocellular carcinomas and squamous-cell carcinomas of the lung, hard palate/nasal turbinates or tongue was observed in rats maintained on diets containing TCDD. In another study, increased incidence of tumors in a variety of organs was observed at all dietary levels of TCDD greater than 0.001 µg/kg.[1] TCDD administered by gavage to rats and mice induced follicular-cell thyroid adenomas in males and neoplastic nodules of the liver in females. TCDD also induced hepatocellular carcinomas in mice of both sexes and follicular-cell thyroid adenomas in females.[2] TCDD applied to the skin was not carcinogenic to male mice but in females it produced fibrosarcomas in the integumentary system.[3]

There is no report of human exposure to TCDD alone without the other chemicals such as 2,4,5-trichlorophenol or 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) being present. The available evidence from human studies is considered as inadequate.[1]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] National Toxicology Program. Carcinogenesis Bioassay of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (CAS No. 1746-01-6) in Osborne-Mendel Rats and B6C3F1 Mice (Gavage Study). Technical Report Series No. 209. NIH Publication No. 82-1765. Research Triangle Park, N.C., and Bethesda, Maryland: NTP, 1982.

[3] National Toxicology Program. Carcinogenesis Bioassay of 2,3,7,8-Tetrachlorodibenzo-p-dioxin (CAS No. 1746-01-6) in Swiss-Webster Mice (Dermal Study). Technical Report Series No. 201. NIH Publication No. 82-1757. Research Triangle Park, N.C., and Bethesda, Maryland: NTP, 1982.

2,3,7,8-Tetrachlorodibenzo-p-dioxin, commonly referred to as TCDD, is a very toxic chemical. TCDD has no reported use other than as a test chemical in basic research.

The total estimated release of TCDD is about 80 lb per year. Sources of potential exposure to TCDD are pesticidal spraying; cigarette smoke; and combustion of gasoline, diesel fuel, and wood. Trace concentrations (3-6 ppb) of TCDD have been reported in 3 of 23 samples of beef adipose tissues.

MONS 222922

EPA, under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), banned detectable TCDD in 2,4,5-T and silvex. An emergency suspension order issued under FIFRA is still under litigation. Under the Resource Conservation and Recovery Act, TCDD has been designated as a hazardous constituent of waste, which subjects the chemical to special handling and record requirements. A health-related water quality criteria document was published under the Clean Water Act.

2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
FIFRA: Ruling forbidding detectable TCDD and related chlorodioxins in 2,4,5-T and silvex, 9/20/79	Limited effectiveness. Probably did result in some reduction in contamination.	PR Notice 79-22, sent to all affected registrants
FIFRA, 6: RPAR issued for 2,4,5-trichlorophenol, 9/15/78.	Based on oncogenicity/teratogenicity. Final decision on proposed action will come after completion of cancellation hearings on 2,4,5-T and silvex.	43 FR, p. 41256
Emergency suspension order, cancellation suspension notices for 2,4,5-T, 2,4,5-T esters, and silvex, 3/15/79.	Litigation seeking temporary injunction against emergency suspension order dismissed. Issues in abeyance pending cancellation hearings, begun 3/16/80, and still in progress.	44 FR, p. 15874
RCRA, 3001-3006: Designates TCDD as a hazardous constituent of waste, and subjects any waste containing this chemical substance to handling and report/recordkeeping requirements, does not require testing. Promulgated 5/19/80.		40 CFR 261.11
CWA, 304(a): Water quality criteria proposed, 10/79.	Final criteria on hold for technical reasons.	OWRS, personal communication, 6/81
CAA: Assessment of sources and exposures completed, 5/80.		OAQPS, personal communication, 6/80
TSCA, 6: Conditions for disposal of TCDD contaminated wastes, including notification to EPA.	Restricts removal of wastes except with EPA approval in compliance with RCRA requirements. (EPA)	44 CFR 775 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene (EPA)		

MONS 222923

THIOACETAMIDE

There is sufficient evidence for the carcinogenicity of thioacetamide in experimental animals.[1] Thioacetamide was carcinogenic in mice and rats following administration in the diet, the only exposure route tested. It induced liver-cell tumors in Swiss mice and liver-cell and bile duct tumors in Wistar rats. No carcinogenicity was observed in hamsters given thioacetamide dissolved in distilled water by stomach tube.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 7. Lyon, France: IARC, 1974, pp. 77-83.

Thioacetamide (TAA) is a synthetic organic chemical, which is soluble in water and in ethanol. TAA is available in the United States as a laboratory chemical containing 99 percent of the active ingredient.

TAA is used as a replacement for hydrogen sulfide in qualitative analyses. TAA has been used as an organic solvent in the leather, textile, and paper industries; as an accelerator in the vulcanization of buna rubber; and as a stabilizer of motor fuel.

Commercial production of TAA in the United States was first reported in 1921. EPA estimated six producers and importers in three regions, with a domestic production of 4000 lb and imports of 4000 lb (Toxic Substances Control Act (TSCA), Chemical Substances Inventory, 1979, public record). TAA production was not reported to the U.S. International Trade Commission for 1979-1980. No evidence was found that this chemical is now commercially produced or imported in the United States, according to NCI.

Human exposure to TAA is principally through inhalation and skin absorption. Chemists and laboratory technicians are at greatest risk of exposure. In 1974, the National Occupational Hazard Survey estimated that 4600 workers were potentially exposed to TAA.

TAA is regulated by EPA under the Resource Conservation and Recovery Act, and regulation is proposed under the TSCA, 8(a), reporting rule that would provide detailed production and marketing data.

MONS 222924

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3004 Subject: off-specification batches, waste products and spill residues in excess of 1000 kg to handling and report/record-keeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261 33
TSCA, 8(a). Reporting rule requiring process and use data, proposed 2/29/80.	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13666 (EPA)
See Carcinogen Assessment Group Statement under 2-acetylaminofluorene (EPA)		

MONS 222925

THIOUREA

There is sufficient evidence for the carcinogenicity of thiourea in experimental animals.[1] Thiourea produced thyroid, liver and Zymbal's gland tumors in several strains of rats after administration in drinking water or diet. Intraperitoneal injection followed by administration in drinking water also produced Zymbal's gland tumors in rats. Administration of thiourea in the diet or by subcutaneous injection to mice did not produce thyroid tumors; however, this experiment was considered inadequate. An increased incidence of liver-cell tumors in a feed experiment with trout was reported, but this result cannot be considered as conclusive.[2]

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[1] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2] International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 7. Lyon, France: IARC, 1974, pp. 95-109.

Thiourea is an almost colorless crystalline solid that is soluble in water and in alcohol.

Thiourea was used in a variety of consumer applications including fire retardants, photographic chemicals, rust removers, animal glue liquefiers, and silver tarnish removers. But a recent evaluation has indicated that it is now used only in animal glue liquefiers and silver tarnish removers. Liquid animal glues may contain 10-20 percent thiourea as a liquefying agent. Even these uses are diminishing.

Thiourea is reported to be used commercially in the production of flame retardant resins and as a vulcanization accelerator.

Two companies began commercial production of thiourea in the United States in 1938. One company transferred the production to Canada in 1952, and the other discontinued production in 1954. In their initial inventory of chemical manufacturers and importers, EPA reported that in 1977 there were 21 producers and importers in six regions, with a domestic production of 4.4 million lb and imports of 2 million lb (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record). Production of thiourea was not reported to the U.S. International Trade Commission in 1979-1980. There are now no manufacturers in the U.S. that produce either thiourea or its

MONS 222926

major derivative, thiourea dioxide. The U.S. consumption depends at present on imports. About 70 companies have been reported by EPA as distributors of thiourea. The chemical is imported mainly from Japan, with small quantities coming from the Federal Republic of Germany. According to CPSC, there has been a recent upsurge in the market for thiourea.

Because liquid animal glues containing thiourea have been largely replaced by better woodworking glues, the chemical is probably a minor source of consumer exposure. In silver tarnish-remover dips, thiourea is used to dissolve silver sulfide tarnish. Thus, substantial skin contact is possible, and small amounts of thiourea may be ingested if newly cleaned utensils are not washed thoroughly before use. Two tarnish-remover dips have been identified, and one is widely distributed (CPSC). In 1974, the National Occupational Hazard Survey estimated that 213,000 workers were potentially exposed to thiourea.

EPA regulates thiourea under the Resource Conservation and Recovery Act. The FDA prohibits the use of thiourea in human food.

Thiourea

REGULATIONS

Regulations and Other Actions	Effect of Regulations: Other Comments	Citation of Regulation
No current action; under evaluation; project to begin in FY83. (CPSC)		
ACRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and reporting/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes. (EPA)	40 CFR 261.11, 261.33 (EPA)
Substance prohibited from use in human food. (FDA)		21 CFR 189 (FDA)

MONS 222927

THORIUM DIOXIDE

Thorotrast (thorium dioxide) has received much attention since 1947 when MacMahon et al.[1] reported the first death due to its use. Their patient developed an endothelial cell carcinoma of the liver 12 years after the intravascular use of Thorotrast. Since that time, there have been over 60 cases of neoplasms attributed to its use.[2] Additional evidence for the carcinogenicity of thorium dioxide (administered diagnostically as "Thorotrast") is given by a study in Portugal.[3] One-thousand one-hundred and seven (46.6 percent of the exposed Thorotrast population) had been traced up to December 31, 1963; of these 699 had died and 408 were still living. Twenty-two cases of a special sarcoma of the liver, hemangioendothelioma, have occurred. This tumor is virtually Thorotrast-specific in the liver. The latent period between Thorotrast administration and onset of the fatal illness was 20 years or more with only one exception.

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[1]MacMahon, H.E., A.S. Murphy, and M.I. Bates. Endothelial-Cell Sarcoma of Liver Following Thorotrast Injection. American Journal of Pathology. Vol. 23, 1947, pp. 585-613.

[2]Barry, W.J., and C.J. Rominger. Thorotrast Granulomas. American Journal of Roentgenology. Vol. 92(3), 1954, pp. 584-90.

[3]Das Horta, J., J.D. Abbatt, L.C. Da Motta, and M.L. Roriz. Malignancy and Other Late Effects Following Administration of Thorotrast. Lancet: 1965, pp. 201-05.

The chemical thorium dioxide is a crystalline powder that is insoluble in water, acids, and alkalies.

This chemical was used in the development of nuclear reactors. Because of its long-life incandescent properties, however, thorium dioxide was primarily used in gas mantles. The chemical was also used in electrodes for arc welding and in Thorotrast, a radiopaque medium for X-ray imaging in medical diagnostic procedures.

EPA reported for 1977 five producers and importers in four regions, with domestic production as 373,000 lb and imports of 4200 lb (Toxic Substances Control Act, Chemical Substance Inventory, 1979, public record).

Exposure to the compound may occur through inhalation of dust or gas, intravenous injection, ingestion of liquid thorium dioxide, and skin absorption. Occupations at greatest risk of exposure were ceramic makers, incandescent lamp makers, magnesium alloy makers, metal refiners, nuclear reactor workers, chemists, and vacuum tube makers. OSHA estimated that 128,500 workers were potentially exposed to the compound during production and use. A number of patients were exposed to Thorotrast when it was administered for X-ray procedures.

NONS 222928

Because of the reported carcinogenic efferts of Thorotrast in humans, several Government Agencies have restricted the use of this material. The FDA has approved thorium dioxide for use as a radiopaque medium for X-ray imaging where there is limited life expectancy. In March 1980, the Nuclear Regulatory Commission (NRC) withdrew authorizations for use and transfer of the material for internal or external medicinal use in humans. Authorizations were issued, however, for research, development, educational, commercial, or operational purposes under conditions specified by the NRC. The Agency further stated that use and transfer of the material for these purposes may not exceed 15 lb at any one time and no more than a total of 150 lb in any one calender year.

Thorium Dioxide

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Although reported for the TSCA Inventory, thorium dioxide appears primarily to be used in medicine. Its production is sufficiently low as to place regulatory interest at a low priority. (EPA)		
FDA Bureau of Drugs, FD&CA. Must meet New Drug Application and labeling requirements. Approved for use as a radiopaque medium for X-ray imaging. (FDA)	Legal limits use to cases where there is limited life expectancy (disease, age). Prohibits use in food-producing animals. (FDA)	21 CFR, Subchapter D, 21 CFR 250.103 (FDA)

MONS 222929

o-TOLUIDINE AND o-TOLUIDINE HYDROCHLORIDE

There is sufficient evidence for the carcinogenicity of ortho-toluidine hydrochloride in experimental animals.[1] Ortho-toluidine hydrochloride was tested in several experiments, but only two experiments in mice and two experiments in rats in which the compound was administered in the diet were adequate. It was carcinogenic in mice, producing hepatocellular carcinomas or adenomas in females and hemangiosarcomas at all sites in males of one strain and hemangiosarcomas and hemangiomas of the abdominal viscera in animals of both sexes of another strain. It was carcinogenic in rats: In animals of one strain it produced sarcomas of multiple organs in animals of both sexes, fibromas of the subcutaneous tissue and mesotheliomas in males, and sarcomas of the spleen, transitional-cell papillomas, and carcinomas of the urinary bladder, and mammary gland fibro-adenomas and adenomas in females. In male rats of another strain, it produced subcutaneous fibromas and fibrosarcomas as well as a slight increase in the incidence of multiple tumors, including transitional-cell carcinomas of the urinary bladder.[2,3]

In epidemiological studies, an increased incidence of bladder cancer has been observed in workers exposed to ortho-toluidine, but as all were exposed to other possibly carcinogenic chemicals, ortho-toluidine cannot be identified specifically as the responsible agent.[1] The evidence is considered inadequate in humans.

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 27. Lyon, France: IARC, 1982, pp. 155-75.

[3]National Cancer Institute. Bioassay of o-Toluidine Hydrochloride for Possible Carcinogenicity. Technical Report Series No. 153. DHHS Publication No. (NIH) 79-1709. Bethesda, Maryland, 1979.

o-Toluidine hydrochloride is a salt of an aromatic amine, and it is used primarily in the manufacture of a large number of commercial dyes including azo pigment dyes, triarylmethane dyes, sulfur dyes, and indigo compounds.

o-Toluidine hydrochloride has been used commercially in the United States for over 50 years. Commercial production was first reported in 1956. In 1977, 1000 lb of o-toluidine hydrochloride were manufactured. In 1976, 25,000 lb of o-toluidine hydrochloride were imported.

MONS 222930

The principal route of human exposure to o-toluidine hydrochloride is the respiratory system, although the compound may also be adsorbed through the skin. OSHA has reported that an estimated 13,900 workers were exposed to o-toluidine. Occupations with the greatest potential for exposure include dyemakers and pigment makers. Consumer exposure to o-toluidine hydrochloride may occur from residues present in commercial dyes used on textiles. The presence of o-toluidine hydrochloride even as a trace contaminant would be a cause for concern. However, in September 1980, the Consumer Product Safety Commission (CPSC) staff preliminarily determined that o-toluidine hydrochloride was not present in consumer products under CPSC jurisdiction. The Commission subsequently requested (45 FR 61344) public comment to verify the accuracy of its information, but no comments were received. Pending the receipt of new information, the Commission plans no action on o-toluidine hydrochloride.

EPA regulates o-toluidine hydrochloride under the Resource Conservation and Recovery Act and is proposing regulation under the TSCA, 8(a), reporting rule. FDA reports that exposure is limited to trace amounts in any products under its jurisdiction. OSHA adopted a permissible exposure limit of 5 ppm (22 mg/m^3) as an 8-hour time-weighted average for occupational exposure to o-toluidine. OSHA adopted this standard for toxic effects other than cancer.

o-Toluidine and o-Toluidine Hydrochloride

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
No current action. (CPSC)		
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Promulgated 1/80.		40 CFR 261.33
Also designates o-toluidine hydrochloride as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11
TSCA, 8(a): Reporting rule requiring process and use data, proposed 2/29/80 (o-toluidine only).		45 FR 42 p 13646 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
Regulatory Authority: FD&CA, 201(s). (FDA)	Action pending completion of contaminants policy. (FDA)	
PEL: 5 ppm (22 mg/m^3) 8-hr TWA (o-toluidine). Potential for skin absorption noted. [Standard adopted for toxic effects other than cancer.] (OSHA)	6/27/71: OSHA Takeover Standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)

MONS 222931

TOXAPHENE

There is sufficient evidence for the carcinogenicity of toxaphene in experimental animals.[1,2] Technical grade toxaphene administered in feed increased the incidence of hepatocellular carcinomas in male and female B6C3F1 mice. An increased incidence of thyroid tumors was observed in Osborne-Mendel rats.[2,3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 327-438.

[3]National Cancer Institute. Bioassay of Toxaphene for Possible Carcinogenicity. CAS No. 8001-35-2-NCI-CG. Technical Report Series No. 37. DHHS Publication No. (NIH) 79-837. Bethesda, Maryland, 1979.

Toxaphene is a mixture of chlorinated camphenes that appears as a waxy amber solid. The exact composition of the mixture is not known.

During the last 10 years, toxaphene has been used in larger quantities in the United States than in previous years. Its use increased, due in part to the phasing out of DDT.

Toxaphene was first commercially produced in the United States in 1947. It is available as wettable powder, emulsifiable concentrate, dust, granule, bait, oil, and emulsion. During 1976-78, a reported 39-42 million lb of the compound were produced. Eighty-five percent of the toxaphene used in this country was for the control of cotton insect pests, and the remaining 15 percent was used for the control of insect pests on livestock, poultry, and for a few field crops other than cotton. In 1976, farmers used 30 million lb of toxaphene on cotton crops, 2.2 million lb on soybeans, 1 million lb on sorghum, and 400,000 lb on peanuts. The Southeast and Delta States consumed most of the toxaphene produced.

Manufacturers of toxaphene, cotton farmers, and pesticide applicators were among the persons at highest risk of exposure. OSHA estimated that only 100 industrial workers were potentially exposed. This figure very likely included only workers involved in the manufacture of the insecticide. No estimates are available on the number of people potentially exposed through agricultural use and handling. This number may be significant because toxaphene represented 41 percent of the total insecticide used on cotton crops in 1976.

MONS 222932

In the National Soils Monitoring Program, few toxaphene residues were found (4.2 percent of 1729 sites sampled). The range of toxaphene residues detected was 0.1 to 11.72 ppm in positive samples. However, the material can be extremely persistent in soil receiving direct application (i.e., crop'and). In one study, 45 percent of the toxaphene applied to a sandy loam soil in 1951 was detectable 20 years later. In some instances, agricultural runoff has polluted local lakes and streams.

In 1980, EPA published a water quality criteria document for the protection of human health. In 1977, under the Clean Water Act, EPA promulgated a toxic pollutant effluent standard and a hazardous spill regulation requiring stringent reporting of spills involving quantities of 1 lb or more. A Rebuttable Presumption Against Registration had been issued under the Federal Insecticide, Fungicide, and Rodenticide Act. In October 1982, the EPA published a notice of intent to cancel or restrict registrations for products containing toxaphene. Under the Safe Drinking Water Act, a maximum contaminant level of 0.005 mg/l was established. The OSHA standard for toxaphene is 0.05 mg/m^3 as an 8-hour time-weighted average. This standard was adopted by OSHA for toxic effects other than cancer.

MONS 222933

REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
CWA, 304(a): Water quality criteria published in final form, 11/28/80.		45 FR 231, p. 79318
CWA, 307(a): Toxic pollutant effluent standards. Promulgated 1/12/77.	Based on general toxicity.	40 CFR 129.4, 129.104
CWA, 311: Hazardous spill requiring an estimating reportable quantity (1 lb, 0.454 kg) and keeping reporting requirements. Promulgated 8/29/79.	Not based on carcinogenicity, most stringent limitation.	40 CFR 117.3, 117.21
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates toxaphene as a hazardous constituent of waste, and subjects wastes shown to contain it to the same requirements. Promulgated 5/19/80.		40 CFR 261.11, 261.33
SDWA, 1412: Revised drinking water maximum contaminant level schedules for proposal, 8/83.	Existing maximum contaminant level of 0.005 mg/l (5 ug/l) remains in force. Chronic toxicity, including carcinogenicity, is being considered. (EPA)	40 CFR 141.11 ODW, memorandum, 9/81
FIFRA, 6: RPAR issued, 5/27/77.		45 FR, p. 26860
FIFRA, 6: Notice of intent to cancel or restrict registrations for products containing toxaphene, 11/29/82.		47 FR 229, p. 53784 (EPA)
See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		
PEL: 0.5 mg/m³ 8-hr TWA.	Regulatory History: 8/27/71: OSHA Takeover standard--current limit effective. (OSHA)	29 CFR 1910.1000 (OSHA)
Potential for skin absorption noted. [illegible] evidence for toxic effects other than cancer.) (OSHA)		

MONS 222934

2,4,6-TRICHLOROPHENOL

2,4,6-Trichlorophenol was tested in one experiment in two strains of mice treated initially by gavage and then given the substance in the diet, but this experiment was not considered as adequate.[1] The National Cancer Institute also tested this compound, and under the conditions of this bioassay 2,4,6-trichlorophenol administered in the diet was carcinogenic in male F344 rats, inducing mononuclear cell leukemias or lymphomas. The test chemical was also carcinogenic in both sexes of B6C3F1 mice, inducing hepatocellular carcinomas and adenomas.[2] The available data are regarded as providing sufficient evidence for the carcinogenicity of this substance in experimental animals.[3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 349-67.

[2]National Cancer Institute. Bioassay of 2,4,6-Trichlorophenol for Possible Carcinogenicity. Technical Report Series No. 155. DHEW Publication No. (NIH) 79-1711. Bethesda, Maryland, 1979.

[3]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

2,4,6-Trichlorophenol, an organic aromatic compound, is soluble in water, acetone, alcohol, and ether.

2,4,6-Trichlorophenol has been used as a wood preservative, a glue preservative, and an antimildew treatment for textiles. The chemical has also been used as a bactericide, a herbicide, and a defoliant.

Commercial production of 2,4,6-trichlorophenol in the United States was first reported in 1950. Production of this compound was limited in 1975, due to the high cost of removing toxic chlorinated dibenzo-p-dioxins, which have been found in samples of 2,4,6-trichlorophenol as impurities.

The U.S. International Trade Commission (USITC) reported in 1976 that 2200 lb were imported. In their initial inventory of commercial chemicals, the EPA estimated four producers and importers, with a domestic production of 37,000 lb and imports of 37,500 lb (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). The production of 2,4,6-trichlorophenol was not reported to the USITC in 1979-1980, but 1980 imports through principal U.S. customs districts were 550 lb. The 1982 Directory of Chemical Producers lists two U.S. companies currently producing this chemical.

MONS 222935

2,4,6-Trichlorophenol is a strong dermal irritant. Human exposure to 2,4,6-trichlorophenol can occur through skin absorption or ingestion. In the 1974 National Occupational Hazard Survey, NIOSH estimated that 110 workers were exposed to 2,4,6-trichlorophenol. Substantial exposure of the population is questionable, according to NCI.

2,4,6-Trichlorophenol can be produced when industrial waste water containing phenol or certain aromatic acids is treated with hypochlorite. Trichlorophenol (unspecified isomers) has been detected in river water samples, landfill leachate samples (40 ng/l), and tapwater samples (2-4 ng/l). Production emissions have been estimated at 1.0 lb/ton.

2,4,6-Trichlorophenol is currently under evaluation by CPSC. EPA regulates 2,4,6-trichlorophenol under the Clean Water Act (CWA, 304 and 311) and under the Resource Conservation and Recovery Act (RCRA, 3001-3006). EPA has published a water quality criteria document (11/28/80) on 2,4,6-trichlorophenol for the protection of human health.

2,4,6-Trichlorophenol

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Under evaluation. (CPSC)		
CWA, 304: Water quality criteria published in final form on 11/28/80.		45 FR, p. 79318
CWA, 311: Hazardous spill regulation established reportable quantity (10 lb, 5.54 kg) and imposed reporting requirement. Promulgated 6/29/79.	Regulation based on aquatic toxicity. Fosters greater care in handling and shipping of chemicals.	40 CFR 117.3, 117.11
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and record/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80. (EPA)	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes. (EPA)	40 CFR 261.11, 261.33 (EPA)

MONS 222936

TRIS(1-AZIRIDINYL)PHOSPHINE SULFIDE (THIOTEPA)

There is sufficient evidence for the carcinogenicity of tris-(1-aziridinyl)phosphine sulfide (thiotepa) in experimental animals.[1] Thiotepa was carcinogenic in mice and rats after administration by various routes, producing a variety of malignant tumors.[2,3]

There are several reports and epidemiological studies suggesting the development of acute non-lymphocytic leukemia in patients treated with thiotepa for ovarian and other malignant tumors,[2] but the evidence is considered as inadequate in humans.[1]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 9. Lyon, France: IARC, 1975, pp. 85-94.
[3]National Cancer Institute. Bioassay of Thiotepa for Possible Carcinogenicity. Technical Report Series No. 58. DHEW Publication No. (NIH) 78-1308. Bethesda, Maryland, 1978.

Thiotepa, a white crystalline solid, is a polyfunctional alkylating agent used in the chemotherapy of some neoplastic diseases.

Thiotepa has been prescribed for a wide variety of neoplastic diseases (adenocarcinomas of the breast and the ovary, superficial carcinoma of the urinary bladder, controlling intracavitary or localized neoplastic disease, lymphomas such as lymphosarcoma and Hodgkin's disease, as well as bronchogenic carcinoma). It is now largely superseded by other treatments.

There is only one known producer of thiotepa in the United States, and production data are not reported. The National Prescription Audit reported that 30,000 prescriptions were dispensed by retail pharmacies in 1980. An unknown quantity was ordered by hospitals.

The EPA designates thiotepa as a hazardous constituent of wastes and regulates it under the Resource Conservation and Recovery Act. The FDA approved thiotepa on February 19, 1959, with the warning that dosing must be carefully individualized.

MONS 222937

Tris(1-aziridinyl)phosphine Sulfide
(Thiotepa)

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
No current action. No known presence in consumer products under CPSC jurisdiction. (CPSC)		
RCRA, 3001-3004: Designates thiotepa as a hazardous constituent of wastes, and subjects wastes known to contain it to handling and report/recordkeeping requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)		40 CFR 261.11 (EPA)
FD&CA: Approved for prescription use in 1959. (FDA)	Limited to approved uses in treatment of cancer. Like all alkylating agents, thiotepa is clearly labeled as a carcinogen with both human and animal data. Thiotepa has now been largely superseded by other treatments. (FDA)	

MONS 222938

TRIS(2,3-DIBROMOPROPYL)PHOSPHATE

There is sufficient evidence for the carcinogenicity of this substance in experimental animals.[1,3] Tris(2,3-dibromopropyl)-phosphate (TRIS) administered in the diet was carcinogenic to B6C3F1 mice, causing increased incidence of tumors in livers, lungs, and stomachs of female mice and in kidneys, lungs, and stomachs of male mice. TRIS was also carcinogenic in Fischer 344 rats, causing an increased incidence of kidney tumors in both sexes.[2] After skin application to ICR/Ha Swiss female mice, it produced tumors of the skin, lung, forestomach and oral cavity.[3]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]National Cancer Institute. Bioassay of Tris(2,3-dibromopropyl)-phosphate for Possible Carcinogenicity. Technical Report Series No. 76. DHHS Publication No. (NIH) 78-1326. Bethesda, Maryland, 1978.

[3]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 20. Lyon, France: IARC, 1979, pp. 575-88.

Tris(2,3-dibromopropyl)phosphate, commonly known as TRIS, is no longer used in the United States.

Major uses of tris(2,3-dibromopropyl)phosphate were in plastics, and as a flame-retardant additive for synthetic textiles used in children's nightwear. Other applications were for the treatment of polyurethane foams used in cushions for aircraft and automotive interiors, home insulating foam, upholstered furniture, packaging, draperies, institutional bedding, toys, doll clothing, and wigs.

All domestic production of TRIS was banned in 1978. Commercial production in the United States was first reported in 1959. In 1975 production was estimated to range between 9 and 11 million lb.

During 1972-76, a significant number of infants and children were exposed to TRIS, primarily through skin absorption and occasionally through ingestion from oral contact with TRIS-treated garments. The Consumer Product Safety Commission (CPSC) stated that over a 6-year period a child wearing TRIS-treated clothing could absorb a total of 2-77 mg/kg TRIS. More recent data indicated this estimate may be even higher. The National Occupational Hazard Survey in 1974 estimated that 29,000 workers were exposed to TRIS through skin absorption.

MONS 222939

In 1977, CPSC acted under the Federal Hazard Substance Act to remove all TRIS-treated children's clothing and other consumer products containing TRIS from the market, and in 1978, it prohibited the export of such products. As a result, in 1977, approximately 20 million garments were recalled and some destroyed; however, some may still be in warehouses. Some TRIS-treated children s sleepwear, manufactured prior to 1978 and stored in warehouses, may reappear illegally in the marketplace. Consumers who suspect they may be purchasing pre-1978 TRIS-treated sleep-wear are advised to contact the manufacturer or call the CPSC Hotline at 800/638-8326. EPA regulates TRIS under the Resource Conservation and Recovery Act and under the Toxic Substances Control Act, 8(a), which requires that EPA be notified of intent to resume manufacture or importation.

Tris(2,3-dibromopropyl)phosphate

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
Federal Hazardous Substances Act: On 4/8/77, CPSC acted under FHSA to remove all TRIS-treated children's clothing from the market--a recall of all articles in the channels of distribution and of any unwashed garments in the hands of consumers was ordered. On 5/5/78, CPSC interpreted FHSA to prohibit the export of the same products. (CPSC)	In the spring of 1977, approximately 16-20 million garments were recalled. Some of the garments were destroyed, some may still be in warehouses. TRIS is no longer manufactured or used domestically. (CPSC)	42 FR, p. 18650 (CPSC)
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designates TRIS as a hazardous constituent of waste and subjects waste known to contain it, to the same requirements. Promulgated 5/19/80.		30 CFR 261.11, 261.33
TSCA, 8(a). Because manufacture of this chemical has been discontinued, no regulatory action under TSCA was deemed necessary; because this chemical was used, it could not be subjected to premanufacturing notification requirements. Accordingly, a rule requiring that EPA be notified of intent to resume manufacture or importation was promulgated, 10/24/80. See Carcinogen Assessment Group statement under 2-acetylaminofluorene. (EPA)	Would severely limit the potential for further introduction of TRIS into the environment. (EPA)	45 FR 268, p. 70720 (EPA)

MONS 222940

URETHANE

There is sufficient evidence of the carcinogenicity of urethane in experimental animals.[1] Urethane was carcinogenic in mice, rats and hamsters following oral administration (in drinking water or by stomach tube), inhalation, and subcutaneous or intraperitoneal injection producing lymphomas, hepatomas, melanomas, and vascular, lung and other tumors. It was an initiator of skin carcinogenesis in mice when given either orally or topically. Urethane also enhanced the leukemogenic effect of X-irradiation in mice. It was carcinogenic in single dose experiments and following prenatal exposure. Neonatal and infant mice were more susceptible to cancer induction by urethane than were adult mice.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.

[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. Vol. 7. Lyon, France: IARC, 1974, pp. 111-40.

Urethane (ethyl carbamate) is a colorless, odorless organic compound that is soluble in water. Urethane is available in the United States in crystal form or as a fused solid.

The primary use of urethane is as a chemical intermediate in the preparation of amino resins. Urethane is also used as an intermediate in the production of pharmaceuticals, insecticides, and fungicides, in biochemical research; and in human and veterinary medicine. In the past, urethane was used as an active ingredient in drugs prescribed for the treatment of neoplastic diseases, as a hypnotic, as a component of a sclerosing solution for varicose veins, and as a topical bactericide. In 1970, approval of new drug applications for products containing urethane as an active ingredient was withdrawn after it had been found that urethane was ineffective. Urethane has also been used as an inactive component or solubilizer in liquid preparations for injections. FDA withdrew the new drug application approval for all drug products containing urethane as an inactive ingredient (Federal Register, 41 FR 8523, 4, 2/27/76). Two anticonvulsant drugs, trimethadione and paramethadione, can be contaminated by urethane. The allowable limit has been set at 1 ppm. These anticonvulsant drugs may be used only to treat epilepsy that is refractory to other available drugs.

MONS 222941

Urethane has been commercially produced in the United States since 1945. Between 1975 and 1977, there were five producers in four EPA regions manufacturing about 4 million lb (Toxic Substances Control Act (TSCA), Chemical Substance Inventory, 1979, public record). Several companies now produce urethane solely for research. No estimate was available to NCI on the volume of urethane currently used in the United States, but the use is believed to be small.

Reports of human exposure are not available. In 1974, the National Occupational Hazard Survey made no estimate on the potential worker exposure to urethane. Urethane is volatile at room temperature, and exposure can occur through inhalation and skin absorption during manufacture and processing. Urethane may also be ingested by humans. Urethane has been found in diethylpyrocarbonate-treated beverages. Urethane was also found in wine, beer, orange juice, and some soft drinks.

Currently, urethane is regulated by EPA under the Resource Conservation and Recovery Act (RCRA), and regulation proposed under TSCA, 8(a), would provide detailed production and marketing data. EPA has also designated urethane as a hazardous constituent of waste and will determine the appropriateness of additional regulatory or other control actions. The use of urethane in drugs is prohibited, and approval has been withdrawn of all drugs containing urethane as an inactive ingredient (2/27/76) (FDA).

Urethane

REGULATIONS

Regulations and Other Actions	Effect of Regulations; Other Comments	Citation of Regulation
RCRA, 3001-3006: Subjects off-specification batches, waste products, and spill residues in excess of 1000 kg to handling and reporting/recordkeeping requirements. Also designates chemical as a hazardous constituent of waste. Promulgated 5/19/80.	Regulation based on chronic toxicity. Fosters greater care in handling of chemical wastes.	40 CFR 261.11, 261.33
TSCA, 8(a): reporting rule requiring process and use data, proposed 2/29/80. (EPA)	Would provide a better basis for estimating exposure potential, which must be considered along with risk in determining appropriateness of regulatory or other control action. (EPA)	45 FR, p. 13646 (EPA)
Prohibits the use of urethane as an active or inactive ingredient in drugs.		41 FR, pp. 8523-4
Withdrew approval of all drugs containing urethane as an inactive ingredient. (FDA)		41 FR, pp. 8523-4, 2/27/76 (FDA)

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VINYL CHLORIDE

There is sufficient evidence that vinyl chloride (VC) is a human carcinogen.[1] Its target organs are the liver (angiosarcomas), brain, lung and hemo- and lymphopoietic systems. Although evidence of a carcinogenic effect of VC in humans has come from groups occupationally exposed to high doses of VC, there is no evidence that there is an exposure level below which no increased risk of cancer would occur in humans.[2]

VC was tested in rats by oral, subcutaneous and intraperitoneal administration, and in mice, rats and hamsters by inhalation exposure. Following gastric intubation of a solution in olive oil, VC was carcinogenic in rats; inhalation exposure produced tumors at different sites in all three species, including angiosarcomas of the liver. VC was carcinogenic in rats following prenatal exposure. A dose response has been demonstrated.[2] There is sufficient evidence of the carcinogenicity of this compound in experimental animals.[2]

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[1]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Supplement 4. Lyon, France: IARC, 1982.
[2]International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans. Vol. 19. Lyon, France: IARC, 1979, pp. 377-437.

VC is a colorless gas that is slightly soluble in water.

The principal use of VC is in the production of plastics. VC is also used in the synthesis of other chemicals, and it was formerly a component of aerosol propellants. The vinyl chloride-vinyl acetate copolymers are used extensively in the production of vinyl asbestos floor tiles.

Annual production of VC in the United States is approximately 7 billion lb. Domestic production of the VC homopolymer is reported as 5 billion lb, and imports amount to 55 million lb. The estimated domestic production of the VC acetate copolymer is 279 million lb.

Human exposure to VC occurs primarily through inhalation and less frequently through skin absorption. More than 3.5 million workers are potentially exposed to this chemical. In addition, there is a potential exposure for 4.6 million people who live within 5 miles of industrial sites at which environmental emissions occur. Air emissions measured near several production facilities contained 3.1-12.5 ppb of VC. Very low exposure may occur if unreacted VC remaining in polyvinyl chloride packaging materials leaches into food and beverages (0.05-25 ng/kg), or medical products.

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The Consumer Product Safety Commission, the EPA, and the FDA each banned the use of VC as an aerosol propellant, eliminating exposure of 1-5 million people annually. Under the Clean Water Act, EPA has published a water quality criteria document for the protection of human health. The document addresses VC. The Clean Air Act, National Emission Standards for Hazardous Air Pollutants, addresses VC emissions from production and manufacturing facilities. The Resource Conservation and Recovery Act (RCRA) subjects VC waste products, off-specification batches, and spill residues in excess of 2200 lb to handling and report/recordkeeping requirements. RCRA also designates VC as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. FDA has eliminated the use of VC in drug products and has alerted food manufacturers to the need for monitoring packaging materials for VC. The Bureau of Foods is presently reevaluating its position on the September 3, 1975, proposal and may withdraw it. The OSHA standard of 1 ppm as an 8-hour time-weighted average, and a 5 ppm ceiling for any 15-minute period, was adopted in October 1974. Medical surveillance, training for workers, use of protective clothing and respirators, warning signs, product labeling, and periodic monitoring are required by OSHA.

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REGULATIONS

Regulations and Other Actions	Effect of Regulations, Other Comments	Citation of Regulation
Ban of self-pressurized household products that contain vinyl chloride monomer as an ingredient or in the propellant. (CPSC)	As a result of bans by CPSC, FDA, EPA, 1.5 million persons no longer exposed. (CPSC)	1600 CFR 1500.17(a)(10) (CPSC)
CAA, 112: NESHAP redressed vinyl chloride emissions from vinyl chloride monomer production and polymerization, and certain ethylene dichloride manufacturing facilities. Promulgated 10/21/76, 12/3/76, 6/7/77.	Imposes engineering controls that have been known to reduce emissions by 85 percent over precontrol levels. 6.8 million people live within 5 miles of facilities subject to these standards.	40 CFR 61 60, 61 71
CWA, 304(a): Water quality criteria published in final form, 11/28/80.		65 FR 231, p. 79318
FIFRA, 3: Cancellation/suspension of all vinyl chloride monomer-containing pesticides registered for use in homes, food-handling establishments, hospitals, and enclosed areas, 3/75.	Most vinyl chloride in pesticides was used as an aerosol in propellants. (EPA)	40 FR, p. 3038
RCRA, 3001-3004: Subjects waste products, off-specification batches, and spill residues in excess of 1000 kg to handling and report/recordkeeping requirements. Also designated vinyl chloride as a hazardous constituent of waste, and subjects wastes known to contain it to the same requirements. Promulgated 5/19/80. See Carcinogen Assessment Group statements under 2-acetylaminofluorene (EPA)		40 CFR 261 11, 261 33 (EPA)
FDA Bureau of Drugs, Bureau of Medical Devices.	Has eliminated the use of vinyl chloride in drug products and as a propellant vehicle in aerosol products.	39 FR, p. 30830 (1974)
Any drug products containing vinyl chloride must pass through the new drugs Application Process.	This has alerted manufacturers to the need to monitor their packaging materials for vinyl chloride monomer. Bureau of Alcohol, Tobacco, and Firearms has banned polyvinyl chloride containers for alcoholic beverages, based on FDA work	40 FR p. 4052* (FDA)
FDA Bureau of Foods published notice to regulate vinyl chloride monomer in packaging material, 40 FR 40528 (1975), but rules were not finalized. (FDA)	The Bureau of Foods is presently reevaluating its position on the 9/3/75 proposal and may withdraw it. (FDA)	
PEL: 1 ppm 8-hr TWA, 5 ppm/15-min TWA ceiling; no direct contact with liquid.	Regulatory History. 1952 Walsh-Healy, 500 ppm exposure allowable concentration.	29 CFR 1910.1017 (OSHA)
Protective clothing, respiratory, training, and medical surveillance requirements for workers, monitoring requirements; sign requirements for regulated areas, labeling requirements for containers. (OSHA)	6/27/71. OSHA Takeover Standard--$4.5 ppm (1330 mg/m³) ceiling. 4/5/74: Emergency Temporary Standard--50 ppm ceiling. 6/5/75: Final Standard--current limit effective. (OSHA)	

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IV. REQUESTS TO DHHS FOR RESEARCH AND TESTING, AND TO PROVIDE INFORMATION

Table 1 lists chemicals nominated to the NTP for carcinogenicity testing in calendar year 1981.

Table 2 contains status changes of compounds previously listed in Table 2, Section IV of the Second Annual Reports on Carcinogens.

Table 3 lists the chemicals acted upon by the NCI Chemical Selection Working Group (CSWG) but not submitted to NTP for Chemical Evaluation Committee (CEC) review.

Table 4 contains information related to the National Center for Toxicological Research's (NCTR) research and testing relevant to the carcinogenicity of substances.

Table 5 contains information requests received by NIOSH pertaining to the chemicals in the Annual Reports.

Table 6 lists the requests for chemical information received by the National Library of Medicine during 1980-1982.

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TABLE 1. CHEMICALS NOMINATED TO THE NTP FOR CARCINOGENICITY TESTING IN CALENDER YEAR 1981

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DRWG
108 24-7	Acetic anhydride	Acetic oxide	NCI	High consumption; representative anhydride	Recommended for pharmacokinetics, acylating ability and strain A mouse lung adenoma assay by CIC
6291-67-9	2-Amino-4-nitrobenzothiazole	4 Nitro-2-amino-benzothiazole	NCI	Possible carcinogen; potential for human exposure	Nominated for carcinogenicity testing
28300-74-5	Antimony potassium tartrate	Isotrometic; tartrated antimony	NCI	Possible carcinogen	Nominated for carcinogenicity testing
1912-24-9	Atrazine	6 Chloro-N-ethyl-N'-(1 methylethyl)-1,3,5-triazine-2,4-diamine	California Regional Water Quality Control Board	Widespread water pollutant and plant mutagen	Nominated for mutagenicity, carcinogenicity and reproductive effects testing
106 31-0	Butyric anhydride	Butyryl oxide	NCI	Anhydride Class Study; acrylic subclass; unknown suspicion of carcinogenicity	No testing recommended by CIC - awaits results from anhydride studies
127-00-4	1-Chloro-2-propanol	Propylene chlorohydrin	NCI	Considerable exposure; suspected carcinogen	Nominated for carcinogenicity testing
96-41-9	2-Chloro-1-propanol	Propylene chlorohydrin	NCI	Considerable exposure, suspected carcinogen	Nominated for carcinogenicity testing
98-56-6	p-Chloro-α,α,α-trifluorotoluene	p Chlorobenzotrifluoride	NCI	Structurally related to known carcinogen	Nominated for carcinogenicity testing
15826-37-6	Cromolyn sodium	Disodium cromoglycate; FPL 6701 Fromoxa	NCI	Possible carcinogen	Nominated for carcinogenicity testing
118-52-5	1,3-Dichloro-5,5-dimethylhydantoin	Nilsan, DCDMH	NCI	Increased usage and exposure; previous invalid results	Recommended for mutagenicity (i.m. absorption & distribution reproductive effects; carcinogenicity (gavage) by CIC
78 88 6	2,3-Dichloropropylene		NCI	High potential for human exposure; structural relationship to known carcinogens	Nominated for carcinogenicity testing

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TABLE I. CHEMICALS NOMINATED TO THE PTP FOR CARCINOGENICITY TESTING IN CALENDER YEAR 1981 (continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY BWG
75321-20-9	1,3-Dinitropyrene		AFL/CIO	High potential for human exposure	Now used for general toxicity, human reproductive effects & carcinogenicity testing
42397-64-8	1,8-Dinitropyrene		AFL/CIO	High potential for human exposure	Nominated for general toxicity, human reproductive effects & carcinogenicity testing
42397-65-9	1,6-Dinitropyrene		AFL/CIO	High potential for human exposure	Nominated for general toxicity, human reproductive effects & carcinogenicity testing
64-18-6	Formic acid		NCI	Structurally related to known carcinogen; high potential for human exposure	Nominated for carcinogenicity testing
506-21-8	Linolelaidic acid	trans,trans,linoleic acid	NCI	Human exposure; suspected carcinogen	Nominated for carcinogenicity testing
6317-18-6	Methylene bis(isocyanate)	Methylenediphenylamide	NCI	High potential for human exposure, unique chemical structure	Nominated for carcinogenicity testing
74-83-9	Methyl bromide	Bromomethane	Calif. Dept. Health Svs.	Lack of info. on toxicology; high production volume	Recommended for carcinogenicity [in vitro] tests by CEC
421-20-5	Methyl fluorosulfonate	Magic methyl	NCI/Cummins	Potential carcinogen; used as methylating agent	Recommended for mouse strain A lung adenoma assay by CEC
108-10-1	Methyl isobutyl ketone	Hexone	NCI	High potential for human exposure	Nominated for carcinogenicity testing
333-27-7	Methyltrifluoromethane sulfonate	Methyl triflate	NCI	Use as methylating agent	Recommended for Salmonella assay system, T-cell mutagenesis and strain A mouse lung adenoma assay by CEC

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TABLE 1. CHEMICALS NOMINATED TO THE NTP FOR CARCINOGENICITY TESTING IN CALENDER YEAR 1981 (continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY NTP
1313-99-1	Nickel oxide	Nickel monoxide	NCI	Rat, I Class Study; relatively large exposure, possible cancer inducing compound	Recommended for carcinogenicity testing (inhalation) by CEC
75-21-8	Nitroethane	Nitroethyl	NCI	High potential for human exposure; structural relationship to known carcinogen	Nominated for carcinogenicity testing
6527-43-9	3-Nitropyrene		AFL/CIH	High potential for human exposure	Nominated for general toxicology, reproductive effects & carcinogenicity testing
2212-67-1	Ordram (molinate)	S-ethyl N,N-hexamethylene-thiocarbamate	California Regional Water Quality Control Board	Found in drinking water associated with fish kills; linked to reproductive effects in workers	Nominated for general toxicology, reproductive effects & carcinogenicity testing
127-91-3	Beta-Pinene	Isopinene	NCI	Structural relationship to known carcinogen; high potential for human exposure	Nominated for tumor promotor studies
110-89-4	Piperidine	Hexahydropyridine	NCI	Wide use as solvent, hardening agent catalyst, rubber additive & constituent of human urine	Rejected due to lack of suspicion of carcinogenicity
38641-94-0	Roundup (glyphosphate isopropylamine salt)	ICIA 2139	Calif. Regional Water Quality Control Board	Widespread use & exposure	Nominated for mutagenicity, carcinogenicity and reproductive effects testing
649-79-1	Salicylazosulfapyridine	Azopyrin	NCI	Aryl sulfonamide class study; low suspicion as a possible carcinogen; high human use	Recommended for Salmonella microsomal assay, Drosophila studies and carcinogenicity by CEC
7775-11-3	Sodium chromate	Chromic acid	NCI	High suspicion of carcinogenicity; great potential for exposure; representative soluble chromium VI compound	Recommended for carcinogenicity by CEC (inhalation)
144-83-2	Sulfamethizole	Thiosulfil	NCI	Aryl sulfonamide class study; suspected carcinogen; used as a major sulfa drug	Recommended for Salmonella microsomal assay, Drosophila studies by CEC

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TABLE 1. CHEMICALS NOMINATED TO THE NTP FOR CARCINOGENICITY TESTING IN CALENDER YEAR 1981 (continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION PENDING
63-74-1	Sulfanilamide	p Sulfanilamidosulfide	NCI	Model for aryl sulfonamides; potential for human exposure	Recommended for Salmonella assay, Drosophila studies by CIC
72-14-0	Sulfathiazole	N'-2-thiazolylsulfanilamide	NCI	Aryl sulfonamide class study; considerable human exposure, low suspicion of possible carcinogen	Recommended for Salmonella assay, Drosophila studies by CIC
95-94-3	1,2,4,5-Tetrachlorobenzene	1-Tetrachlorobenzene	NCI	Structurally related to known carcinogen	Nominated for carcinogenicity testing
25167-83-3	2,3,4,6-Tetrachlorophenol	Dowicide 4; TCP	Calif. Regional Water Quality Control Board	Found in drinking water, wide exposure	Nominated for mutagenicity, carcinogenicity & reproductive effects testing
117-08-8	Tetrachlorophthalate anhydride	Tetrathal	NCI	Anhydride class study; suspicion of potential carcinogenicity	Recommended for in vitro cytogenetics, Drosophila studies & carcinogenicity by CIC
20767-61-6	1,2,3,3-Tetrachloropropene		AFL/CIB	High potential for human exposure	Nominated for general toxicology, reproductive effects & carcinogenicity testing
110-02-1	Thiophene	Thiofuran; thiole; divinylene sulfide	NCI	Potential carcinogen	Nominated for carcinogenicity testing
4818-58-9	2,4,5-Trimethoxybenzaldehyde	Asaronaldehyde	NCI	Structural lateral; potential exposure	Recommended for battery of short term mutagenicity tests, reproductive effects & carcinogenicity by CIC
51075-78-2	Trimethylsarcosium Isochloroantimonite		NCI/Cummins	Potential carcinogenicity, used as methylating agent	Recommended for mutagenicity and strain A mouse lung neoplasm assay by CIC

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TABLE 1. CHEMICALS NOMINATED TO THE NTP FOR CARCINOGENICITY TESTING IN CALENDER YEAR 1981 (continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
121-76-3	2,4,7-Trinitrofluorenone	TNF	AFL/CIH	Widespread exposure, structurally related to known carcinogen	Nominated for general toxicology, reproductive effects, carcinogenicity & epidemiology testing
75321-19-8	1,3,5-Trinitropyrene		AFL/CIH	High potential for human exposure	Nominated for general toxicology, reproductive effects, & carcinogenicity testing
87-62-7	2,6-Xylidine	2,6-Dimethylbenzamine	NCI/Weisburger	Decomposition product of xylocaine; structure activity relationship	Recommended for no additional testing at this time by CEC

CEC = NTP Chemical Evaluation Committee

Nominated = Executive Summaries written but no action by CEC.

Recommended = Rationale for request accepted by CEC. Executive Summary reviewed by CEC and recommendation for testing given.

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TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
75-07-0	Acetaldehyde	Ethanal	NCI	Class Study; potential for high exposure, suspicion of carcinogenic activity	Nominated but not selected (deferred 6/81)
75-05-8	Acetonitrile	Cyanomethane, methyl nitrile, methane carbonitrile, methyl cyanide	NCI	Potential for high exposure (found in water supplies)	Prechronic test in progress
10361-37-2	Barium chloride		NCI	Class Study; potential for considerable human exposure	Assigned for carcinogenicity testing
17804-35-2	Benomyl	Benlate® Methyl 1-(butylcarbamoyl)-2-benzimidazole carbamate	NCI	Class Study; potential for significant exposure; ability to cause point mutations in microbial systems and chromosomal aberrations in both microbial and mammalian systems	Nominated for mutagenicity testing
100-52-7	Benzaldehyde		NCI	Potential for high human exposure	Chronic test in progress
121-54-0	Benzalkonium chloride	Hyamine® 1622	NCI	Class Study; nominated by CIHR because suspicion of carcinogenicity was judged to be high	Nominated for battery of short term mutagenicity tests, reproductive effects & carcinogenicity (6/81)
100-47-0	Benzonitrile	Cyanobenzene Phenyl cyanide	NCI	Present in water supplies, unknown suspicion of carcinogenicity; mod-high production	Nominated for carcinogenicity testing
85-02-9	Benzo[f]quinoline	β Naphthoquinoline Naphthopyridine	NCI	Class Study; potential for exposure; presence of activity in Ames Salmonella; representative nitrogen-containing aromatic heterocycle	Nominated for carcinogenicity testing
98-07-7	Benzotrichloride		Air Pollution Board, Chattanooga, TN	Potential for lung cancer in production workers involved with one many production facilities in the U.S.	Nominated for carcinogenicity testing (6/81)
98-88-4	Benzoyl chloride	Benzenecarbonyl chloride alpha-Chlorobenzaldehyde	NCI	Class Study; potential for significant human exposure; use as an acylating agent, therefore suspicion of carcinogenicity	Nominated for in vitro cytogenetics, mutagenic studies, sister chromatic exchange & carcinogenicity (4/81)

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TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
100-44-7	Benzyl chloride		Air Pollution Board, Chattanooga, TN	Potential for lung cancer in production workers involved with the dyes production facilities in the U.S.	Chronic test in progress
120-32-6	o-Benzyl-p-chlorophenol	Chlorophene; Santophen 1	NCI	Class Study, high potential for human exposure	Selected for testing by NTP, assigned to contractor
84130-69-9	[4,4'-Bi]thiazole]2,2'-diamine		NCI	Class Study; model test compound structurally analogous to the drugs in hydroxyurea using carcinogen bonding	Nominated for strain A lung adenoma assay and other short term tests
357-57-3	Brucine	2,3-Dimethoxystrychnidin-10-one	NCI	Class Study; potential for considerable human exposure; unknown suspicion of carcinogenicity	Nominated for mutagenicity, dermal absorption study (1/81)
112-56-1	2-[2-Butoxyethoxy]ethyl thiocyanate	Butyl carbitol rhodanate Lethane® 384	NCI	Class Study; potential for significant human exposure	Nominated for carcinogenicity testing
614-45-9	t-Butyl perbenzoate	Benzoyl t-butyl peroxide Esperox 1B Trigonox C	NCI	Selected; potential for human exposure	Nominated for battery of short term mutagenicity tests, reproductive effects & carcinogenicity (4/81)
123-72-8	Butyraldehyde	n-butyl aldehyde	NCI	Class Study; suspicion of carcinogenicity, significant potential for human exposure; occurrence in water	Nominated to NTP for testing
1306-19-0	Cadmium oxide	Cadmium monoxide	NCI	Class Study; reported carcinogenicity of other cadmium containing inorganics, significant potential for human exposure	Nominated but not selected (deferred 6/81)
1306-23-6	Cadmium sulfide		NCI	Class Study, reported carcinogenicity of other cadmium-containing inorganics, significant potential for human exposure	Nominated but not selected (deferred 6/81)

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TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
58-08-2	Caffeine		FDA	High human exposure	Prechronic test in progress
1260-17-9	Carminic acid	C.I. 75570 C.I. Natural Red 4	NCI	Class Study; high exposure estimates for carmine and cochineal (both of which use carminic acid as the chief coloring principle)	Nominated for carcinogenicity testing
2244-16-8	d-Carvone		NCI	Potential for high human exposure	Prechronic test in progress
120-80-9	Catechol		NCI	Known cocarcinogen	Prechronic test in progress
5915-40-1	Chloramine		EPA	Very large potential for exposure	Prechronic test in progress
108-42-9	m-Chloroaniline	C.I. Azoic Diazo Component 2	NCI	Occurs in water; potential for human exposure; high tonnage production	Nominated for battery of short-term mutagenicity tests, reproductive effects & carcinogenicity (4/81)
106-47-8	p-Chloroaniline		NCI	High production and exposure; potential carcinogen	Report available
89-63-4	4-Chloro-2-nitroaniline	2-Nitro-4-chloroaniline; C.I. Azoic Diazo Component 8, Base	NCI	Class Study; high suspicion of possible carcinogenicity; potential for considerable human exposure	Selected & assigned for carcinogenicity by NTP
57-88-5	Cholesterol	Cholest-5-en-3-ol Cholesterin	FDA/NCI	Class Study; representative sphenomenol steroid; widespread use	No testing recommended (12/81)
1250-85-9	Cholesterol 5 ,6 -epoxide	---	FDA/NCI	Potential for human exposure; suspicion of potential carcinogenicity	No testing recommended (12/81)
42373-04-6	C.I. Basic Red 29	C.I. 11460 Bascryl Red BL	NCI	Class Study; potential for human exposure; structurally analogous to azobenzene which reportedly is carcinogenic and mutagenic, and to 4-biphenylazo-m-toluene which reportedly is a weak carcinogen in rats	Nominated for strain A mouse lung adenoma assay and other short term tests

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MONS 222954

TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
6128 31-9	C.I. Direct Black 19	C.I. 35255	NCI	Class Study; potential use in a direct laser printing technique	Deferred (1/81)
2610-05-1	C.I. Direct Blue 1	C.I. 24410, Calcomine Sky Blue 6BX, Fenamin Sky Blue 3F, Atlantic Sky Blue BB	NIOSH	Derived from known carcinogen; no test data, potential high human exposure	Nominated but not selected
2429-73-4	C.I. Direct Blue 2	C.I. 22590; Diazo Black RN, Fenamin Navy Blue RL, Phenazo Black BR	NIOSH	Derived from known carcinogen; potential for considerable human exposure; no adequate test data	Nominated but not selected
2420-74-5	C.I. Direct Blue 15	C.I. 24400 Cotocyl Sky Blue 4BX	NIOSH/CPSC	High potential for human exposure, suspicion of potential carcinogenicity as an o-dianisidine-based dye	Recommended for no additional tests (1/81)
20407-37-6	C.I. Direct Blue 218		NCI	Class Study; potential for considerable human exposure; high suspicion of potential carcinogenicity	Selected for testing by NTP, assigned to contractor
897-89-8	C.I. Direct Red 2	C.I. 23500 Benzopurpurin 4B	NIOSH/CPSC	Significant potential for human exposure; suspicion of potential carcinogenicity as an o-tolidine-based dye	Recommended for no additional tests (1/81)
8350-20-6	C.I. Direct Red 28	C.I. 23630 Congonic Scarlet 3B	NIOSH/CPSC	Significant potential for human exposure; suspicion of potential carcinogenicity as an o-tolidine-based dye	Recommended for no additional tests (1/81)
8471-68-4	C.I. Pigment Red 23	1-(hydrazo-4-[2-methoxy-5-nitrophenyl]-azo)-N-[3-nitrophenyl]-2-naphthalenecarboxamide	NCI	Class Study; high suspicion of possible carcinogenic activity, reductive cleavage of azo linkage would yield compound related to proven carcinogens, potential for considerable human exposure	Prechronic test in progress
6358-31-2	C.I. Pigment Yellow 14	2-([2-Methoxy-4-nitrophenyl]azo]-N-[2-methoxyphenyl]-2-oxobutanamide	NCI	Class Study, potential for considerable human exposure; high suspicion of possible carcinogenic activity because reductive cleavage of azo linkage would yield compound related to proven carcinogen	Selected for testing, assigned for carcinogenicity testing

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MONS 222955

TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
482 89-3	C.I. Vat Blue 1	C.I. 73000 C.I. Pigment Blue 66 D & C Blue No. 6 Indigo (synthetic)	NIMSH/CPSC	High exposure; common use as a dye for denim jeans	Nominated for mutagenicity, reproductive effects, skin absorption, & distribution & carcinogenicity (i p) tests (1/81)
470-82-6	1,8-Cineole	Eucalyptol	FDA	High human exposure	Prechronic test in progress
104-55-2	Cinnamaldehyde	3-Phenyl-2-propenal	FDA	High human exposure	Prechronic test in progress
76 57-3	Codeine	Methylmorphine	NCI	Class Study; potential for considerable human exposure; unknown suspicion of carcinogenic activity	Nominated for reproductive effects & carcinogenicity tests (5/81)
64-86 8	Colchicine		NCI	Class Study; potential for considerable human exposure; representative of the tropolone group of the phenylalanine- and tyrosine-derived alkaloids	Nominated for epidemiological testing & mutagenicity tests
91-64-5	Coumarin		FDA	Structure relationship; special specificity	Prechronic test in progress
458-37-7 8021-3/-1	Curcumin (See tumeric)				
52-90-4	L-Cysteine	β Mercaptoalanine	FDA/NCI	Class Study; potential for significant exogenous exposure; unique structure containing a mercapto moiety	Under consideration by NTP
65-46-3	Cytidine	Cytosine riboside 1- β-D-Ribofuranosyl-cytosine	FDA/NCI	Class Study; representative pyrimidine which, after administration to animals in large doses, might lead to the accumulation of cytosine and/or cytosine products	No testing recommended (12/81)
6011-36-1	Dehydroemetine hydrochloride		FDA	Potential exposure as a drug	Under consideration by NTP

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TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
81-11-8	4,4'-Diamino-2,2'-stilbenedisulfonic acid		EPA	Large production; wide exposure; lack of data	Prechronic test in progress
24072-76-1	4,5-Dichloro-2-benzothiazolamine	2-Amino-5,6-dichlorobenzothiazole	NCI	Class Study, potential for significant human exposure suspicion of potential carcinogenicity because of its structural analogy to 2-naphthylamine	Nominated for carcinogenicity testing
54789-48-2	N,N-Diethyl-4-[(5-nitro-2-thiazolyl)azo]benzenamine		NCI	Class Study, suspicion of potential carcinogenicity	Nominated for strain A mouse ddahome assay and other short term tests
84-66-2	Diethyl phthalate		EPA	Chemical identified in drinking water	Withdrawn after carcinogenesis testing began
119-84-6	3,4-Dihydrocoumarin		NCI	Potential for high human exposure	Prechronic test in progress
828-00-2	Dimethosone ("diorin")		NCI	Potential carcinogen	Prechronic test in progress
68-12-2	N,N-Dimethylformamide	Dimethylformamide; DMF; DMFA; N-formyldimethylamine	NCI	Present in water; potential for human exposure	Selected for testing by NTP, assigned to contractor
1854-26-8	Dimethylolethylenurea	4,5-dihydroxy-1,3-bis(hydroxymethyl)-2-imidazolidinone; dimethylolglyoxalurea; DMEU	NCI	Class Study; low/moderate suspicion of carcinogenicity based on potential of N-nitrosation; potential for human exposure	Prechronic test in progress
97-77-8	Disulfiram		Dr. Shapporo (FDA)	High exposure and potential as a human teratogen	Under consideration by NTP
480-21-8	Doxylamine		FDA	No carcinogenicity testing	Prechronic test in progress
316-42-7	Emetine hydrochloride		FDA/NCI	Potential high exposure; old drug never studied by present standards	Under consideration by NTP
51-31-2	Ephedrine hydrochloride		FDA/NCI	Lack of toxicological data; devise meaningful tests	Prechronic test in progress

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TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
88.06-2	Eporal		Drs. Huff & Schumacher (NIP)	Potential for neurological damage by inhalation of exothermal products	Under consideration by NTP
106-88-7	1,2-Epoxybutane		EPA/OSHA/ CPSC/NCI		Prechronic test in progress
60-79-7	Ergonovine	Ergotrate®	NCI	Class Study; potential for considerable human exposure	Nominated for Ames tests (1/81)
113-15-5	Ergotamine		NCI	Class Study; potential for considerable human exposure; low level of carcinogenic suspicion based on its potential to undergo N-nitrosation	Nominated for battery of short term tests including Ames (1/81)
74-96-4	Ethyl bromide		OSHA/NCI	Structurally related to known carcinogens	Chronic test in progress
75.00-3	Ethyl chloride		OSHA/NCI	High production & exposure	Chronic test in progress
107-15-3	Ethylenediamine		EPA	Chemical related to hydrazines, a group containing known carcinogens	Withdrawn after carcinogenesis testing begun
107-21-1	Ethylene glycol		FDA/NCI	High production & potential exposure	Prechronic test in progress
75-21-8	Ethylene oxide		OSHA/EPA/NCI	High production & exposure, potential carcinogen	Chronic test in progress
104-76-7	2-Ethylhexanol	2-Ethyl-1-hexanol 2-Ethylhexyl alcohol	Dr. Gould (EPA)	Metabolite of di(2-ethylhexyl)-phthalate (DEHP) which has been found to be carcinogenic in rats and mice	Nominated for carcinogenicity testing
7720-78-7	Ferrous sulfate	Copperas Green vitriol Iron (II) sulfate	FDA/NCI	Class Study; potential for human exposure; moderately high production; used in the treatment of iron-deficient anemia and as a nutritional supplement	No testing recommended (12/81)
2188-57-2	Fluometuron		Drs. Huff & Schumacher (NIP)	Suspicion of carcinogenicity; positive in rats	Report available

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TABLE 8. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 1 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
59-30-3	Folic acid	Folacin Pteroylglutamic acid Vitamin B_c	FDA/NCI	Class Study; interest in the 2-aminopteridine moiety; potential for accumulation after administration to animals in large doses	No testing recommended (12/81)
50-00-0	Formaldehyde		OSHA/CPSC/NIOSH/NCI	High production & exposure	Withdrawn after carcinogenesis testing begun
57-48-7	D-Fructose	Fructose Fruit sugar Levulose	FDA/NCI	Class Study; representative hexose with potential for accumulation of its anabolic and/or catabolic intermediates after administration to animals in large doses	Under consideration by NTP
110-17-8	Fumaric acid	trans-1,3-Ethylene-dicarboxylic acid	Dr. A. Gregory (NIOSH)	Class Study; role as a intermediate in the tricarboxylic acid cycle and potential for bioaccumulation of its anabolic and/or catabolic intermediates after administration to animals in large doses	Recommended for genotoxicity assay (12/81)
98-00-0	Furfuryl alcohol		NCI	Potential carcinogen	Withdrawn after carcinogenesis testing begun
1303-00-0	Gallium arsenide		Dr. J. Munn (NCI)	Projected use in the semiconductor industry for photovoltaic cells, structural interest	Nominated for metabolism studies
9005-65-6	Glytpl (Polysorbate 60)		CPSC/NIOSH	Wide industrial exposure, oxalic acid formation	Prechronic test in progress
73-40-5	Guanine	2,6-Diamino-6-hydroxypurine Natural Pearl Essence	FDA/NCI	Class Study, representative purine; endogenous exposure	No testing recommended (12/81)
67-72-1	Hexachloroethane		EPA/NIOSH	Potential carcinogen; industrial exposure	Report available at NTP
548-62-9	Gentian violet	4-[4,4'-bis(dimethylamino)benzhydrylidene]-N-methylcyclohexa-2,5-dien-1-imine hydrochloride	FDA/NCI	Potential large exposure through tissue residues; for regulatory purposes	Chronic test in progress

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TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY NTP
124-09-4	1,6 Hexanediamine		EPA	Occupational and non-occupational exposure	Scheduled for mutagenicity tests
56 69-9	5-Hydroxytryptophan		FDA	Wide exposure, need to develop protocols	Withdrawn after carcinogenesis testing begun
73-32-5	L-Isoleucine	2 Amino 3-methylpentanoic acid	FDA/NCI	Class Study; representative neutral amino acid	Under consideration by NTP
88-33-3	elaidic acid	isooleoidic acid (E,E)-9,12-Octadecadienoic acid	FDA/NCI	Class Study; representative unsaturated fatty acid; significant exogenous exposure	No testing recommended (12/81)
463-40-1	Linolenic acid	-Linolenic acid (Z,Z,Z)-9,12,15-Octadecatrienoic acid	Dr. Gould (EPA)/NCI	Class Study; potential for bioaccumulation of its anabolic and/or catabolic intermediates after administration to animals in large doses	No testing recommended (12/81)
56-87-1	L-Lysine	2,6-Diaminohexanoic acid; Lysine	FDA/NCI	Class Study; representative basic amino acid, potential for exogenous exposure	Under consideration by NTP
7785-87-7 10124-55-7	Manganese sulfate		NCI	Class Study; significant potential for human exposure; high suspicion of carcinogenicity of manganese chloride	Selected for testing by NTP, assigned to contractor
149-30-4	2-Mercaptobenzothiazole		NCI	Potential wide exposure, [medicinal solution oppose with rubber (trapp' containing compound]	Chronic test in progress
7786-83-1	2-Mercapto-4-methyl-5-thiazolyl methyl ketone	1-(2,5-Dihydro-4-methyl-2-thioxo-5-thiazolyl) ethanone	NCI	Class Study; suspicion of potential carcinogenicity because of the relationship to ethylenethiourea and thiabendazole which are carcinogenic in rats	Nominated for Strain A acute lung adenoma assay and other short term tests
7487-94-7	Mercuric chloride		NCI/FDA	Metal class study	Prechronic test in progress
1344-48-5	Mercuric oxide	C.I. 77190 Yellow mercuric oxide	NCI	Class Study; potential for significant human exposure; representative mercury (II) salt	No testing recommended (1/81)

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TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION TO DATE
1002 37-2	Methadistarion		FDA	No carcinogenicity testing	Selected for testing by NTP, assigned to contractor
91-80-5	Methapyrilene		FDA	Use as positive control	Prechronic test in progress
126 31-8	Methiodal sodium	Sodium iodomethanesulfonate Sitosol® sodium	NCI	Probably significant human exposure, previously tested with inadequate test results	Selected for mutagenicity testing (5/81)
1107-66-8	8-Methoxy-2-benzothiazolamine	2-Amino 8-methoxybenzothiazole 8-Methoxy-2-aminobenzothiazole	NCI	Class Study; suspicion of potential carcinogenicity because of its activity as a mutagen in the Ames procedure; structurally analogous to 2-naphthylamine, a carcinogen	Nominated for carcinogenicity testing
07-36-4	4-[(6-Methyl-2-benzothiazolyl)-benzenamine	Dehydrothio-p-toluidine	NCI	Class Study, estimated significant potential for human exposure; structurally analogous to the carcinogenic biphenylamines	Nominated for carcinogenicity testing
74-83-9	Methyl bromide		Dept. of Health, State of California	Two recent in vitro tests showed mutagenic activity	Under consideration by NTP
75-09-2	Methylene chloride		EPA/NCI	High production & exposure	Chronic test in progress
624-83-9	Methyl isocyanate	Isocyanatomethane MIC	NCI	Potential for exposure; review of chemicals produced in the largest quantities in the United States in 1979	Nominated for mutagenicity testing (1/81)
24340-76-9	3-Methyl-5-isothiazolamine	5-Amino-3-methylisothiazole	NCI	Class Study; potential for human exposure; suspicion of potential carcinogenicity because of its relationship to single-ring carbocyclic aromatic amines and 5-N-substituted thiazoles found to be carcinogenic in the laboratory	Nominated for strain A lung adenoma assay & other short term tests

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TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (continued)

CAS NO.	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
80-62-6	Methyl methacrylate		NCI	Considerable potential for human exposure and carcinogenic activity	Chronic test in progress
80-33-1	N-Methyl-N-nitroso-p-toluenesulfonamide	Diazald®; N-Nitroso-N-methyl-4-tolylsulfonamide; p-tolylsulfonylmethylnitrosamide	Dr. E. Weisburger (NCI)	Nominated as a research chemical because it is considered to be structurally interesting; suggestive evidence of carcinogenicity from previous study	Nominated for strain A mouse lung adenoma assay (5/81)
924-42-5	N-Methylolacrylamide	N-(hydroxymethyl) 2-propenamide; N-methanol-acrylamide; N-(hydroxymethyl)acrylamide	NCI	Class study; moderate suspicion based on structural relationship to known carcinogen; potential for nitrosation; considerable potential for exposure	Prechronic test in progress
513-45-1 299-58-9	Methylphenidate	Ritalin®; alpha-phenyl-2-piperidine-acetic acid methyl ester	NCI/FDA	Class study, significant levels of estimated exposure; chronic use in children; lack of data	Selected for testing by NTP assigned to contractor
79-11-8	Monochloroacetic acid		EPA	High toxicity in animals indicated potential hazard to humans	Prechronic test in progress
4376-20-9	Mono(2-ethylhexyl) phthalate	2-Ethylhexyl hydrogen phthalate	Dr. Gould (EPA)	One of the two major primary metabolites of di(2-ethylhexyl)phthalate which was reported to be hepatocarcinogenic	Nominated for carcinogenicity testing
9116-3.30-3	Nickel carbonyl		NIEHS	Potential human carcinogen	Under consideration by NTP
485-47-2	Ninhydrin		Maryland State Police Dept.	Used in forensic medicine by Maryland State Police Departments	Nominated for Salmonella assay (7/81)
100-01-6	p-Nitroaniline	1-Amino-4-nitrobenzene; Azoic Diazo Component 37	NCI	Class study; high suspicion of possible carcinogenicity; potential for considerable human exposure	Selected for testing by NTP, assigned to contractor
91-23-6	o-Nitroanisole	2-Methoxynitrobenzene	NCI	Class study; high suspicion of carcinogenic activity because it is a nitro analog of known carcinogen; potential for considerable human exposure	Selected for testing by NTP, assigned to contractor

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TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY NTP
-98-95-3	Nitrobenzene	Nitrobenzol; oil of mirbane	NIOSH/NCI	Class Study; moderate suspicion of carcinogenicity; potential for considerable human exposure	Prechronic test in progress
121-90-3	o-Nitrobenzoyl chloride	3-Nitrobenzoyl chloride	NCI	Class Study; high production; possible carcinogen because of its structure as an aryl nitro compound and acyl chloride	Nominated for cell transformation studies
122-04-3	p-Nitrobenzoyl chloride	4-Nitrobenzoyl chloride	NCI	Class Study, high U.S. imports; possible carcinogen because of its structure as an aryl nitro compound and acyl chloride	Nominated for cell transformation studies
100-02-7	p-Nitrophenol		OSHA/NCI	Large production/exposure; potential carcinogen	Histopathology in progress
1616-58-7	N-Nitrosodiethanolamine		FDA		Report available
1321-12-6	Nitrotoluene		NIOSH	Wide occurrence/exposure; potential carcinogen	Report available
370-62-1	Reserpine	[- rauwolfia [serpentina]	NCI	Class Study; potential for considerable human exposure; of interest as an antitussive which is not controlled	Nominated for mutagenicity tests (I/BI)
303-47-9	Ochratoxin A		FDA	Potential wide exposure, potential carcinogen	Prechronic test in progress
[6530 84-1	2-Octyl-2-isothiazolone	Kathon® LP Kathon® 893 SP Skane® M-8 2-Octyl-4-isothiazolin-3-one	NCI	Class Study; high potential for human exposure; single representative of the untreated tetrafet	Nominated for carcinogenicity testing
7647-10-1	Palladium (2+) chloride		OSHA	Potential environmental pollutant; lack of toxicology data	Prechronic test in progress
3875-25-4	Pentachloroanisole		FDA/NCI	Potential high exposure to low levels from fish and finished water	Prechronic test in progress
78-11-5	Pentaerythritol tetranitrate		NCI	Potential exposure as drug	Prechronic test in progress

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TABLE 2. STATUS FLAGS OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY NTP
22224-92-6	Phenamiphos	Bay 68138 Fenamiphos Nemacur	NCI	Class Study; significant potential for human exposure; unique structure as a phosphoramide	Nominated for carcinogenicity testing
66-71-7	o-Phenanthroline	4,5-Diazaphenanthrene 1,10-Phenanthroline	Dr. Harry Ellouby (Stella) Research Institute)	Structurally interesting because it contains two nitrogens in the phenanthrene nucleus	Nominated for battery of mutagenicity tests (4/81)
108-55-1	5-Phenyl-2,4-thiazole-diamine	Amiphenazole 2,4-Diamino 5-phenylthiazole	NCI	Class Study, model compound on the basis of its structural analogy to carbocyclic aromatic amine carcinogens	Nominated for strain A lung adenoma assay & other short term tests
57-41-0	Phenytoin		NIEHS/NCI	Large production/exposure, inadequate carcinogenicity data; used as an anticonvulsant	Prechronic test in progress
75-44-5	Phosgene		EPA	Occurs in environment; data on extremely low level inhalation	Withdrawn
9003-39-8	Polyvinylpyrrolidone polymers		CPSC/FDA/DSHA	Potential wide exposure	Withdrawn
7681-11-0	Potassium iodide	Potassium monoiodide	FDA/NCI	Class Study; most widely used form of iodine as a nutritional supplement; representative iodine-containing inorganic	On testing recommended (12/81)
57-66-9	Probenecid		NCI	High exposure as drug	Prechronic test in progress
60-87-7	Promethazine		FDA	No carcinogenicity testing	Prechronic test in progress
50-34-0	Propantheline bromide	beta-Diisopropylaminoethyl xanthene-9-carboxylate methobromide; Pro-Banthine®	FDA/NCI	Class Study; chronic use and large estimated level of exposure; lack of carcinogenicity data	Selected for testing by NTP, assigned to contractor
107-06-2 78-59-7	Propylene chlorohydrins	1-Chloro-2-propanol/ 2-chloro-1-propanol mixture	NCI	Class Study; potential for significant human exposure; suspicion of possible carcinogenicity, associated with short chain chlorinated alcohols	Under consideration by NTP

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TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
91-94-1	Pyrimethamine		FDA	No carcinogenicity testing	Prechronic test in progress
127-17-3	Pyruvic acid	2-Oxopropanoic acid	FDA/NCI	Class study; potential for accumulation of its anabolic and/or catabolic intermediates after administration to animals in large doses	Under consideration by NTP
117-39-5	Quercetin		FDA	Wide exposure/potential mutagen	Assigned to contractor
106-51-4	p-Quinone		NCI	Potential carcinogen	Prechronic test in progress
100-99-2	Reserpine		CPSC	Occurs in environment and ground waters; potential large exposure	Prechronic test in progress
83-88-5	Riboflavin	Lactoflavin Vitamin B_2 Vitamin B^2	FDA/NCI	Class study; significant potential for exogenous exposure	No testing recommended (17/81)
51-34-3	Scopolamine	Hyoscine	NCI	Class study; potential for considerable human exposure; suspicion of potential carcinogenicity	Nominated for reproductive effects and carcinogenicity tests (5/81)
480-81-9	Seneciphylline		FDA	Potential wide exposure, potential carcinogen	Withdrawn
127-65-5	Sodium propionate		FDA	Potential large exposure due to presence in food and environment; chemical form of arsenic in tissue unknown; may present health effects	Nominated but not selected
26628-22-8	Sodium azide		EPA	Potential wide exposure/ mutagenic agent; needs retesting	Prechronic test in progress
57-68-1	Sulfamethazine	4,6-Dimethyl-2-sulfanilamidopyrimidine; Sulfadimidine	NCI	Class study; low suspicion of carcinogenicity; potential for considerable human exposure; potential tissue residue in swine	Chronic test in progress

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TABLE I. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
129-17-9	Sulfan Blue		FDA	Nonprofit drug with no current replacement, suspicion of carcinogenicity	Under consideration by NTP
5746-01-6	2,3,7,8-Tetrachlorodibenzo-dioxin		FDA	Occurs in environment; IARC could not evaluate carcinogenicity from available data	Report in press
116-14-3	Tetrafluoroethylene	Tetrafluoroethene Perfluoroethylene TFE	NCI	Significant potential for human exposure; no adequate carcinogenicity tests have been conducted	Nominated for mutagenicity & carcinogenicity tests by IRC
28160-32-3	Tetraglycidal methylene dianiline		Drs. Huff & Schumacher (NTP)	Potential for neurological damage & inhibition of erythroid products	Under consideration by NTP
109-99-9	Tetrahydrofuran	Diethylene oxide; THF; tetramethylene oxide	NCI/NIOSH	Medium exposure, Class Study	Prechronic test in progress
509-14-8	Tetranitromethane		NCI	Potential for wide exposure	Prechronic test in progress
61-78-2	Thenylidamine		FDA	No carcinogenicity testing	Prethronic test in progress
58-55-9	Theophylline		NCI	Class Study; potential for considerable human exposure; some suspicion of potential carcinogenicity	Nominated for strain A mouse lung adenoma assay (5/81)
148-79-8	Thiabendazole	Mertect[1] Metasol TK-100[2] Mintezol[3] Tiabendazole	NCI	Class Study; potential for human exposure; minimum suspicion of carcinogenicity	Nominated for carcinogenicity testing
67-03-8	Thiamin hydrochloride	Aneurine hydrochloride Thiamine hydrochloride Vitamin B_1 hydrochloride	FDA/NCI	Class Study; potential for accumulation of the cytotoxic products of thiamin after administration to animals in large doses	No testing recommended (12/81)
96-50-4	2-Thiopolamine	Abadol Basedol 2-Aminothiazole	NCI	Class Study; potential for human exposure; some suspicion of its potential carcinogenicity	Under consideration by NTP

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TABLE 2. STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
886-50-0	Thiazole		NCI	Class Study; unknown suspicion of carcinogenicity; model compound for thiazoles class	Nominated for carcinogenicity testing
96-69-5	4,4'-Thiobis(6-tert-butyl-m-cresol)	Santowhite crystals	NCI	Class Study; potential for human exposure; unknown suspicion of carcinogenicity	Nominated for mutagenicity, reproductive effects, uptake & distribution, carcinogenicity tests (1/81)
108-88-3	Toluene		EPA/NCI	Large production/exposure	Nominated but not selected
306-83-2	Trichlorane	2,4,7-Trimethyl-6-phenyl-pteridine; Pyrenium	FDA/NCI	Class Study; high estimated level of exposure, ceramic use; lack of carcinogenicity data; suspicious structure; interest of FDA	Selected for testing by NTP, assigned to contractor
95-95-4	2,4,5-Trichlorophenol	Dowicide 2	NCI	Class Study; significant potential for human exposure; moderate suspicion of carcinogenicity	Nominated but not selected
25735 29-9	1,1,3-Trichloropropene		NIOSH	Potential carcinogen, potential substitute for chlorinated solvents	Selected for testing by NTP, assigned to contractor
98-07-7	a,a,a-Trichlorotoluene	Benzotrichloride (Trichloromethyl)-benzene	NCI	Class Study; potential for significant human exposure; interest in possible carcinogenic activity which may be associated with the benzyl trichloride structure	Nominated for carcinogenicity testing
1330-78-5	Tricresyl phosphate	Tritolyl phosphate; phosphoric acid tris (methylphenyl)ester	EPA/NCI	Class Study; representative aromatic phosphate plasticizer	Selected for testing by NTP, assigned to contractor
101-21-6	Triethanolamine	TEA	Dr. E. Weisburger (NCI)	Potential for exposure; high incidence of malignant lymphomas reported in a preliminary study using female mice	Nominated for battery of short term mutagenicity assays, metabolism, reproductive effects and carcinogenicity (4/81)

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TABLE 2 STATUS CHANGES OF COMPOUNDS PREVIOUSLY LISTED IN TABLE 2 OF THE SECOND ANNUAL REPORT ON CARCINOGENS (Concluded)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
551-30-7	Trimellitic anhydride		EPA	Potential carcinogen	Assigned to contractor
91-91-8	Triphenylamine		FDA	No carcinogenicity testing	Prechronic test in progress
12070-12-1	Tungsten carbide	Tungsten monocarbide	NCI	Close study; considerable potential for human exposure representative tungsten with 44 valence	Nominated for testing by NTP
458-37-7 8024-37-1	Turmeric	Curcumin (Diferulin)	NCI	High potential for exposure	Nominated for bal capacity assay [1/81] Assigned to contractor
60-18-4	L-tyrosine	Tyrosine	FDA/NCI	Close study; highest potential for exogenous exposure of the candidate aromatic amino acids	No testing recommended [1/81]
106-87-6	Vinyl cyclohexene dioxide		NIOSH	Potential carcinogen, occupational exposure	Prechronic test in progress
75-38-7	Vinylidene fluoride		OSHA	Wide exposure; potential carcinogen	Selected for testing by NTP
1330-20-7	Vinyl toluene		NCI	High production & exposure; potential carcinogen	Chronic test in progress
59-02-9	Vitamin E	α-tocopherol	FDA/NCI	Close study; highest U.S. production of the fat soluble vitamins considered; effects of very large doses is of interest	Recommended for no further testing except Salmonella testing [12/80]
87-62-7	2,6-Xylidine		NCI	Potential exposure & carcinogen	Withdrawn after carcinogenesis testing begun
13463-41-7	Zinc pyrithione	Zinc omadine	NCI	Close study; potential for human exposure	Under consideration by NTP

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Table 3. Chemicals Acted Upon by NCI (CSWG*) but not Submitted to NTP for CEC Review

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
84-65-1	Anthraquinone	9,10-Anthracenedione Anthradione	NCI	Air Pollutants Class Study; one of two representatives of the polycyclic aromatic hydrocarbon subclass; interest in testing parent compound of class of carcinogenic amino- nitro-substituted anthraquinones	CSWG-Rejected-no reason given
225-11-6	Benz(a)acridine	7-Azabenz(a)anthracene 1,2-Benzacridine	NCI	Air Pollutants Class Study; single nomination from N-heterocycles subclass; suspicion of carcinogenic risk, environmental occurrence and environmental fate	CSWG-Short Term Tests
2634-33-5	1,2-Benzisothiazolin-3-one	1,2-Benzisothiazolone Proxel	NCI	Biocides Class Study; single representative of nitrogen heterocyclic compounds; significant potential for human exposure from its use as a slimicide and fungicide	CSWG-Rejected. Negative mutagenicity tests; limited carcinogenicity studies
104-88-1	p-Chlorobenzaldehyde	4-Chlorobenzaldehyde p-Chlorobenzenecarboxaldehyde	NCI	Chemicals found in dumps; high potential for human exposure; unknown suspicion of carcinogenicity	CSWG-Short term tests only
2373-98-0	3,3-Dihydroxybenzidine	4,4'-Diamino-(1,1'-biphenyl)-3,3'-diol	CPSC/NCI	No previous adequate carcinogenicity tests; confirm suggestive evidence that it is carcinogenic in rodents	CSWG-Rejected. Awaiting results of benzo-dyes short term tests

*NCI Chemical Selection Working Group

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Table 3. Chemicals Acted Upon by NCI (CSWG) but not Submitted to NTP for CEC Review

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
124-40-3	Dimethylamine	N-Methylmethanamine	NCI	Air Pollutants Class Study; mutagenic in Ames test; high potential for human exposure	CSWG-Rejected. Cell testing.
193-43-1	Indeno(1,2,3-cd)-fluoranthene	1,2,:5,6-Dibenzo-pyracylene a-Phenylenefluoranthene 4,5-(1,2-Phenylene)-fluoranthene	NCI	Air Pollutants Class Study; one of two representatives of the PAG subclass; structural interest in PAH	CSWG-Mutagenicity tests only
74-93-1	Methanethiol	Mercaptomethane Methyl mercaptan	NCI	Air Pollutants Class Study; sole nomination from the alkane sulfur compounds subclass whose potential carcinogenicity is unknown; environmental occurrence	CSWG-Short term tests only
107-25-5	Methyl vinyl ether	Methoxyethylene Vinyl methyl ether	NCI	Ethers Class Study; representative of simple aliphatic ethers; moderate suspicion of carcinogenicity; commercial importance as a monomer and comonomer	CSWG-Rejected. Readily hydrolyzed; limited exposure
21564-17-0	2-(Thiocyanomethylthio)-benzothiazole	Busan 30® Busan 72® TCMTB	NCI	Thiazoles Class Study; potential carcinogenicity and significant potential for human exposure	CSWG-Rejected. Low exposure.
75-69-4	Trichlorofluoromethane	Freon® 11	NCI	Air Pollutants Class Study; sole nomination from alkyl halides subclass; widespread presence in atmosphere; structural relationship to chloroform and carbon tetrachloride	CSWG-Rejected. Already regulated; low exposure

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TABLE 4. INFORMATION RELATED TO NCTR'S RESEARCH & TESTING RELEVANT TO CARCINOGENICITY OF SUBSTANCES

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
53-96-3	2-Acetylaminofluorene	2-AAF; N-2-fluorenyl acetamide; fluorene-2 acetamide; N-acetyl-2 aminofluorene	NCI/DHCP/ FDA	Methodology development	Chronic study phase
5326-63-0	3,3'-Dimethoxybenzidine		EPA	Regulatory, potential carcinogenicity	Review of final report, chronic study phase; analytical methods development
119-93-7	3,3'-Dimethylbenzidine		EPA	Regulatory, potential carcinogenicity	Review of final report; chronic study phase; analytical methods development
1937-37-7	Direct Black 38	C.I. 30235	EPA	Environmental contamination	Review of final report (metabolism)
8217-83-7	Direct Dyes 114	Cuprophenyl Black; BWL	CPSC/EPA	Consumer exposure	Review of final report (metabolism)
32-57-1	Direct Blue 53	C.I. 23860	CPSC/EPA	Consumer exposure	Review of final report (metabolism)
4198-19-0	Direct Blue 90 (substituted with Blue 10)	Pergasol Blue 4BAL	CPSC/EPA CPSC/EPA	Consumer exposure Consumer exposure	Dropped Review of final report
28407-30-0	Direct Blue 218	C.I. 24401	NIOSH/OSHA	Occupational exposure	Dropped
992-59-8 993-52-7	Direct Red 7	C.I. 23500	NIOSH/OSHA	Occupational exposure	Review of final report (metabolism)
6358-29-8	Direct Red 39	C.I. 23630	CPSC/EPA	Consumer exposure	Review of final report (metabolism)
5731 07-3 6420-94-8	Direct Yellow 86 (substituted with Violet 32)	Cuprophenyl yellow RL	CPSC/EPA CPSC/EPA	Occupational exposure Occupational exposure	Dropped Review of final report
548-62-9	Gentian Violet	Hexamethyl-p-rosaniline chloride	FDA/NF/ISVM	Regulatory; residues in edible meats	Chronic study phase
58-89-9	Lindane	g-Hexachlorobenzene	EPA	Evaluation of liver tumors	Chronic study phase

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TABLE 4. INFORMATION RELATED TO N.I.H. RESEARCH & TESTING RELEVANT TO CARCINOGENICITY OF SUBSTANCES (continued)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	AGENCY REQUESTING	RATIONALE FOR REQUEST	ACTION BY DHHS
134-32-7	1-Naphthylamine	alpha-Naphthylamine	FDA/EPA	Possible carcinogenicity	On test
91-59-8	2-Naphthylamine	beta-Naphthylamine	FDA/EPA	Possible carcinogenicity	On test
83-79-4	Rotenone		EPA	Regulatory, potential carcinogenicity	Review of final report
81-07-2	Saccharin	o-Benzosulfimide;	FDA	Regulatory, potential carcinogenicity	Chronic study/ phase
887-65-1	Sulfamethazine	4-Amino-N-(4,6-dimethyl-2-pyrimidinyl)-benzene sulfonamide	FDA/BF/DHM	Regulatory, residues in edible meats	Chronic study phase

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CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	REQUESTING AGENCY	APPLICABLE STANDARD	CDC/NIOSH RESPONSE
71-43-2	Benzene	benzin benzine benzol	DOE		Field study in progress to assess health effects of coal gasification system
do	do	do	OSHA		NIOSH developing tests for skin absorption
92-87-5	Benzidine		NTP		Research in progress to study the pharmacokinetics of carbon-14 labelled amines and dyes in the rat including metabolism and tissue distribution.
101-14-4*	4,4'-methylene bis (2-chloro)	benzeneamine MOCA	OSHA		Skin study in draft form where rates of skin absorption and excretion of carbon 14 MOCA were determined in experimental animals.
119-90-4*	3,3'-dimethoxybenzidine		NTP		Research in progress to study the pharmacokinetics of carbon-14 labelled amines and dyes in the rat including metabolism and tissue distribution.
119-93-7*	3,3'-dimethylbenzidine		NTP		do
2602-46-2*	Direc. Blue 6 (C.I.22610)		NTP		do
65996-93-2	Coal tar pitch volatiles	CTPV	OSHA (4 requests)	(coke oven emissions)	Provide technical input and literature.
8052-42-4	Asphalt fumes	bitumen	OSHA (4 requests)	(coke oven emissions)	Provide results of ongoing contract study
59-89-2	N-nitrosomorpholine	NMOR, 4-nitroso-morpholine	Library of Congress	29CFR 1910	Provided technical information.
50-00-0	Formaldehyde	methylene oxide formalin	CPSC	29CFR 1910	Provided technical information.
1333-82-0	Chromium VI		OSHA		Mortality study of chrome plating in progress.

(Continued)

* New chemical for the Third Annual Report.

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TABLE 5. 1981 REQUESTS TO NIOSH TO EVALUATE INFORMATION REGARDING THE RISK OF CARCINOGENICITY DUE TO EXPOSURE TO CHEMICALS LISTED IN THE ANNUAL REPORTS ON CARCINOGENS - Completed 1/1/82 (Concluded)

CAS NUMBER	CHEMICAL NAME	SYNONYM(S)	REQUESTING AGENCY	APPLICABLE STANDARD	CDC/NIOSH RESPONSE
7738-94-5	Chromic Acid				
1333-82-0	Chromium VI		MSHA		Field study in progress of exposure to welding fumes.
1332-21-4	Asbestos		Postal Service U.S. Customs		Health hazard evaluation report and recommendation provided
	Nickel		MSHA		Field study in progress of exposure to welding fumes.
	Benzo(a)pyrene		DOE		Field study in progress to assess health effects of coal gasification system
117-81-7*	Di-(2-ethylhexyl)phthalate	DEHP	EPA		NIOSH determining feasibility of conducting mortality study of workers exposed to DEHP.

* New chemical for the Third Annual Report.

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TABLE 6. REQUESTS FOR INFORMATION (INCLUDING CARCINOGENESIS) ABOUT 118 CHEMICALS: 1980-1982

Search Requested by (date):	Chemical	Sources searched*	No. of References Located
A. NCI (1980)	Cadmium Sulfide	TOX/MED DIALOG LIT LIB TIRC LIB	158
" "	Di-(2-ethylhexyl) phthalate	as above	893
" "	Cadmium Oxide	as above	301
" "	Nickel Sulfate	as above	484
" "	Thiourea	TOX/MED DIALOG TIRC LIB	690
" "	Thioacetamide	as above	609
" "	Diethylstibestrol	as above	695
" "	Cyclophosphamide	as above	1857
" "	Benz(a)anthracene	as above	2832
" "	Lead Acetate	as above	466
" "	Benzo(a)pyrene	as above	1648
" "	Formaldehyde	TOX/MED DIALOG	293

(Continued)

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TABLE 6. REQUESTS FOR INFORMATION (INCLUDING CARCINOGENESIS) ABOUT 118 CHEMICALS: 1980-1982

Search Requested by (date):	Chemical	Sources Searched*	No. of References Located
A. NCI (1981)	Cadmium Sulfide	TOX/MED DIALOG	0
" "	Cadmium Oxide	as above	16
" (1982)	Cadmium Nitrate	MEDLARS DIALOG	578
B. NIEHS (1980)	Reserpine	TOX/MED	253
C. Naval Ordnance Station (1980)	Chromium Octoate	TOX/MED	0
" "	Urethane	TOX/MED	649
D. Dept. of Energy (1981)	Arsenic in coal	RECON	294
E. Industry (1980)	Nickel Nitrate	TOX/MED DIALOG	18
" "	Formaldehyde	TOX	1505
" "	Cadmium	TOX/MED	630
" "	Nickel formate	TOX	1
F. Attorneys (1980)	Diethylstilbestrol (review articles only)	MED	35
" (1980)	Benzene	TOX/MED	337

(Continued)

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TABLE 6. REQUESTS FOR INFORMATION (INCLUDING CARCINOGENESIS) ABOUT 118 CHEMICALS; 1900-1982

Search Requested by (date):	Chemical	Sources Searched*	No. of References Located
F. Attorneys (1981)	Formaldehyde (gas)	MED	221
" "	" in Mobile Homes	TOX/MED	3
" (1982)	Formaldehyde in Mobile Homes	DIALOG RECON	15
" (1982)	Benzene	MEDLARS	540
G. Libraries (1980)	Polychlorinated Biphenyls (teratogenicity of)	TOX/MED	200
" "	Cadmium (teratogenicity of)	TOX/MED	572
" "	Chloroform (teratogenicity of)	TOX/MED	104
" "	Carbon tetrachloride (teratogenicity of)	TOX/MED	93
" "	Benzene (teratogenicity of)	TOX/MED	229
N. Government Contractor (1981)	2-Naphthylamine, N-Phenyl; N-Nitrosodibutylamine; N-Nitroso-di-N-Propylamine; Benzo(b)fluoranthene	MED	4
" "	Dodecane;benzene; Benzo(a)pyrene;formaldehyde (reviews only desired)	TOX/MED	390
" "	Benzo(b)fluoranthene and Cycloheximide	TDB	2

(Continued)

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TABLE 6. REQUESTS FOR INFORMATION (INCLUDING CARCINOGENESIS) ABOUT 118 CHEMICALS: 1980-1982 (Concluded)

Search Requested by (date):	Chemical	Sources Searched*	No. of References Located
H. Government Contractor (1981)	Beryllium	MEDLARS	423
" (1982)	Thioacetamide, acetamide, & sulfanilamide	TOX/TOB	52
" (1982)	Lead Acetate	TOX/MED DIALOG	197
" (1982)	Benzidine	MED/DIAL CANCERLIT	74
" (1982)	Chromium	MED/DIAL CANCERLIT	663
" "	Nickel Subsulfide	as above	63
" "	formaldehyde	as above	473
" "	Benzo(a)Pyrene	as above	482
I. Private Individual (1980)	Chloroform update	TOX/MED	69
J. Private Individual (1981)	Tetraethyl Lead and Cadmium	TOX/MED TIRC LIB	370
K. Foreign Requestor	Carbon Tetrachloride	TOX/MED	488
L. U.S. Government	Asbestos	MEDLARS	707

* TOX = TOXLINE and back files
MED = MEDLINE and back files
MEDLARS = All NLM databases
DIALOG = CAS and BIOSIS files, plus others as appropriate
LIT LIB = Standard Library References
TIRC LIB = Library resources available in Toxicology Information Response Center

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V. APPENDIXES

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A. Alphabetized Synonym and Trade Name Index to the Substances Listed*

* The index also includes the trade names of preparations or formulations only because they contain the listed substance as a part of a mixture of several chemicals.

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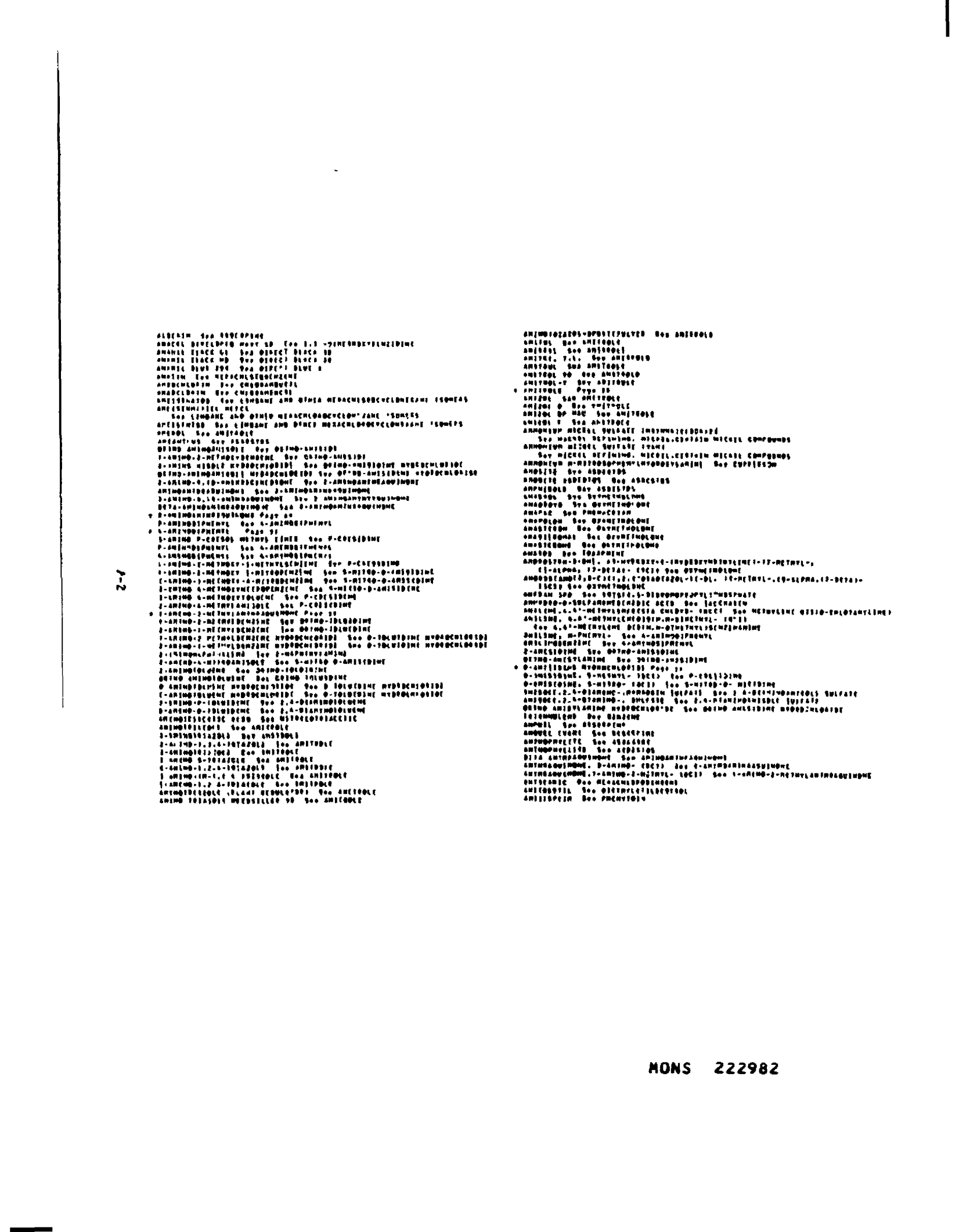
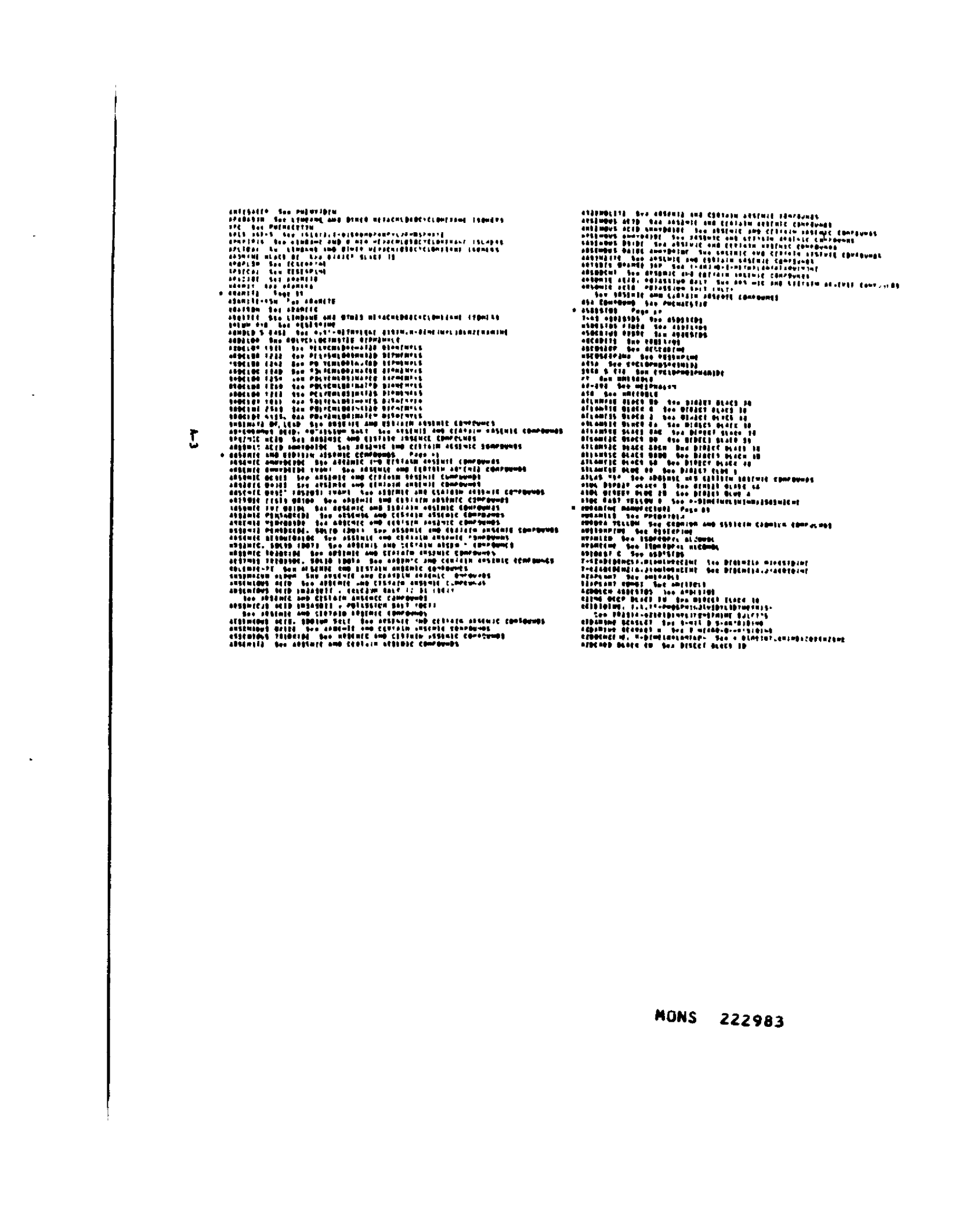
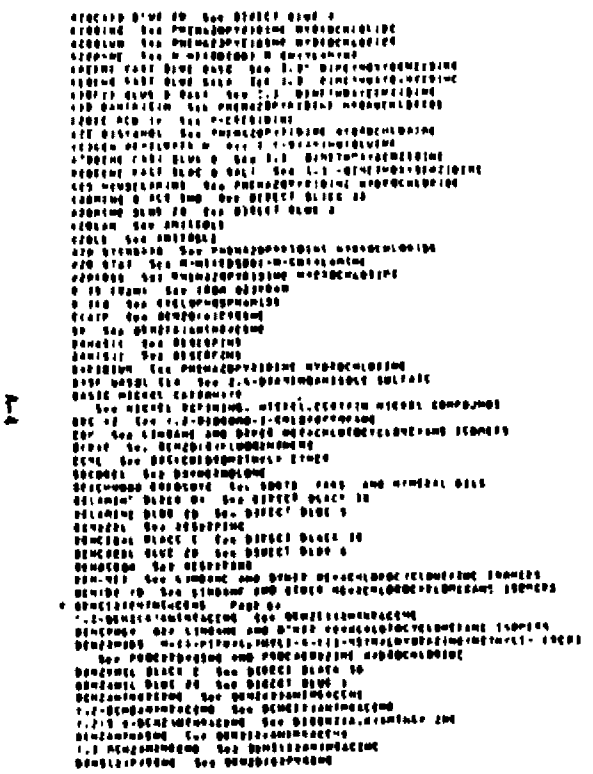
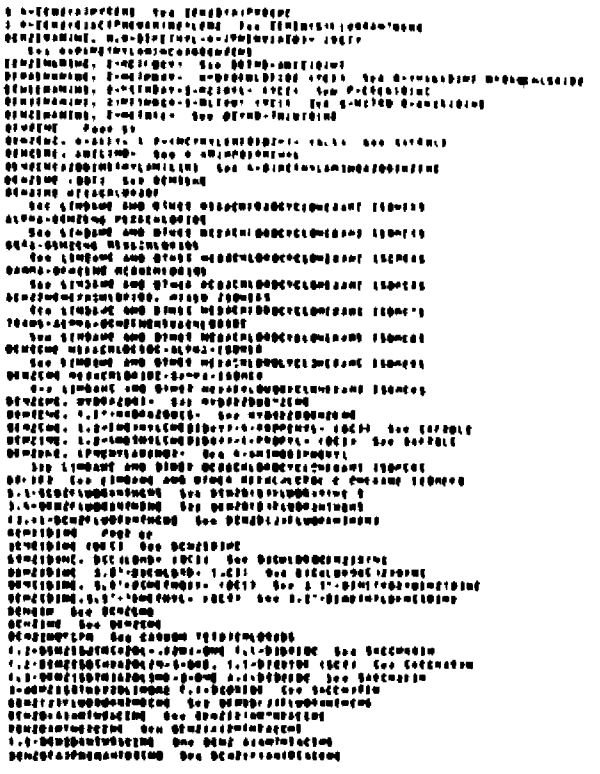
ALPHABETIZED SYNONYM AND TRADE NAME INDEX TO THE SUBSTANCES LISTED

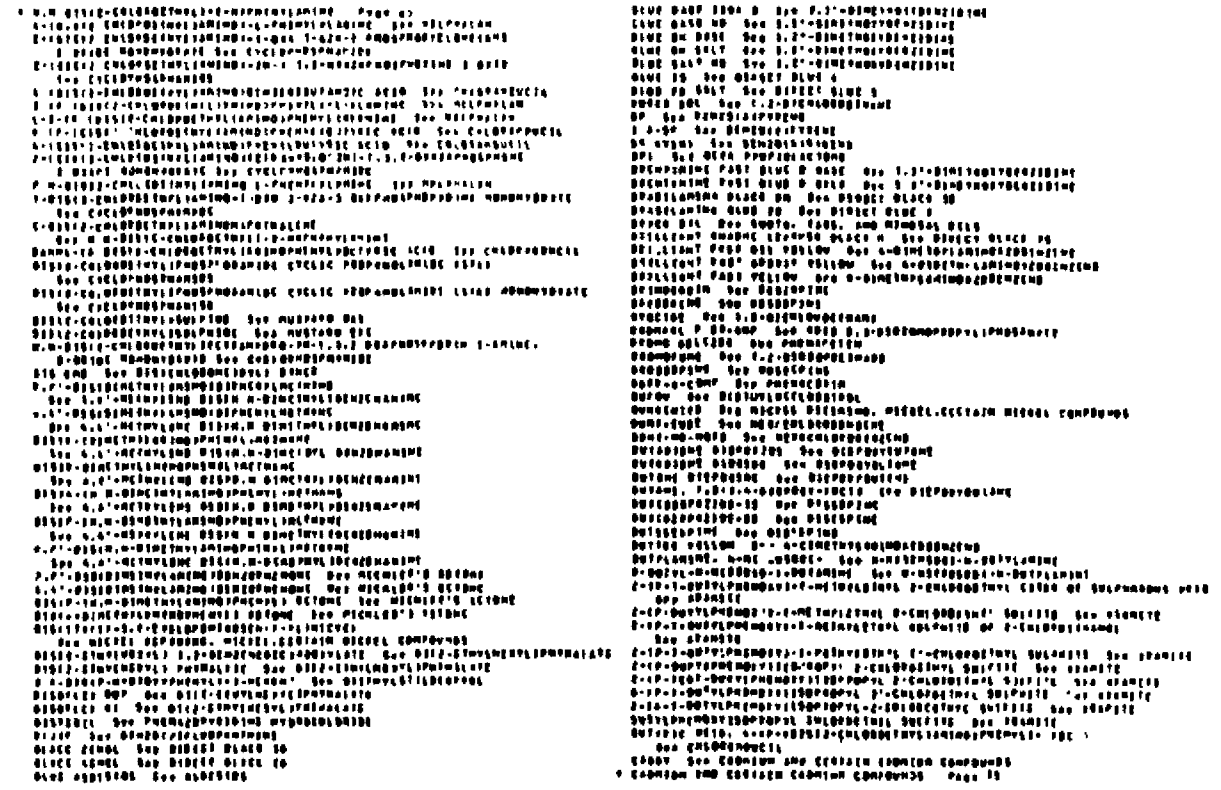
3 ROS [1'-PHENYLACETOPHENONE] See IRON DEXTRAN
4 IRON [YAM] See IRON DEXTRAN
5,6-I See OMITHOLN
5-BROMO-2'-DEOXYURIDINE See BROMODEOXYURIDINE
5HT See 3-(2-AMINOETHYL)INDOL-5-OL
7-AAT See 7-AMINOACTINOMYCIN D
7-AMINOACTINOMYCIN D See ACTINOMYCIN D
8-AZA See AZASERINE
8-AZAGUANINE See AZAGUANINE
8-BROMO-2'-DEOXYURIDINE See BROMODEOXYURIDINE
8-CHLOROADENOSINE See CORDYCEPIN
8-METHOXYPSORALEN See METHOXSALEN
9-AMINOACRIDINE See AMINACRINE
9-AMINOACRIDINE HYDROCHLORIDE See AMINACRINE
9-BROMO-2'-DEOXYURIDINE See BROMODEOXYURIDINE
9-HYDROXYELLIPTICINE See HYDROXYELLIPTICINE
A 23187 See CALCIMYCIN
A-ACETYLDIHYDROCODEINONE See ACETYLDIHYDROCODEINONE
A-ACETYLMETHADOL See ACETYLMETHADOL
A-ACETYLMORPHINE See ACETYLMORPHINE
A-ACETYLPROMEDOL See ACETYLPROMEDOL
A-ALPHA-ACETYLMETHADOL See ACETYLMETHADOL
A-ALPHA-ACETYLPROMEDOL See ACETYLPROMEDOL
A-ALPHA-METHYLFENTANYL See ALPHAMETHYLFENTANYL
A-ALPHA-METHYLMETHADOL See ALPHAMETHYLMETHADOL
A-ALPHA-METHYLTHIOFENTANYL See ALPHAMETHYLTHIOFENTANYL
A-ANHYDROTETRACYCLINE See ANHYDROTETRACYCLINE
A-BETA-ACETYLMETHADOL See ACETYLMETHADOL
A-BETA-ACETYLPROMEDOL See ACETYLPROMEDOL
A-BETA-METHYLFENTANYL See ALPHAMETHYLFENTANYL
A-BETA-METHYLMETHADOL See ALPHAMETHYLMETHADOL
A-BETA-METHYLTHIOFENTANYL See ALPHAMETHYLTHIOFENTANYL
A-BROMOMORPHIDE See APOMORPHINE
A-CHLOROMORPHIDE See APOMORPHINE
A-DIHYDROCODEINONE See ACETYLDIHYDROCODEINONE
A-METHADOL See ACETYLMETHADOL
A-METHYLFENTANYL See ALPHAMETHYLFENTANYL
A-METHYLMETHADOL See ALPHAMETHYLMETHADOL
A-METHYLTHIOFENTANYL See ALPHAMETHYLTHIOFENTANYL
A-PROMEDOL See ACETYLPROMEDOL
A-TETRACYCLINE See ANHYDROTETRACYCLINE
ABBOTT 44211 See ABBOTT-44211
ABBOTT-44211 See ABBOTT-44211
ABELCIN See ABELCIN
ABELCIN-EBERHEX See ABELCIN-EBERHEX
ABORTIN See OXYTOCINASE
ABORTOCIN See OXYTOCINASE
ACEBUTOLOL See ACEBUTOLOL
ACEDAPSONE See DIACETYLDAPSONE
ACEDIASULFONE See DIACETYLDAPSONE
ACEDOXONE See DIACETYLDAPSONE
ACEMETACIN See ACEMETACIN
ACENOCOUMAROL See ACENOCOUMAROL
ACEPROMAZINE See ACEPROMAZINE
ACETAMIDE See ACETAMIDE
ACETAMIDO-4'-HYDROXYPHENYL-(DCI) See PHENACETIN
ACETAMIDO-N-PHOSPHONOMETHYL-(DCI) See PHOSPHONOACETIC ACID
ACETAMIDOBENZOIC ACID See ACETYLANILIC ACID
ACETAMIDOCAPROIC ACID See ACETYLAMINOCAPROIC ACID
ACETAMIDOPHENOL See ACETAMINOPHEN
ACETAMINOPHEN See ACETAMINOPHEN
ACETAMINOPHEN-CODEINE See ACETAMINOPHEN WITH CODEINE
ACETAMINOPHEN-DEXTROMETHORPHAN See ACETAMINOPHEN WITH DEXTROMETHORPHAN
ACETAMINOPHEN-DIPHENHYDRAMINE See ACETAMINOPHEN WITH DIPHENHYDRAMINE
ACETAMINOPHEN-PHENYLPROPANOLAMINE See ACETAMINOPHEN WITH PHENYLPROPANOLAMINE
ACETAMINOPHEN-PROPOXYPHENE See ACETAMINOPHEN WITH PROPOXYPHENE
ACETAMINOPHEN-PSEUDOEPHEDRINE See ACETAMINOPHEN WITH PSEUDOEPHEDRINE
ACETAMINOPHEN-SALICYLAMIDE See ACETAMINOPHEN WITH SALICYLAMIDE
ACETAMINOPHEN-SALICYLIC ACID See ACETAMINOPHEN WITH SALICYLIC ACID
ACETAMINOPHEN-SALICYLIC ACID-CAFFEINE See ACETAMINOPHEN WITH SALICYLIC ACID AND CAFFEINE
ACETAMINOPHEN-SALICYLIC ACID-CODEINE See ACETAMINOPHEN WITH SALICYLIC ACID AND CODEINE
ACETAMINOPHEN-SALICYLIC ACID-PHENACETIN See ACETAMINOPHEN WITH SALICYLIC ACID AND PHENACETIN
ACETAMINOPHEN-SALICYLIC ACID-PHENYLPROPANOLAMINE See ACETAMINOPHEN WITH SALICYLIC ACID AND PHENYLPROPANOLAMINE
ACETAMINOPHEN-SALICYLIC ACID-PROPOXYPHENE See ACETAMINOPHEN WITH SALICYLIC ACID AND PROPOXYPHENE
ACETAMINOPHEN-SALICYLIC ACID-PSEUDOEPHEDRINE See ACETAMINOPHEN WITH SALICYLIC ACID AND PSEUDOEPHEDRINE
ACETAMINOPHEN-SALICYLIC ACID-TRIPROLIDINE See ACETAMINOPHEN WITH SALICYLIC ACID AND TRIPROLIDINE
ACETAMINOPHEN-TRIPROLIDINE See ACETAMINOPHEN WITH TRIPROLIDINE
ACETANILIDE See ACETANILIDE
ACETARSOL See ACETARSOL
ACETARSONE See ACETARSONE
ACETAZOLAMIDE See ACETAZOLAMIDE
ACETEST See ACETEST
ACETHYLMORPHINE See ACETYLMORPHINE
ACETIC ACID, (3,5-DIBROMO-4-HYDROXYPHENYL)- (DCI) See DIBROMOACETIC ACID
ACETIC ACID, (4-HYDROXYPHENYL)- (DCI) See HYDROXYPHENYLACETIC ACID
ACETIC ACID, [(2,6-DICHLOROPHENYL)AMINO]- (DCI) See DICLOFENAC
ACETOHEXAMIDE See ACETOHEXAMIDE
ACETOPHENAZINE See ACETOPHENAZINE
ACETOPHENETIDIN See PHENACETIN
ACETOPHENETIDINE See PHENACETIN
ACETOPHENETIDINE, O- See PHENACETIN
ACETOPHENONE See ACETOPHENONE
ACETOPHENONE, 4'-HYDROXY- See PARACETAMOL
ACETOPHENONE, 4'-HYDROXY-3'-(2-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)- See PHENYLBUTAZONE
ACETOPHENONE, 4'-HYDROXY-3'-(3-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)- See OXYPHENBUTAZONE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)- See OXYPHENBUTAZONE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O- See OXYPHENBUTAZONE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-(DIETHYLAMINOACETYL)- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-(DIETHYLAMINOACETYL)-, HYDROCHLORIDE See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-ACETATE See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-ACETATE, HYDROCHLORIDE See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-ACETATE, MONOHYDROCHLORIDE See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-ACETATE, MONOHYDROCHLORIDE, (+)- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-ACETATE, MONOHYDROCHLORIDE, (-)- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-ACETATE, MONOHYDROCHLORIDE, (S)- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-ACETATE, MONOHYDROCHLORIDE, [R-(R*,R*)]- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-ACETATE, MONOHYDROCHLORIDE, [S-(R*,R*)]- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-ACETATE, [R-(R*,R*)]- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-ACETATE, [S-(R*,R*)]- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-[(DIETHYLAMINO)ACETATE] See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-[(DIETHYLAMINO)ACETATE], HYDROCHLORIDE See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-[(DIETHYLAMINO)ACETATE], MONOHYDROCHLORIDE See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-[(DIETHYLAMINO)ACETATE], MONOHYDROCHLORIDE, (+)- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-[(DIETHYLAMINO)ACETATE], MONOHYDROCHLORIDE, (-)- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-[(DIETHYLAMINO)ACETATE], MONOHYDROCHLORIDE, (S)- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-[(DIETHYLAMINO)ACETATE], MONOHYDROCHLORIDE, [R-(R*,R*)]- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-[(DIETHYLAMINO)ACETATE], MONOHYDROCHLORIDE, [S-(R*,R*)]- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-[(DIETHYLAMINO)ACETATE], [R-(R*,R*)]- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-[(DIETHYLAMINO)ACETATE], [S-(R*,R*)]- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-[(DIETHYLAMINO)ACETATE], [S-(R*,R*)]-, HYDROCHLORIDE See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-[(DIETHYLAMINO)ACETATE], [S-(R*,R*)]-, MONOHYDROCHLORIDE See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-[(DIETHYLAMINO)ACETATE], [S-(R*,R*)]-, MONOHYDROCHLORIDE, (+)- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-[(DIETHYLAMINO)ACETATE], [S-(R*,R*)]-, MONOHYDROCHLORIDE, (-)- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-[(DIETHYLAMINO)ACETATE], [S-(R*,R*)]-, MONOHYDROCHLORIDE, (S)- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-[(DIETHYLAMINO)ACETATE], [S-(R*,R*)]-, MONOHYDROCHLORIDE, [R-(R*,R*)]- See PHENDIMETRAZINE
ACETOPHENONE, 4'-HYDROXY-3'-(4-METHYL-4-PYRROLIDINO-5-PYRAZOLONYL)-, O-[(DIETHYLAMINO)ACETATE], [S-(R*,R*)]-, MONOHYDROCHLORIDE, [S-(R*,R*)]-











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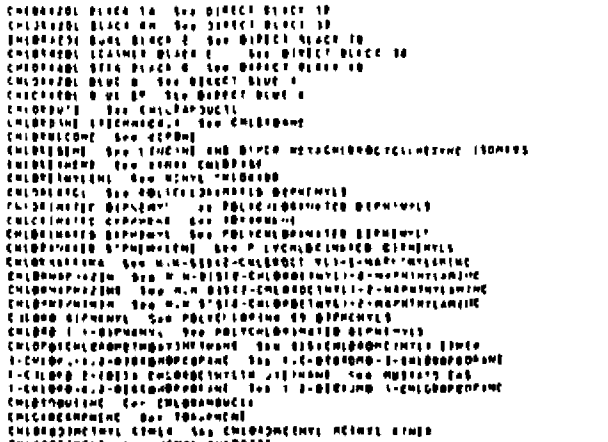

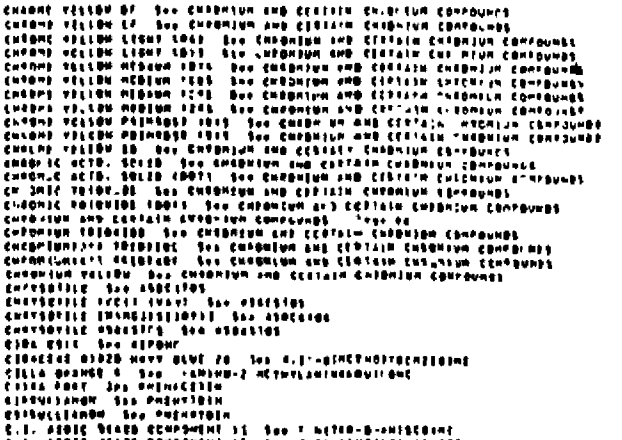

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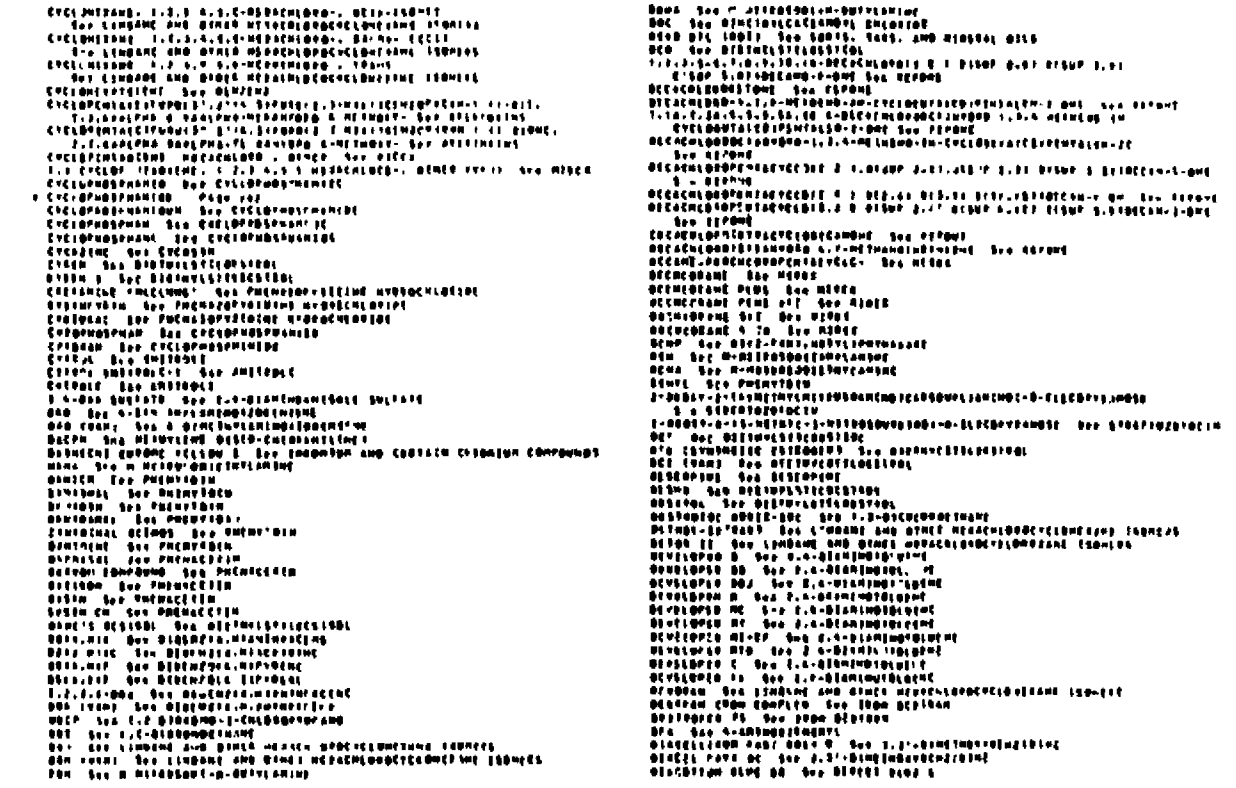


MONS 222990



MONS 222991

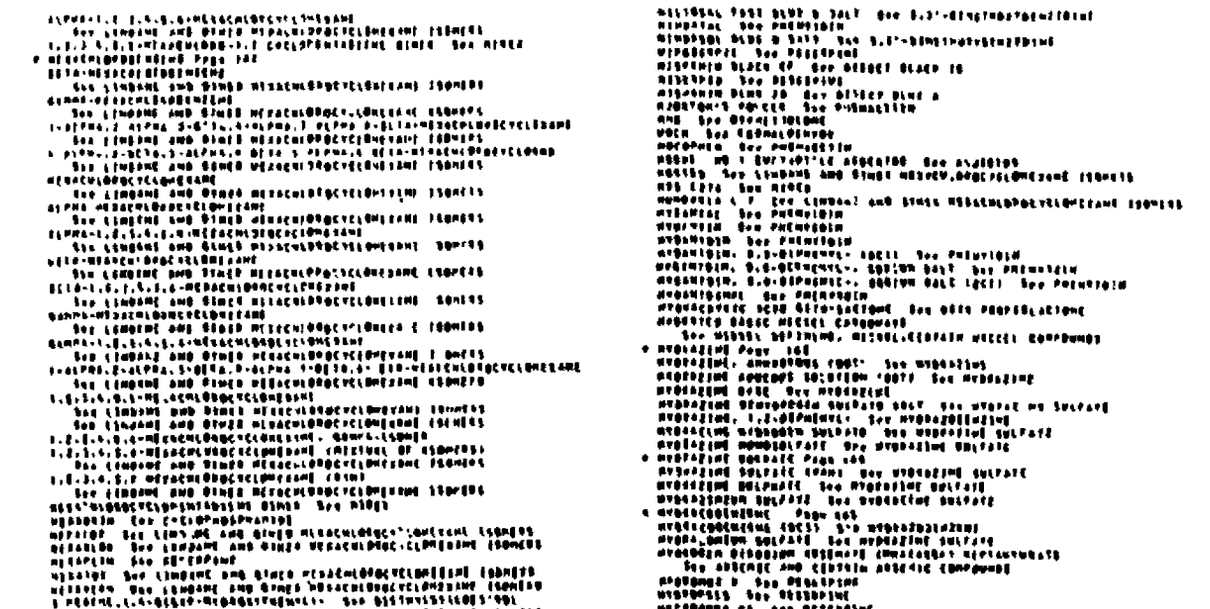


MONS 222992

MONS 222993

MONS 222994

MONS 222997



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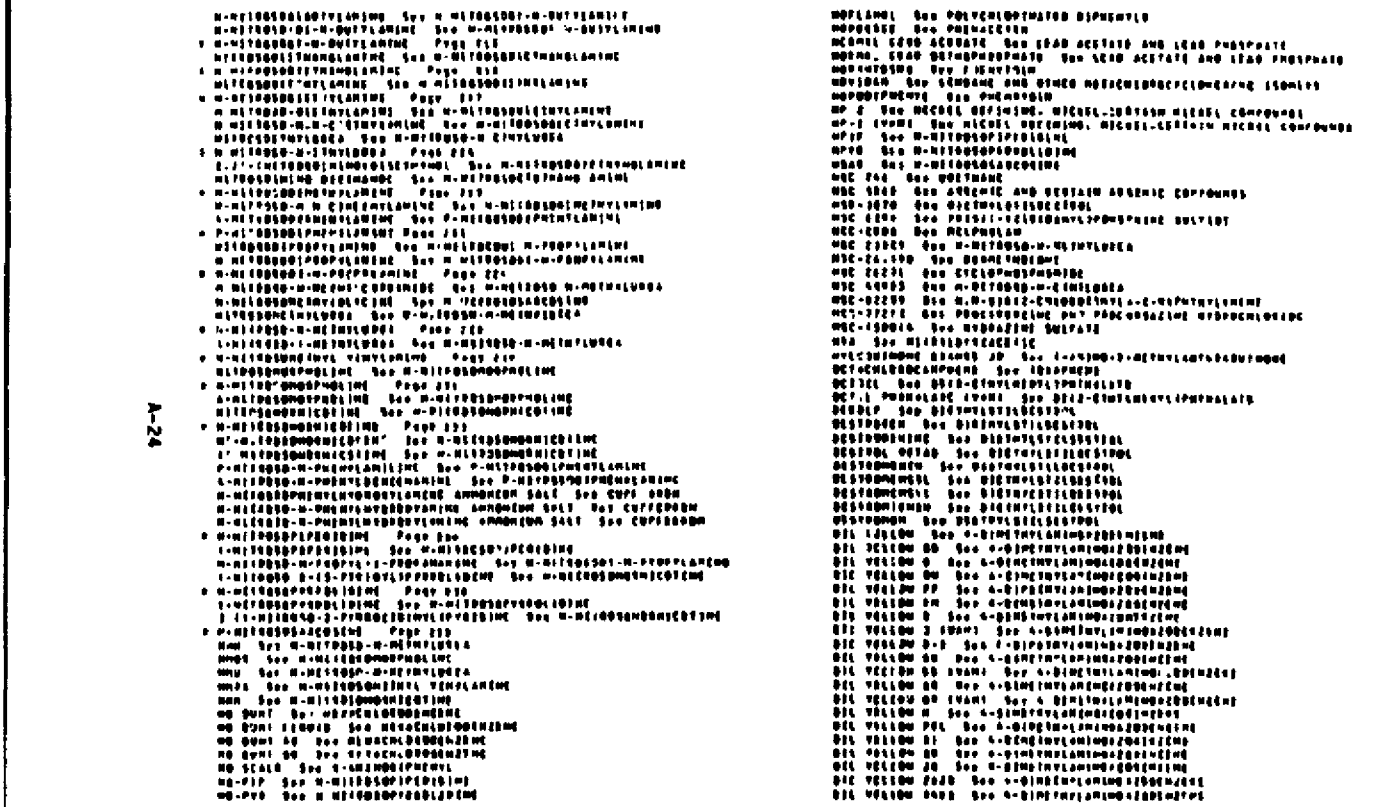
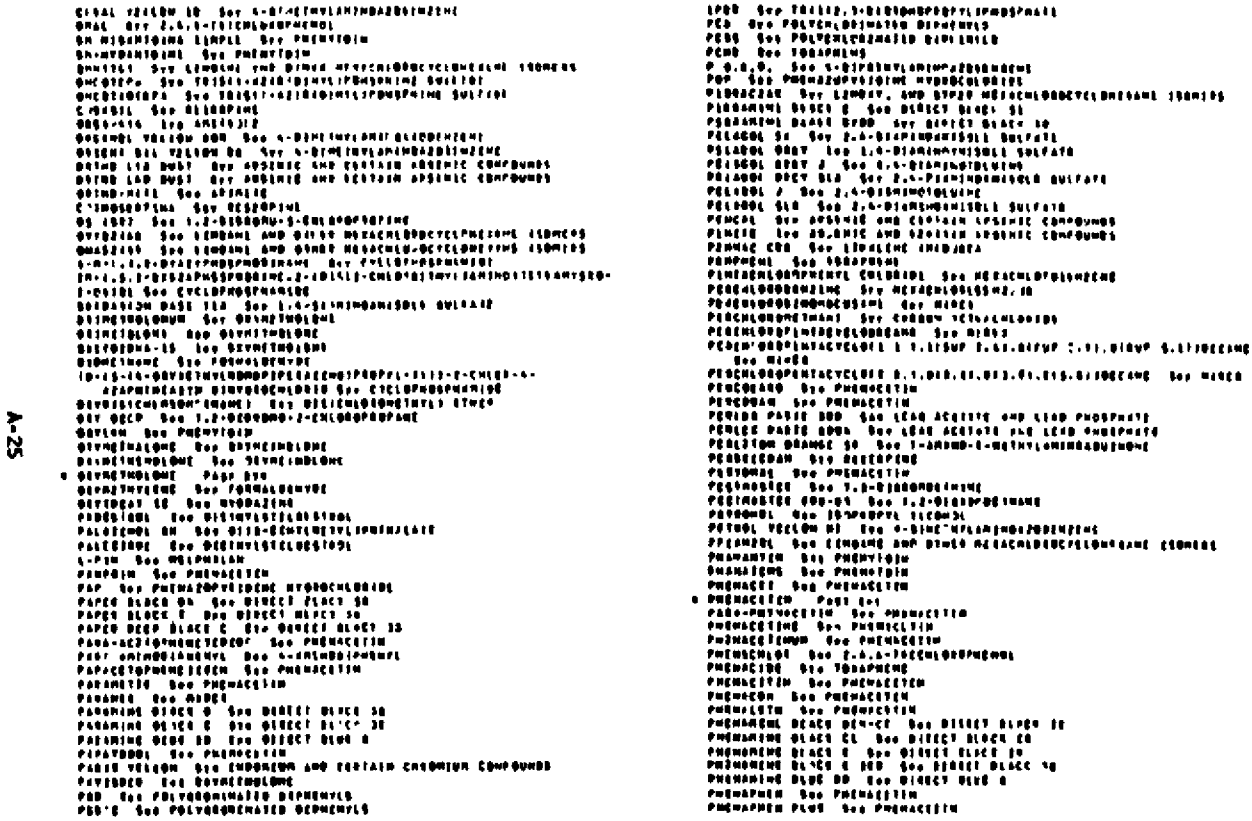
MONS 223003





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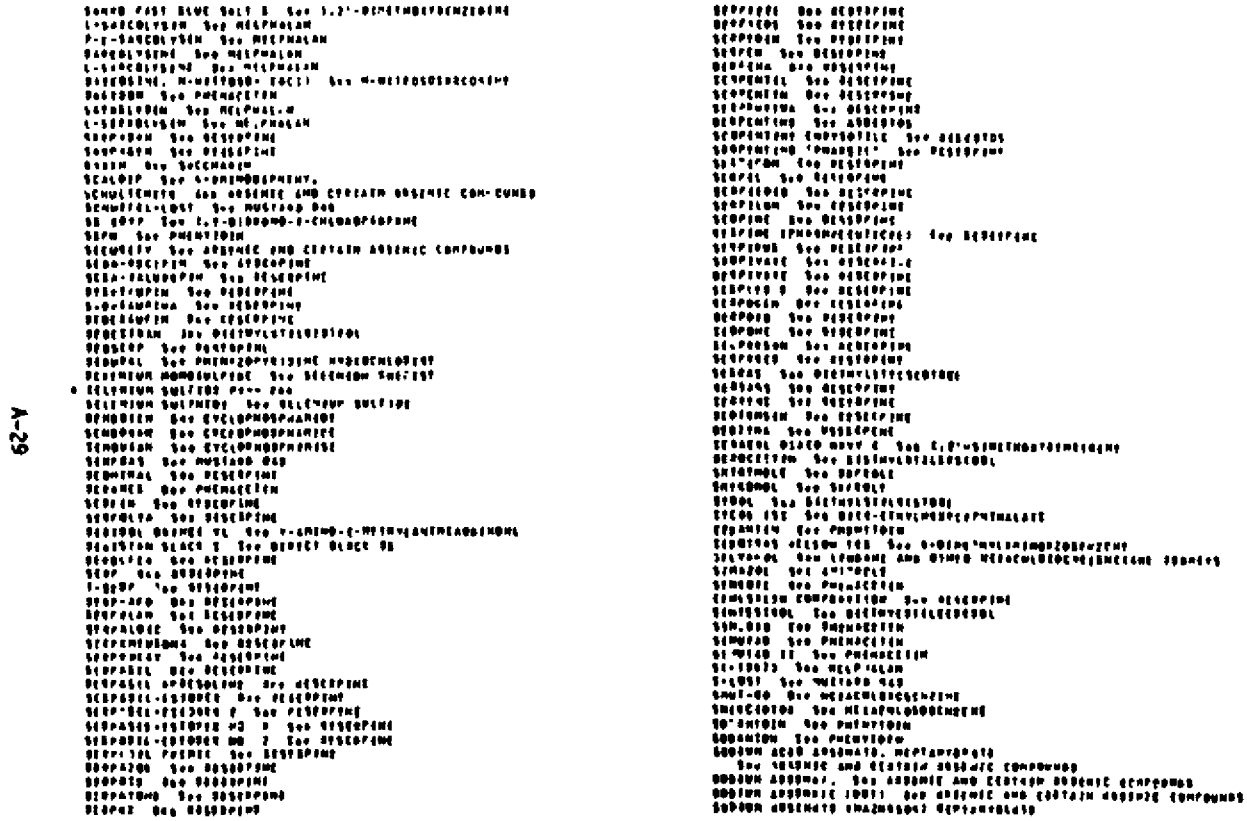

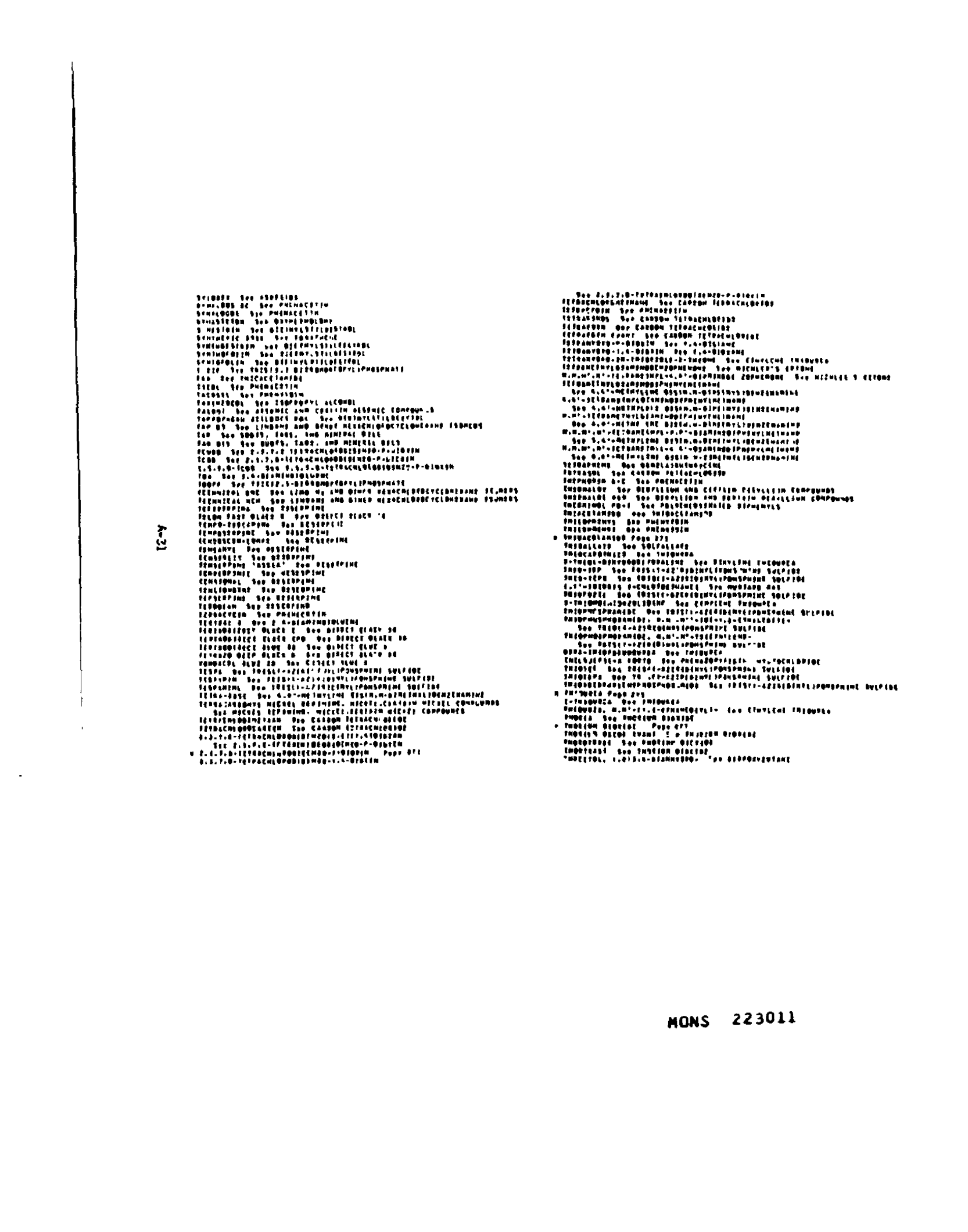

B. Glossary, Acronyms, and Units of Measurement

MONS 223014

GLOSSARY

adenocarcinoma--a malignant epithelial tumor arising from the glandular epithelial tissue

adenoma--a benign neoplasm of glandular epithelial tissue

adrenal gland--a hormone-secreting organ located near each kidney

albino--an organism exhibiting deficient pigmentation in skin, eyes, and/or hair

alkylating agent--a substance that produces a reaction product containing an alkyl group

alveolar--small saclike pouches that may be located in the jaws where the teeth arise, the air cells of the lungs, or in glands

amines--any member of a group of chemical compounds formed from ammonia by replacement of one or more hydrogen atoms by organic radicals

amyloidosis--the accumulation of amyloid (an abnormal complex material most probably a protein compound with a carbohydrate) in various body tissues

analgesic--pain relieving

analytical grade--the highest available purity of a chemical

anemia--a condition in which the number of red blood cells or the amount of hemoglobin in a given volume of blood is less than normal

antibiotic--a chemical substance produced by a microorganism that has the capacity to inhibit the growth of or kill other microorganisms

anticonvulsant--relieving convulsions

antiepileptic--preventing epileptic seizures

anti-inflammatory--counteracting or suppressing inflammation

antimicrobial--destroying microorganisms or arresting their growth

antineoplastic--inhibiting the survival and proliferation of malignant cells

MONS 223015

antioxidant--synthetic or natural substance added to a product to prevent or delay its deterioration by the action of oxygen

antipyretic--relieving or reducing fever

aorta--the main trunk of the arterial system, conveying blood from the left ventricle of the heart to all of the body except the lungs

aplastic anemia--a form of anemia characterized by greatly decreased formation of red blood cells and hemoglobin

aromatic amine--an organic base characterized by a benzene-type ring system containing one or more amino groups

aromatic hydrocarbon--an organic base characterized by the presence of at least one benzene ring and containing only carbon and hydrogen atoms

arsenical--a compound containing arsenic

auditory sebaceous gland--gland of the skin, secreting an oily substance, sebum, and situated in the corium

basal diet--the ordinary adequate diet fed to animals during experiments and to which special ingredients to be tested may be added

benign tumor--a tumorous growth that is not malignant and usually is not life threatening

bile duct--a tube for the passage of bile from the liver into the intestine

bioaccumulation--the process by which the amount of an environmental contaminant present in a living organism increases with time

breakdown product--a chemical derived from a parent compound that has been altered, usually by heat, light, or enzymes

bronchogenic--originating in one of the larger air passages in the lung

cancer--a general term used to indicate any of various types of malignant neoplasms

carbonization--the process of converting carbon or a carbonic residue

carcinogen--a cancer-producing agent

carcinogenesis--formation of cancer

carcinogenic--producing carcinoma, a malignant neoplasm of epithelial tissue

carcinogenicity--the power, ability, or tendency to produce carcinoma, a malignant neoplasm of epithelial tissue

carcinoma--a malignant neoplasm of epithelial tissue

carcinostatic--tending to check the growth of carcinoma

cardiovascular--of, relating to, or involving the heart and blood vessels

central nervous system (CNS)--the division of the nervous system comprising the brain and spinal cord

cervix--the neck of the uterus

chemosterilant--a chemical compound that causes sterility of an organism when ingested

chemotherapeutic--pertaining to the treatment of disease by chemical agents

cholangiocarcinoma--adenocarcinoma of the bile ducts

cholangiocellular--of or pertaining to the gallbladder or bile ducts

chronic--continuing for a long time

clitoral--pertaining to a small, elongated, erectile body situated at the anterior or ventral part of the vulva

colon--the part of the large intestine extending from the cecum (blind gut) to the rectum (terminal portion of the digestive tube)

conjunctiva--the membrane that lines the eyelid and covers part of the eyeball

connective tissue--a tissue that connects, supports, or surrounds other tissues or organs

contaminant--an impurity; in the environment, a chemical that is not usually present and that may have deleterious effects

copolymer--a polymer containing more than one kind of monomer

corpus uteri--the main part of the uterus

cystitis--inflammation of the urinary bladder

cytology--study of cells, their origin, structure, function, and pathology

cytotoxic--having a toxic action to cells

dermal--pertaining to skin

MONS 223017

desiccator--a heavy glass container from which moisture is removed by vacuum or chemicals

diabetes--a disease in which the ability of the body to use sugar is impaired and sugar appears abnormally in the urine and is characterized by excessive urination

diamine--a compound that contains two amino groups

distant tumor--a tumor that is located far from the point of attachment or origin

distillation--a process that consists of driving gas or vapor from liquids or solids by heating and condensing to liquid products

D,L--refers to mirror images of compounds that rotate polarized light to the right (D) or left (L)

dose-response relationship--a relationship between dose (amount) of a chemical administered, or taken into the body, and the effects

dyscrasias--a pathological condition resulting from the presence of abnormal material in the blood

effluent--waste material discharged into the environment

endometrium--the mucous membrane that lines the uterus

enzyme--a complex organic compound (protein) produced in the organism that can accelerate a particular biochemical reaction; a biological catalyst

epidemiology--a science concerned with the occurrence and distribution of disease in human populations

epilepsy--a nervous disease usually characterized by seizures with convulsions and loss of consciousness

epithelium--tissue covering internal and external surfaces of the body

esophagus--the passage that carries food from the throat to the stomach

estrogen--any of a group of female sex hormones

estrus--the female sexual cycle

fibroadenoma--a benign neoplasm that contains fibrous tissue

fibrocarcinoma--carcinoma with a hard structure owing to the formation of dense connective tissue

MONS 223018

fibrosarcoma--a malignant neoplasm derived from fibrous connective tissue

follicular cell--modified epithelial cells that surround the ovum in various follicles and secrete follicular fluid

forestomach--a nonglandular section of the stomach that is lacking in the human organism

fungi--a major group of saprophytic and parasitic lower plants, that lack chlorophyll and the tissue differentiation of higher plants

fungicide--an agent that destroys fungi

gallbladder--a reservoir for the bile located near the liver

gastric (stomach) intubation--insertion of a tube into the stomach

gastric tube--a tube passed through the mouth and into the stomach

gastrointestinal--pertaining to or communicating with the stomach and intestine

gavage--feeding through a tube passed through the mouth into the stomach

genitourinary--pertaining to the genital and urinary organs

geothermal--of or relating to the heat of the earth's interior

gestation--pregnancy; in mammals, the period of the development of the young from the time of fertilization of the ovum (egg)

gland--an aggregation of cells specialized to secrete certain substances of biological importance

glomerulonephritis--a renal disease characterized by inflammation of the capillary loops in the glomeruli of the kidney

gonad--the sex gland of the male or female

gonadal dysgenesis--impaired development of the gonads

grand mal seizure--major epileptic convulsion

hemangioendothelioma--a neoplasm derived from blood vessels in which the endothelial cells are the most prominent component

half-life--the time in which a substance will be reduced to one-half of its present value through degradation or elimination from the organism

harderian gland--accessory lacrimal glands at the inner corner of the eye in animals referred to as the "third eyelid" or the semilunar conjunctival fold

hard palate--the anterior, rigid portion of the partition separating the nasal and oral cavities

hemangiosarcoma--a rare malignant neoplasm of endothelial cells derived from blood vessels

hematopoietic--pertaining to or affecting the formation of blood cells

hepatic--pertaining to the liver

hepatitis--inflammation of the liver

hepatocellular--pertaining to liver cells

hepatoma--a tumor of the liver

herbicide--an agent that is destructive to weeds

histological--pertaining to the study of the microscopic structure and composition of tissues

histology--the study of anatomy that deals with the minute structure, composition, and function of tissues

Hodgkins disease--a malignant condition characterized by painless, progressive enlargement of the lymph nodes, spleen, and general lymphoid tissues

hormone--chemical substances produced by the endocrine glands that have specific regulatory effects on the activity of certain organs

hyperglycemia--an abnormally increased content of sugar in the blood

hyperplasia--an increase in the size of a tissue or organ due to an increase in the number of cells

hypnotic--sleep-inducing; a sleep-inducing drug

hypotensive--causing diminished blood pressure

impurity--a contaminant; an unnecessary part of a mixture or compound

inhalation--the drawing of air or other substances into the lungs

initiator--a chemical that permanently alters a cell or group of cells and in the case of carcinogens is tumor producing

integumentary system--an enveloping layer (as a skin, membrane) of an organism or one of its parts

intrabronchial--situated or occurring within a bronchus, a division of the trachea that leads into the lung

intragastric--within the stomach

intramuscular (im) injection--injection into muscle tissue

intraperitoneal (ip) injection--injection into the abdominal cavity that is lined by a serous sac (peritoneum)

intrapleural--within the pleura, a serous membrane enveloping the lungs and lining the walls of the pleural cavity

intratracheal--within the trachea (windpipe)

intravenous (iv) injection--injection into a vein

in utero--within the uterus

invasive--spreading beyond specific body tissues

labile--unstable; tending to dissociate into component parts

lactation--the secretion of milk

larynx--the upper end of the trachea (windpipe)

latency period--a seemingly inactive period, as that between the exposure of tissue to an injurious agent and the manifestation of response, or that between the instant of stimulation and the beginning of a response

leaching--a process by which a substance or contaminant in the soil is displaced, usually by water, to another location

lesion--a wound or injury

leukemia--a cancer of the blood-forming tissues characterized by a marked increase in the number of abnormal white blood cells

leukemogenic--causing leukemia, an acute or chronic disease characterized by an abnormal increase in the number of leukocytes

lymph--a clear liquid that is collected from the tissues throughout the body and flows in lymphatic vessels

MONS 223021

lymphatic--pertaining to vascular channels that transport lymph or to a lymph node

lymphoid--resembling lymph or lymphatic tissue

lymphoma--a neoplasm of the lymphatic tissue

lymphoreticular--proliferation of the reticuloendothelial cells of the lymph glands

lymphosarcoma--malignant neoplastic disorders of lymphoid tissue, but not including Hodgkin's disease

malignant--tending to become progressively worse; life-threatening

mammary--pertaining to the breast

marmoset--a soft furred, clawed monkey found in South and Central America

melanoma--a neoplasm derived from cells that are capable of forming melanin

menopause--the cessation of menstruation

mesentery--a fold of peritoneum that attaches the small intestine to the posterior abdominal wall by which the viscera are supported

meso--a compound whose molecules are superimposable on their mirror images

mesothelioma--a neoplasm derived from cells lining the pleural and peritoneal cavities

metabolism--the transformation of chemicals by which energy is made available for the uses of the organism and by which contaminants may be converted to different compounds for easier elimination

metabolite--any substance produced by metabolism or by a metabolic process

metastasis--in cancer, the appearance of a neoplasm in parts of the body remote from the site of its origin

miscible--capable of being mixed without separation into phases

mononuclear--a cell having a single nucleus, especially a monocyte of the blood or tissues

multiple myeloma--a malignant neoplasm derived from plasma cells and found at several foci in the body

mutagenicity--the property of being able to induce an inheritable change

myasthenia gravis--a disease of the muscular system characterized by progressive weakness of muscles

myeloma--a malignant neoplasm derived from plasma cells

myeloproliferative disorder--a disorder characterized by proliferation of one or more bone marrow elements

nasal turbinates--the convoluting supportive structure of the nose

necropsy--the examination of a dead body by dissection for detailing the effects of disease

neonatal--relating to or effecting the first four weeks after birth

neoplasia--the process that results in the formation and growth of a tumor

neoplasm--Any new and abnormal growth; neoplasms may be either benign or malignant

neoplastic--pertaining to or like any new or abnormal growth

neural--pertaining to the nerves

neuroblastoma--a malignant tumor of the nervous system

neurogenic--originating in the nervous tissue; forming nervous tissue

nodule--a swelling or protuberance

oat cell carcinoma--a type of lung cancer

olfactory--pertaining to the sense of smell

oropharynx--a division within the tube connecting the mouth and nasal passages to the esophagus

osteoporosis--an abnormal thinning of the bone

ovarian--pertaining to an ovary or ovaries, the female reproductive organ in which eggs develop

ovary--the female reproductive organ in which eggs develop

palate--the partition separating the nasal and oral cavities

pancreas--a large gland behind the stomach that secretes both hormones and enzymes involved in digestion and metabolism

MONS 223023

papilloma--a benign tumor derived from epithelial tissue

parathyroid--any one of four small glands situated beside the thyroid gland

parenteral--not through the alimentary (food) canal, but by subcutaneous, intramuscular, or intravenous injection

Parkinson's syndrome--a disease characterized by muscular rigidity, tremor, and salivation

particulates--composed of separate particles having characteristic properties and structures

pathologist--an expert in the study of the nature of diseases

pelvis--the lower (caudal) portion of the trunk of the body, bounded anteriorly and laterally by the two hip bones and posteriorly by the sacrum and coccyx

percutaneous absorption--absorption through the skin

peritoneum--the lining surrounding the abdominal cavity and containing the viscera

pesticide--a poison used to destroy pests of any kind

pH--the negative logarithm of the hydrogen ion concentration used in expressing both acidity and alkalinity. On a scale of 0-14, 7 represents neutrality

pituitary--a small gland at the base of the brain that secretes several important hormones

pleural--pertaining to the membrane surrounding the lungs and lining the thoracic cavity

polycyclic--containing more than one benzene ring

polycythemia vera--a disease characterized by an absolute increase in red cell mass and total blood volume, associated frequently with splenomegaly, leukocytosis, and thrombocythemia

postpartum--occurring after childbirth

prenatal--existing or occurring before birth with reference to the fetus

primary cancer--the original cancer developed in an organism

MONS 223024

promoter--a chemical that, though not itself carcinogenic, serves to potentiate, sometimes quite dramatically, the effect of a carcinogen

prostate--a gland in males that surrounds the neck of the urinary bladder and the urethra, and secretes a milky fluid that is discharged at the time of emission of semen

protastatitis--inflammation of the prostate gland

pulmonary--pertaining to the lungs

pyelonephritis--inflammation of the kidney and its pelvis

pyrolysis--decomposition of a substance by heat

quarternary--containing four chemical elements or groups

racemate--the rotation of an isomer that is exactly cancelled by an equal and opposite rotation

radioactive--having the property of emitting radiation (such as alpha, beta, or gamma rays) from an atomic nucleus

remission--a diminuation or abatement of the signs or symptoms of a disease

renal--pertaining to the kidney

respiratory--pertaining to the act of breathing

reticulum cell--a network, especially a protoplasmic network in cells, such as the flattened double membrane sheets of the endoplasmic reticulum

retrospective study--a study (epidemiological) that collects information about past events that may be related to the present distribution of disease

rheumatoid arthritis--a chronic disease of the joints, marked by inflammatory changes of joint structures

rodenticide--any agent used for destroying rodents

salivary--pertaining to the saliva, or the glands that secrete saliva

sarcoma--a malignant neoplasm derived from connective tissue

scrotum--the pouch that contains the testes and their accessory organs

secondary cancer--a cancer arising through metastases of primary cancer

MONS 223025

sedative--an agent that relieves excitement or anxiety and induces sleep

small intestine--the small tube of the intestine, about 20 feet long, extending from the opening of the stomach to the large intestine

smelter--an establishment used to separate or refine a metal often with accompanying chemical change

spleen--a large vascular lymphatic organ that lies in the upper abdominal cavity; it stores blood cells and produces lymphocytes

squamous cells--thin, flat cells

stomach tube--a tube passed through the mouth down into the stomach, used sometimes as a means of dosing animals

subcutaneous (sc)--beneath the skin

systemic--pertaining to or affecting the body as a whole

target organ--the organ affected by a specific chemical in a specific species

technical grade chemical--a chemical that has not been purified after production and may contain multiple impurities

testes--the male gonads situated in the scrotum that produce sperm

thorax--the part of the body between the neck and the respiratory diaphragm encased by ribs; the chest

topically--pertaining to a particular surface area and affecting only that area

toxic--poisonous

tracheal--pertaining to the trachea, the main trunk of the system of tubes by which air passes into the lungs

transitional cell--a cell that is changing, such as in movement, development, or evolution from one form, stage, or style to another

transplacental--through the placenta (the organ uniting mother and fetus)

thrombophlebitis--inflammation of a vein with secondary clot (thrombus) formation

thymus--a gland that is located in the lower neck

thyroid gland--a gland that produces, stores, and secretes hormones that regulate the rate of metabolism

MONS 223026

tubular cell--pertaining to a cell, with a tubule or small tube-like structure

tumor--a neoplasm; a mass of new tissue that persists and grows independently of its surrounding structures and that has no physiological use; it may be benign or malignant

tumorigenic--causing or producing tumors

urinary tract--pertaining to the organs and passageways concerned with the formation and discharge of the urine

uterus--the hollow muscular organ in female animals that is the abode and place of nourishment of the fetus

vagina--the passage leading from the uterus to the outside of the female body

valency--the electrical charge of a chemical atom

vascular--pertaining to blood vessels or indicative of a copious blood supply

vector control--control of insects and other organisms transmitting infectious agents of disease

vehicle--the substance in which a compound is dissolved or mixed prior to dosing an animal with that compound

vesicant--causing blisters; a small round hollow outgrowth of the skin

volatile--readily changes to a vapor

X-irradiation--X-ray exposure

Zymbal's glands--sebaceous glands surrounding the external ear canal in rodents

MONS 223027

ACRONYMS AND ABBREVIATIONS

AFL/CIO	American Federation of Labor/Congress of Industrial Organizations
ANPR	Advance Notice of Proposed Rulemaking
BATF	Bureau of Alcohol, Tobacco, and Firearms
BC	Bureau of Census
BD	Bureau of Drugs, FDA
BF	Bureau of Foods, FDA
BMD	Bureau of Medical Devices, FDA
BVM	Bureau of Veterinary Medicine, FDA
CAA	Clean Air Act
CAG	Carcinogen Assessment Group, EPA
CAS	Chemical Abstract Service
CDC	Centers for Disease Control
CEC	Chemical Evaluation Committee, NTP
CFR	Code of Federal Regulations
CI	Colour Index
CIIT	Chemical Industry Institute of Toxicology
CMR	Chemical Marketing Register
CPSA	Consumer Product Safety Act
CPSC	Consumer Product Safety Commission
CSWG	Chemical Selection Working Group, NTP
CWA	Clean Water Act
DHEW	U.S. Department of Health, Education, and Welfare
DHHS	U.S. Department of Health and Human Services
DNCP	Diet, Nutrition, and Cancer Programs, NCI
DOC	U.S. Department of Commerce
DOE	U.S. Department of Energy
EDF	Environmental Defense Fund
EEC	European Economic Community
EPA	U.S. Environmental Protection Agency
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FD&CA	Food, Drug, and Cosmetic Act
FHSA	Federal Hazard Substances Act
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register
FY	Fiscal Year
GRAS	Generally Recognized As Safe
HCN	Hydrogen Cyanide
H_2O_2	Hydrogen Peroxide
hr	hour

MONS 223028

IARC	International Agency for Research on Cancer
insol	insoluble
ip	Intraperitoneal
IRLG	Interagency Regulatory Liaison Group
iv	Intravenous
max	maximum
MCL	Maximum Contaminant Level
min	minute
MSHA	Mine Safety and Health Administration
NCI	National Cancer Institute
NESHAP	National Emissions Standards for Hazardous Air Pollutants
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
NOHS	National Occupational Hazard Survey
NORS	National Organic Reconnaissance Survey
NOS	Not Otherwise Specified
NPDES	National Pollutant Discharge Elimination System
NRC	Nuclear Regulatory Commission
NTP	National Toxicology Program
OAQPS	Office of Air Quality Planning and Standards, EPA
ODW	Office of Drinking Water, EPA
OPP	Office of Pesticide Programs, EPA
OPTS	Office of Pesticides and Toxic Substances, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTC	Over The Counter
OTS	Office of Toxic Substances, EPA
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PEL	Permissible Exposure Limit
PHS	Public Health Service
PL	Public Law
PPPA	Poison Prevention Packaging Act
PR	Pesticide Registration
RCRA	Resource Conservation and Recovery Act
R&D	Research and Development
RPAR	Rebuttable Presumption Against Registration
RTECS	Registry of Toxic Effects of Chemical Substances
SDWA	Safe Drinking Water Act
sec	section
sol	soluble
SPRD	Special Pesticide Review Division
SUS	Saybolt Universal Seconds

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TB	Tuberculosis
TDB	Toxicology Data Bank
TLV	Threshold Limit Value
TSCA	Toxic Substances Control Act
TWA	Time-Weighted Average
USDA	United States Department of Agriculture
USITC	United States International Trade Commission
USP	United States Pharmacopeia
Vol.	volume
WHO	World Health Organization

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UNITS OF MEASUREMENT

Weights

g	gram	1 g	=	0.035 oz
kg	kilogram	1 kg	=	2.2 lb
lb	pound(s)	1 lb	=	0.45 kg
mg	milligram	1 mg	=	10^{-3} g
mg/kg	when referring to dosing, it means mg of chemical administered per kg body weight of the dosed animal			
ng	nanogram	1 ng	=	10^{-9} g
oz	ounce	1 oz	=	28.3 g
ppb	parts per billion	1 ppb	=	ug/kg
ppm	parts per million	1 ppm	=	mg/kg
ppt	parts per trillion	1 ppt	=	ng/kg
ug	microgram	1 ug	=	1 x 1^{-6} g

Volumes

cc	cubic centimeter	1 cc	=	1 ml
gal	gallon (U.S.)	1 gal	=	3.8 l
l	liter	1 l	=	0.95 liquid quart
m^3	cubic meter	m^3	=	35 cubic feet
ml	milliliter	1 ml	=	10^{-3} l

Lengths

cm	centimeter	100 cm	=	1 m
km	kilometer	1 km	=	0.6 mile
m	meter	meter	=	3.3 feet
mm	millimeters	1 mm	=	1/1000 m
mppcf	million parts per cubic foot			

Temperature

° C	degree Centigrade	1° C	=	(° F-32)
° F	degree Fahrenheit	1° F	=	(° C x 9/4) + 32

Exponentials

10^2, 10^3, 10^6, etc.: superscripts refer to the number of times "10" is multiplied by itself, e.g., 10^2 = 10 x 10 = 100; 10^3 = 10 x 10 x 10 = 1000.

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C. List of Substances and Their Synonyms and Trade Names*

* The index also includes the trade names of preparations or formulations only because they contain the listed substance as a part of a mixture of several chemicals.

1-ACETYLAMINOFLUORENE CAS# 53-96-3 33
2AF
2-AAF
ACETAMIDE, N-FLUOREN-2-YL- (8CI)
ACETAMIDE, N-9H-FLUOREN-2-YL- (9CI)
2-ACETYLAMINOFLUORENE
2-ACETYLAMINOFLUORENE
N-ACETYL-2-AMINOFLUORENE
2-FACETYLAMINOFLUORENE
FAA
2-FAA
FAA (VAN)
N-(9-FLUOREN-2-YL)ACETAMIDE
N-2-FLUORENYLACETAMIDE
2-FLUORENYLACETAMIDE

ACRYLONITRILE CAS# 107-13-1 39
ACETIN
ACETYLENE CYANIDE
ACRYLIC ACID NITRILE (8CI)
ACRYLONITRILE
CARBACRYL
CYANOETHYLENE
EMC 84
INHIBISIN
MILLED'S POWDER#1M
PROPENENITRILE
2-PROPENENITRILE
VC 314
VCN
VINICOR
VINYL CYANIDE

AFLATOXINS CAS# 1402-68-2 57
AFB1
AFLATOXIN B
AFLATOXIN B1
AFLATOXIN G1
AFLATOXIN M1
AFLATOXIN B2
AFLATOXIN G2
AFLATOXIN M2
DICHLOROETHYL ETHER 71
DICHLOROETHYLETHER 71

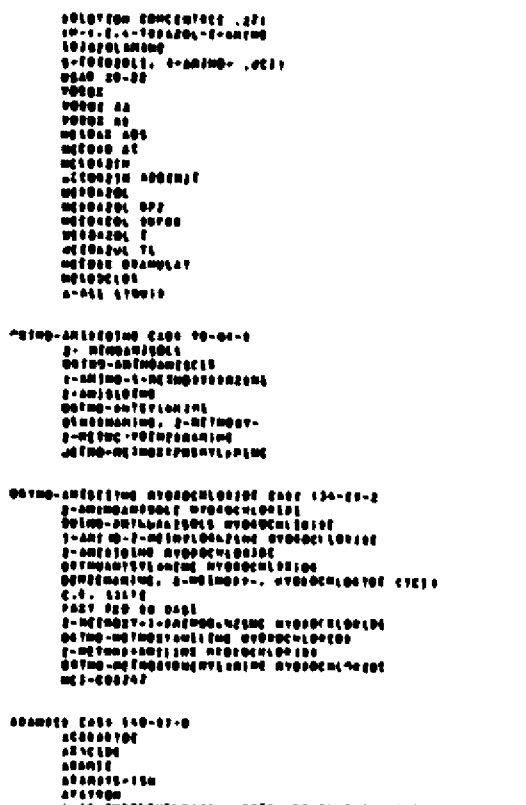
2-AMINOANTHRAQUINONE CAS# 117-79-3 59
AAQ
AMINOANTHRAQUINONE
2-AMINO-9,10-ANTHRACENEDIONE

2-AMINOANTHRAQUINONE 59
2-AMINO-9,10-ANTHRACENEDIONE
AMINOANTHRAQUINONE, 2-AMINO- (8CI)
BETA-AMINOANTHRAQUINONE
NCI-C03826

4-AMINOBIPHENYL CAS# 92-67-1 31
P-AMINOBIPHENYL
P-AM-BOOKMARK1
4-AMINODIPHENYL
AMILINE, M-PHENYL-
AMILINOBENZENE
BIPHENE, AMILINO-
BENZENE, 1PHENYLAMINO-
BIS QUPPIE
BIPHENYLAMINE
P-BIPHENYLAMINE
11,1'-BIPHENYL-4-AMINE
4-BIPHENYLAMINE (8CI)
4-BIPHENYLAMYLAMINE
C.I. 10035
DPA
DIPHENYLAMINE
BIPHENYLAMINE (8CI)
N,N-DIPHENYLAMINE
DPA
DPA (VAN)
NO SCALE
PARA AMINODIPHENYL
N-PHENYLANILINE
P-PHENYLAMILINE
4-PHENYLAMILINE
N-PHENYLBENZENAMINE
QUALQUIP
FUNGIAMINE
P-BIPHENYLAMINE

4-AMINO-4'-NITROSTILBENE-2,2'-DISULFONIC CAS# 81-11-8 51
ACETATE BASE QUINONE 9
NITROQUINOLINONE LIGHT BRANCH #1
4-AMINO-4'-NITROSTILBENE-2,2'-DISULFONIC
AMINOSTILBENEDISULFONIC,4-AMINO-4'-NITRO- (9CI)
APRICOT BRANCH 89P
BILLITON BRANCH 1
B.T.DISPOSE BRANCH 13
BRIA BRANCH 8
C.I. 40760
DISPOSE BRANCH STAR
DUBRAL BRANCH 8
2-NITRO-4-AMINOSTILBENE-2,2'-DISULFONIC
NITROSTILBENE BRANCH 8A
NCI-C03781
NITROQUINOLINONE BRANCH #1
PEBBLE BRANCH 10





MONS 223036

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CADMIUM SULFIDE CAS# 1306-23-6
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CADMIUM SULFIDE
CADMIUM YELLOW

CADMIUM AND CERTAIN CADMIUM COMPOUNDS
CADMIUM CAS# 7440-43-9
C.I. PIGMENT
CADMIUM CHLORIDE CAS# 10108-64-2
CADDY
CADMIUM DICHLORIDE
DICHLOROCADMIUM
VI-CAD
CADMIUM OXIDE CAS# 1306-19-0
CADMIUM DUST
CADMIUM MONOXIDE
CADMIUM OXIDE
CADMIUM SULFATE CAS# 10124-36-4
CADMIUM MONOSULFATE
CADMIUM SULFATE
CADMIUM SULPHATE
SULPHURIC ACID, CADMIUM[2+] SALT
SULPHURIC ACID, CADMIUM SALT

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CHLORAMBUCIL; CAS# 305-03-3

[illegible]

CHLORDANE; CAS# 57-74-9

[illegible]

CHLORDECONE; CAS# 143-50-0

[illegible]

CHLORDIMEFORM; CAS# 6164-98-3

[illegible]

CHLOROBENZILATE; CAS# 510-15-6

[illegible]

CHLOROFORM; CAS# 67-66-3

[illegible]

CHROMIUM AND CERTAIN CHROMIUM COMPOUNDS

CHROMIUM; CAS# 7440-47-3

CHROME

CALCIUM CHROMATE; CAS# 13765-19-0

CALCIUM CHROMATE

CALCIUM CHROMATE (CaCrO4)

CALCIUM CHROMATE (1:1)

CALCIUM CHROME YELLOW

CALCIUM CHROMIUM OXIDE (CaCrO4)

CALCIUM CHROMIUM OXIDE; CaCrO4

CALCIUM MONOCHROMATE

CANARY CHROME YELLOW 46-2358

C.P. PERMANENT YELLOW 52

C.P.- 07225

C.I. 77284 (1988)

DOLOMIN

YELLOW ULTRAMARINE

CHROMIUM TRIOXIDE; CAS# 1333-82-0

CHROMIC ACID

CHROMIC ACID

CHROMIC ACID, SOLID

CHROMIC ACID, SOLID (8017)

CHROMIC ANHYDRIDE

CHROMIC ANHYDRIDE (8011)

CHROMIC TRIOXIDE

CHROMIC ULTRAIOL (8011)

CHROMIUM TRIOXIDE

CHROMIUM(3+); TRIOXIDE

CHROMIUM(6+); TRIOXIDE

HEXAVALENT CHROMIUM TRIOXIDE

PLEOCHROIC CHROMIUM TRIOXIDE

LEAD CHROMATE; CAS# 7758-97-6

A. C. PERMANENT YELLOW 34

C.I. 77600

C.P. CHROME YELLOW LIGHT

C.P. CHROME YELLOW MEDIUM

C.P. CHROME YELLOW PERMANENT

CHROME YELLOW

CHROME YELLOW O

CHROME YELLOW OP

CHROME YELLOW LO

CHROME YELLOW LIGHT 1851

CHROME YELLOW LIGHT 1870

CHROME YELLOW MEDIUM 1874

CHROME YELLOW, MEDIUM 1905

CHROME YELLOW MEDIUM 1778

CHROME YELLOW MEDIUM 1774

CHROME YELLOW PRIMROSE 1818

CHROME YELLOW PRIMROSE 1819

CHROME YELLOW RO

CHROMINA YELLOW

CHLOME YELLOW

DELMICENT CHROME YELLOW O

GEMG'S YELLOW

LEAD CHROMATE

LEAD CHROMATE (PbCrO4)

LEAD CHROMATE (YAM)

LEAD CHROMATE(VI)

LEIPZIG YELLOW

LEMON YELLOW

PARIS YELLOW

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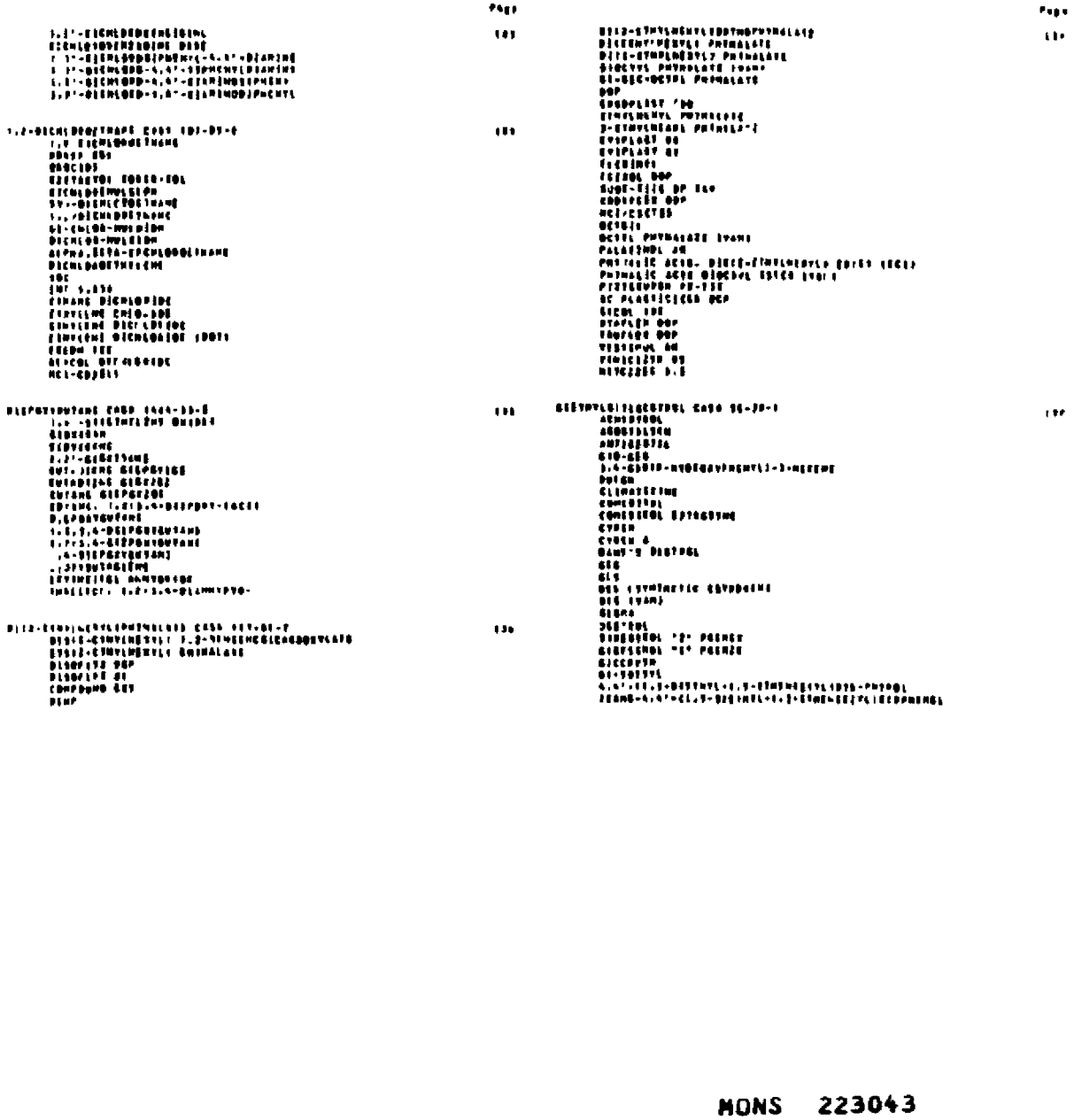

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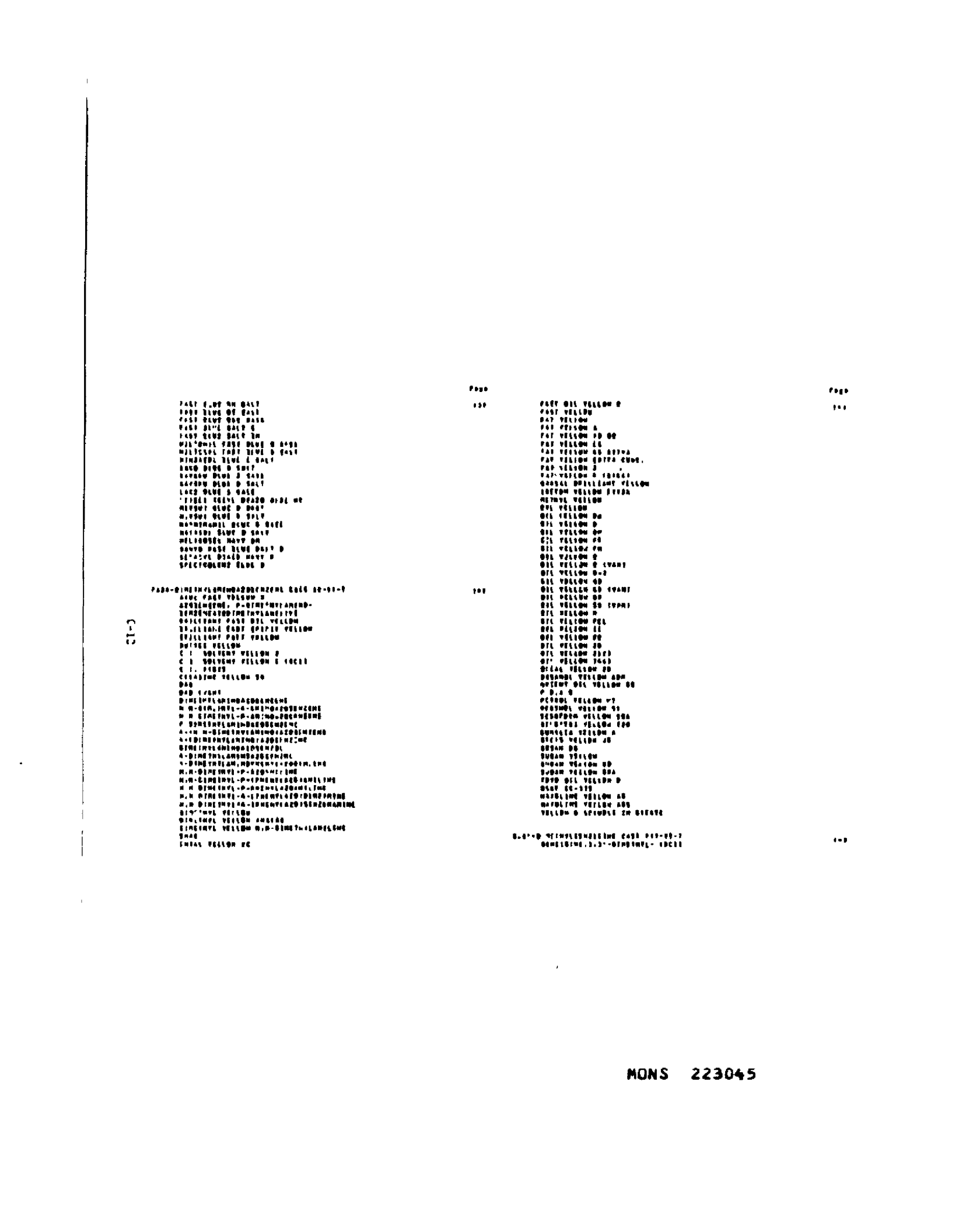

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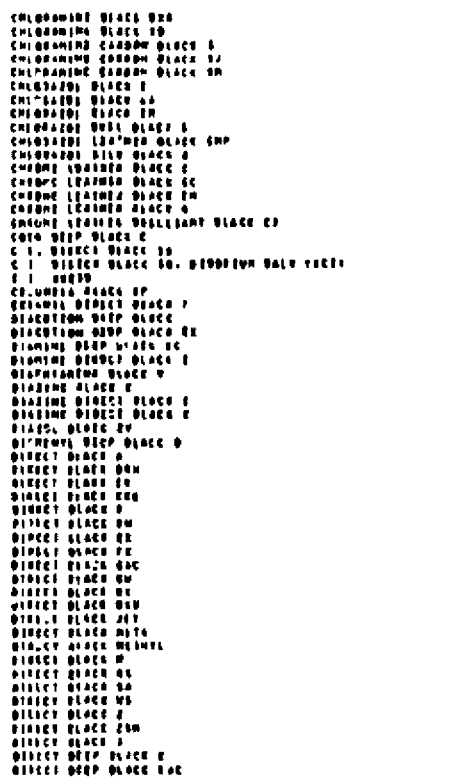

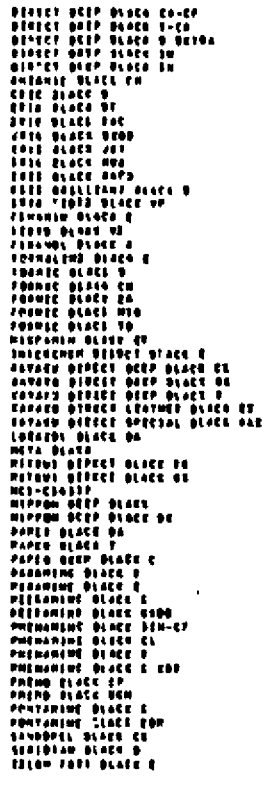

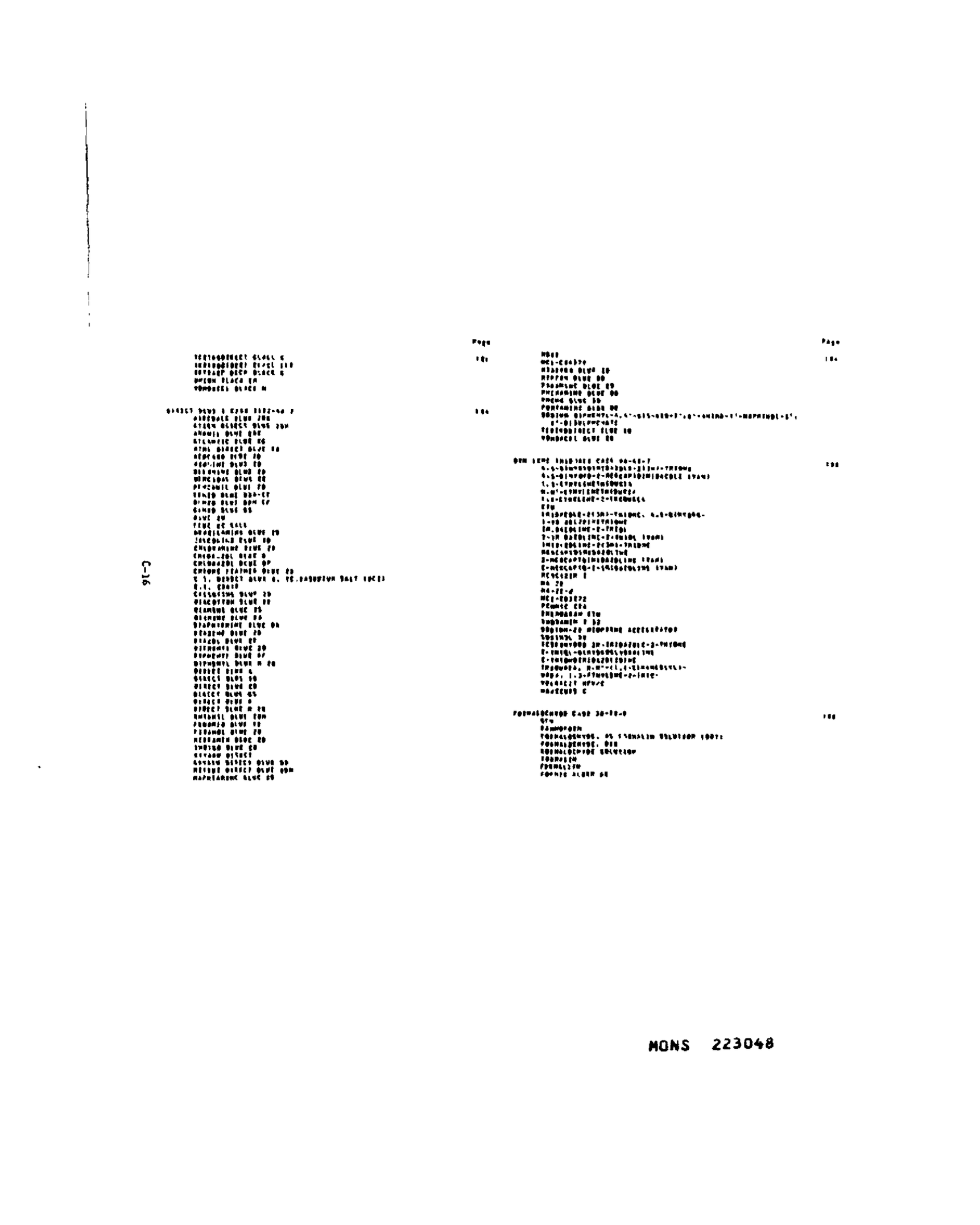

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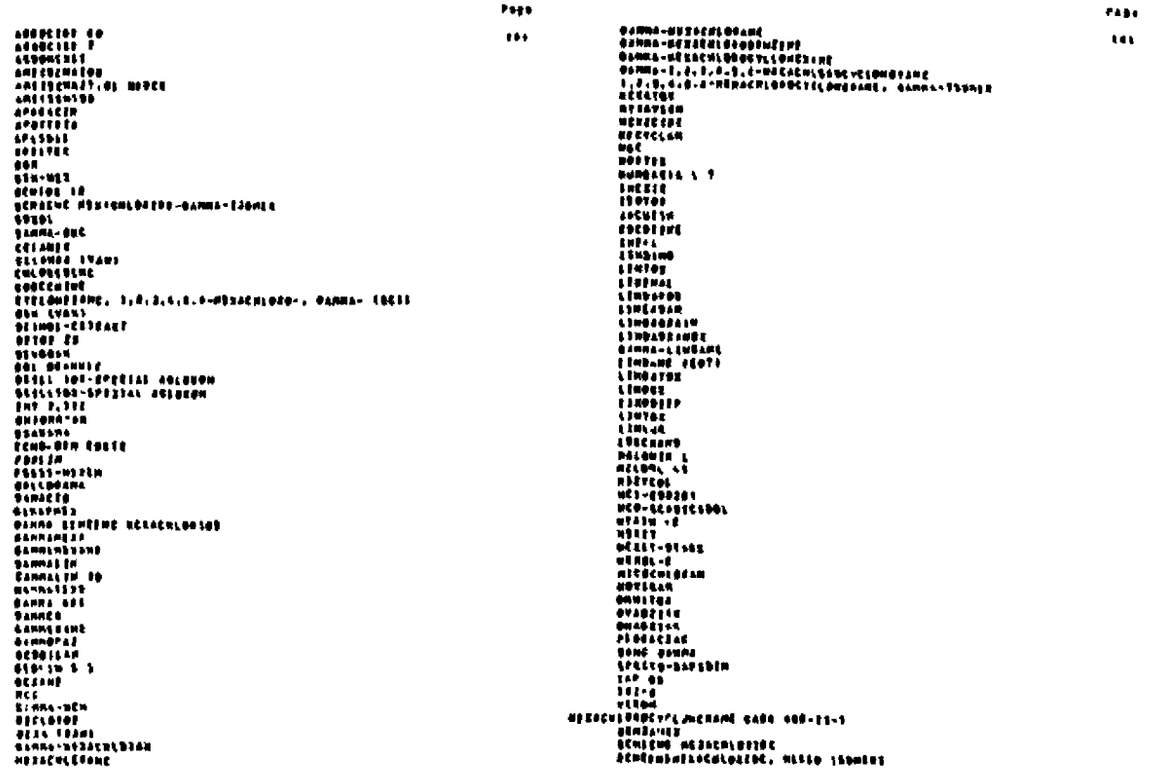
MONS 223050



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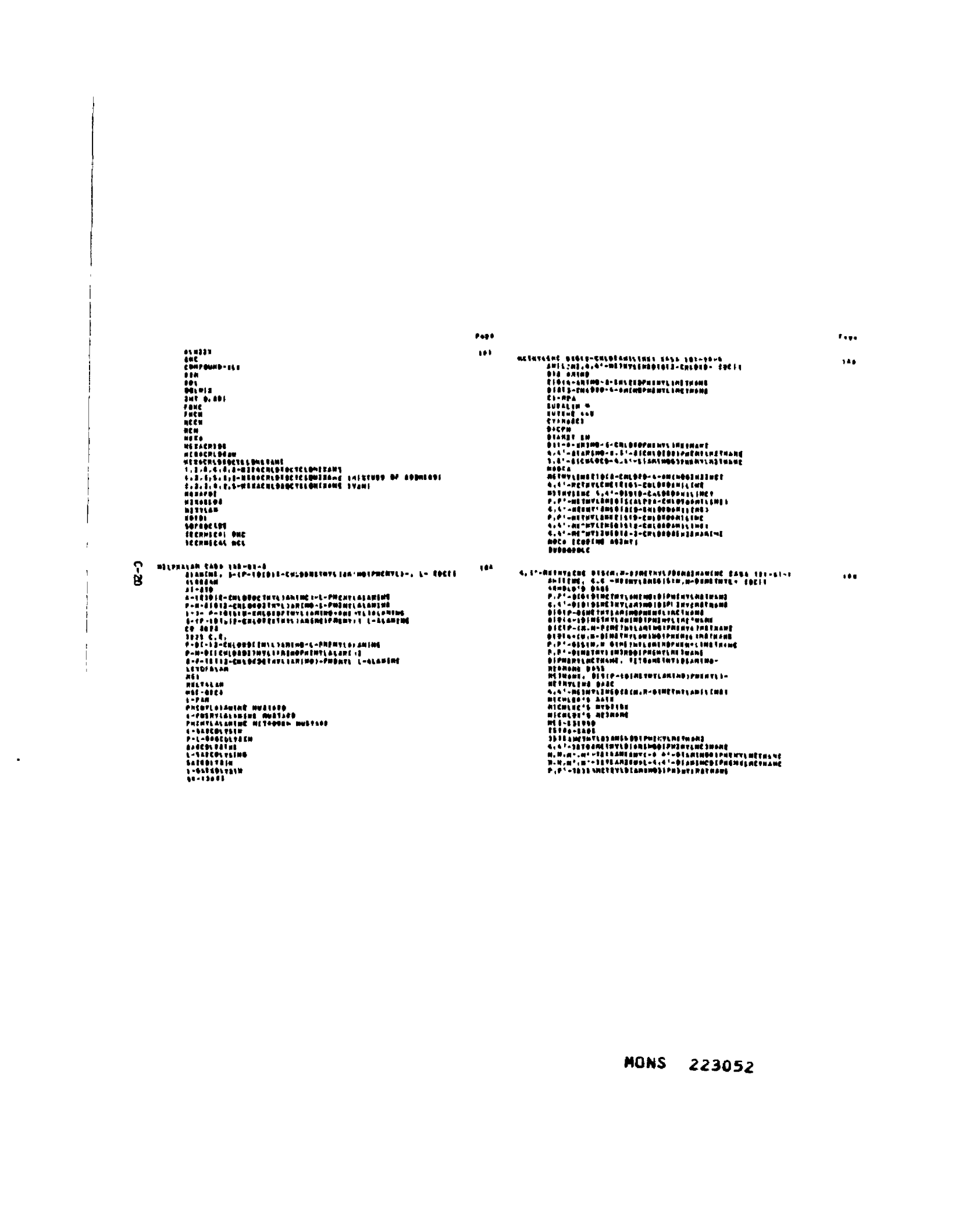

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NICKEL CARBONATE [NICO3]
NICKELOUS CARBONATE
NICKEL(II) CARBONATE
NICKEL(+2) CARBONATE
NICKEL(2+) CARBONATE (NICO3)
NICKELOUS CARBONATE
NICKEL CARBONYL CAS# 13463-39-3
NICKEL CARBONYL (NI(CO)4)
NICKEL CARBONYL TYAN
NICKEL CARBONYL (NI(CO)4) (OC)4
NITRIC TETRACARBONYL
TETRACARBONYL NICKEL
NICKEL CHLORIDE CAS# 7718-54-9
NICKEL(II) CHLORIDE
NICKEL(2+) CHLORIDE
NICKEL DICHLORIDE
NICKELOUS CHLORIDE
NICKEL HYDROXIDE CAS# 12054-48-7
NICKEL DIHYDROXIDE
NICKEL(II) HYDROXIDE
NICKEL(2+) HYDROXIDE
NICKELOUS HYDROXIDE
NICKELOCENE CAS# 1271-28-9
BIS(ETA5-2,4-CYCLOPENTADIEN-1-YL)NICKEL
BIS(CYCLOPENTADIENYL)NICKEL
BI-PI-CYCLOPENTADIENYLNICKEL
NICKEL BIS(CYCLOPENTADIENE)
NICKEL, BIS(ETA5-2,4-CYCLOPENTADIEN-1-YL)-
NICKEL BIS(CYCLOPENTADIENYL)
NICKEL, BI-PI-CYCLOPENTADIENYL- (OC)2
NICKELOCENE
PI-CYCLOPENTADIENYL COMPD. WITH NICKEL
NICKEL OXIDE CAS# 1313-99-1
BUNSENITE
E.I. 77777
GREEN NICKEL OXIDE
MONONICKEL OXIDE
NICKEL MONOOXIDE
NICKEL MONOXIDE
NICCOLITE
NICKELITE O*ODE
NICKEL(II) OXIDE
NICKEL OXIDE (YAN)
NICKEL OXIDE BINDER TP
NICKEL PROTOXIDE
NICKELOUS OXIDE
NICKEL PHOSPHIDE CAS# 12035-74-8
NICKELOPHOSPHITE
NICKEL DIPHOSPHIDE
NICKEL DIPHOSPHIDE
NICKEL PHOSPHIDE
NICKEL TRITUNGSTENPHOSPHIDE
NICKEL PHOSPHATE CAS# 7786-61-4
NICKEL PHOSPHATE
NICKEL SULFATE (NI(SO4)
NICKEL SULFATE (1:1)
NICKEL(II) SULFATE

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NICKEL(2+) SULFATE (1:1)
NICKELOUS SULFATE
ELECTRIC ACID NICKEL(II) SALT
SULFURIC ACID, NICKEL(2+) SALT (1:1)

NITRILOTRIACETIC ACID CAS# 139-13-9
ACETIC ACID, NITRILOTRI- (OC)3
AMINOTRIACETIC ACID
N,N-BIS(CARBOXY*METHYL)GLYCINE
CHEL 100
COMPLEXON I
GLYCINE, N,N-BIS(CARBOXYMETHYL)- (OC)1
HAMPSHIRE NTA ACID
NEI-CODIAK
NTA
SEQUESTREX I
TRICLYCOLLAMIC ACID
TRIDLYCINE (TRIM)
TRILON A
ALPHA,ALPHA',ALPHA''-TRIMETHYLAMINETRICARBOXYLIC ACID
VERSENE NTA ACID

NITROPEN CAS# 1836-75-1
2,4-DICHLORO-4'-NITRODIPHENYL ETHER
2,4-DICHLORODI-(4-NITROPHENOXY)ETHANE
2,4-DICHLORODIPHENYL P-NITROPHENYL ETHER
4,4-DICHLORODIPHENYL 4-NITROPHENYL ETHER
4-(2,4-DICHLOROPHENOXY)-3'-METHOXY-4'-NITRODIPHENYL ETHER
DICHLOR, 2,4-DICHLOROPHENYL P-NITROPHENYL (OC)1
KN 004
NOXFISH
NEI-CODIAK
NITROFISH
NIP
NITROMIN
NITROPHEN
4-NITRO-2',4'-DICHLORODIPHENYL ETHER
4'-NITRO-2,4-DICHLORODIPHENYL ETHER
NITROPHEN (YAN)
NITROPHENE (YAN)
TOA
TOE E
TOE E-II
TOE-E
YDIZLIN

P-NITRO-O-ANISIDINE CAS# 99-59-2
1-AMINO-2-METHOXY-4-NITROBENZENE
1-AMINO-2-METHOXY-4-NITROPHENYL
2-AMINO-4-NITROANISOLE
2-METHOXY-4-NITROANILINE
O-ANISIDINE, 4-NITRO- (8CI)

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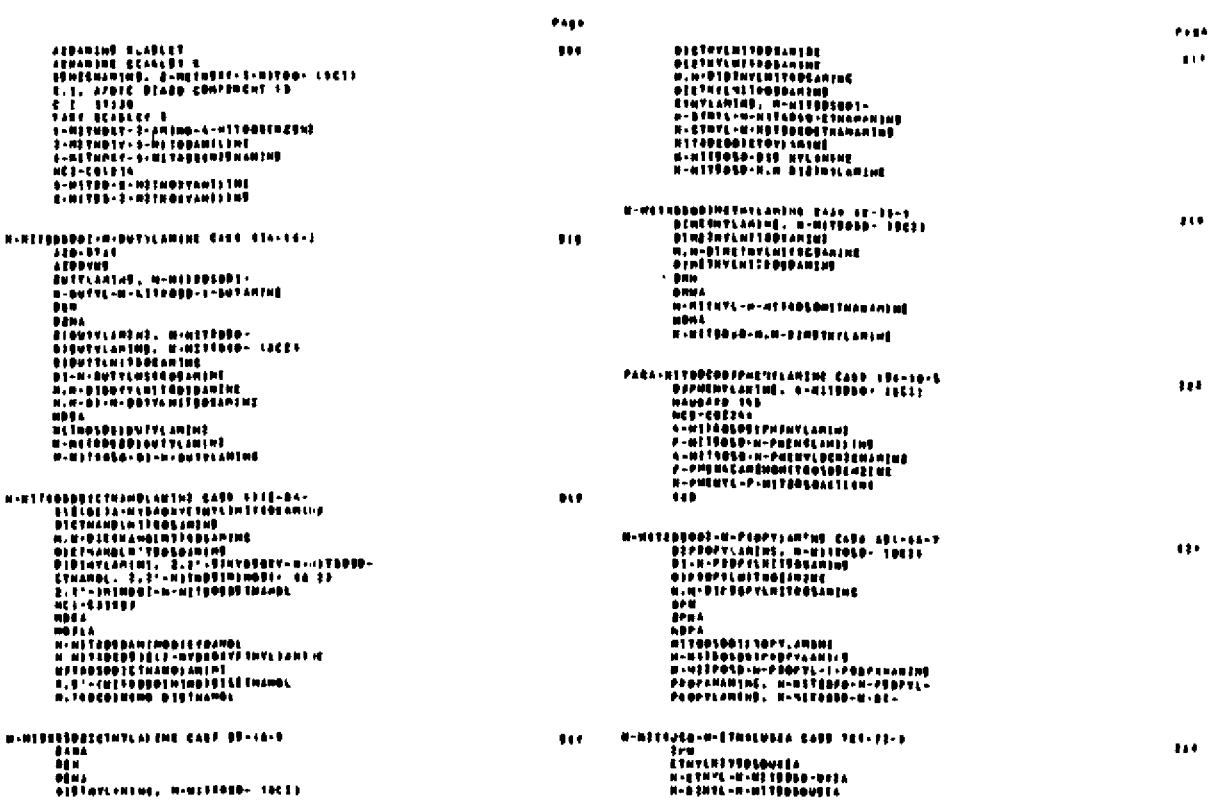

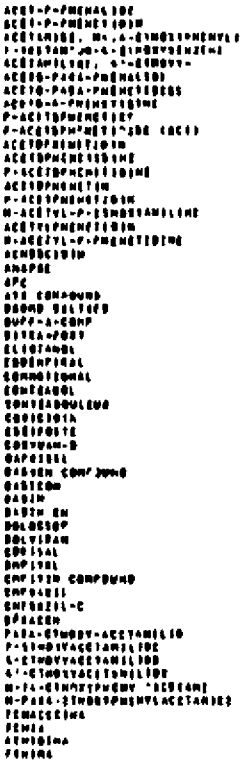

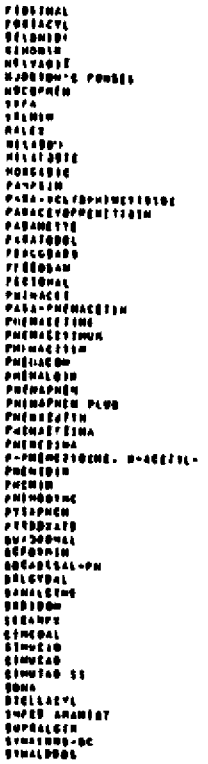

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TACDL
TEBUACYDIN
TEBUACYDIN
THIPHOSIM 4-S
TRIAPOL
VITAMIN2
VIDIN
WINTAIMS
ZADIL
ZACIDOIN COMPOUND

PHENACIDPYRIDINE HYDROCHLORIDE CAS# 133-40-3
AEDSINE
AIRATUM
AIR CANTAISIN
AZO BASIANGL
AZO-MAMDSLAMINE
AZO-STANDARD
AZURAIT
BARIDIUM
BISIDE A
CRYSTAMINE 'ACCLUMB'
CYSIGPYRIN
ETRIVOIL
GI-488
GINIDONE
DRONIL
HECTOTIN
SIDACSS
MALIDTECH
MALIDPHOMZ
MC 198
MCI-COLIZO
MSTHECIL
PAP
PDP
PHEMAID
PHINAZOOINE
PHENAZOPYRIDINIUM CHLORIDE
PHENYLSED
PHENYLAZE TABLETS
PHENYLAZOPYRIDINE HYDROCHLORIDE
PHENYL-IDIUM
PHENYL-IDIUM 200
PICID
PIRIDAGIL
PYRAZOSANZ
PYRAZOTICH
PYRSEAL
PYRIDACIL
PYRIDOMAL
PYRIDCAP
Pyridiaid
PYRIDIUP
PYRIDIVITE

PYRIPYRIDIUM
PIRIDIN
SIDURAL
SURIOYNG
TRIPOBULFIL-A PDISC
WARISUP
WORIONAL
WORLDS
WYOPIDIC-350
WYODIMA
WYOPICH
WYOMIOG
WYZPHENYL
WYOPYRIDIN
WYOPYRIMA
WYPOOAA
YERFIN
W 1500

PHENYTOIN SACD 57-41-0
ALEPSIN
ALSYDAZID
ALSYDATIN SODIUM
AMTILEPSIN
AMTISACID
AUTAMILE
CAMBOIN
DIPHULLANON
DIPHLEIAMON
EPHITAL
EPHITOINA
EPHYUL
DANTIN
DANTINAL
DANTOIN
DANTOINAL
DANTOINAL SLIMS
DANTOYNA
DEMYL
DI-HYDAN
DI-LAN
DI-LAN 2DANI
DI-PHETINE
DIDAN-ROC-EDU
DIFENEN
DIPTOIN
DIPHIDAN
DIHYDAN
DINTOANTOIN
DILAPID
D'LANTIN
DILANTIN 000INA
DILANTINE
DILLANTIN
DINTOIN

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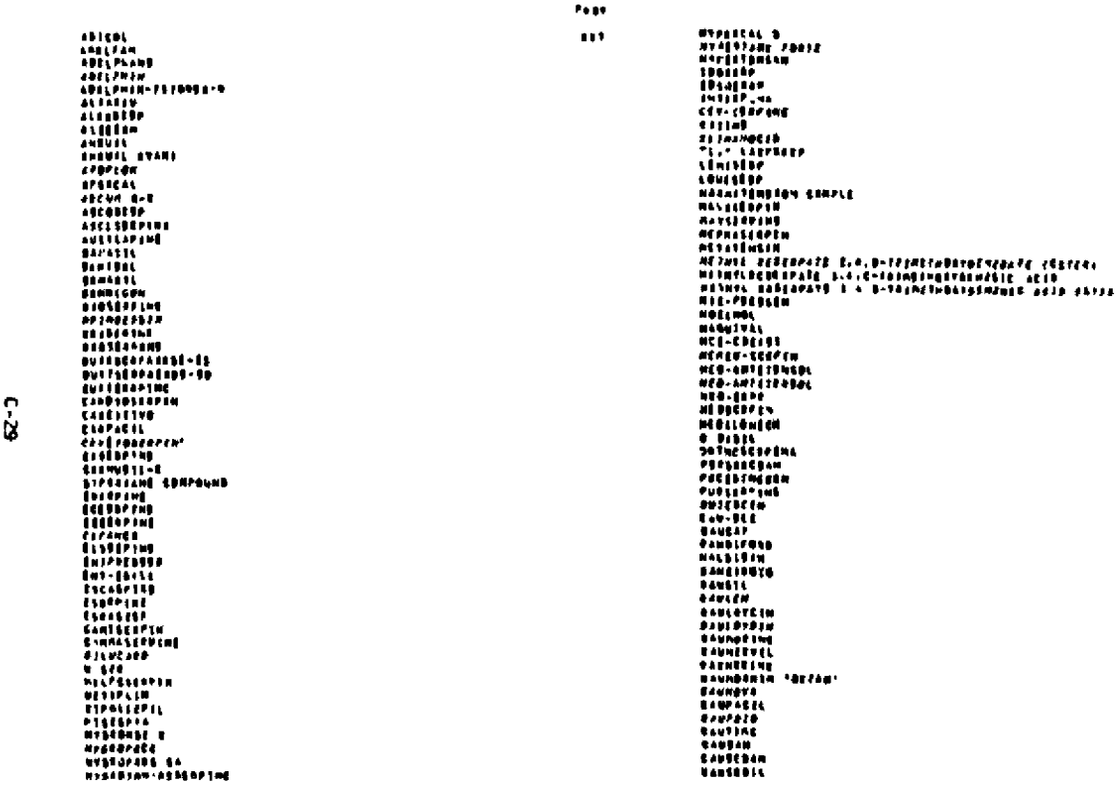

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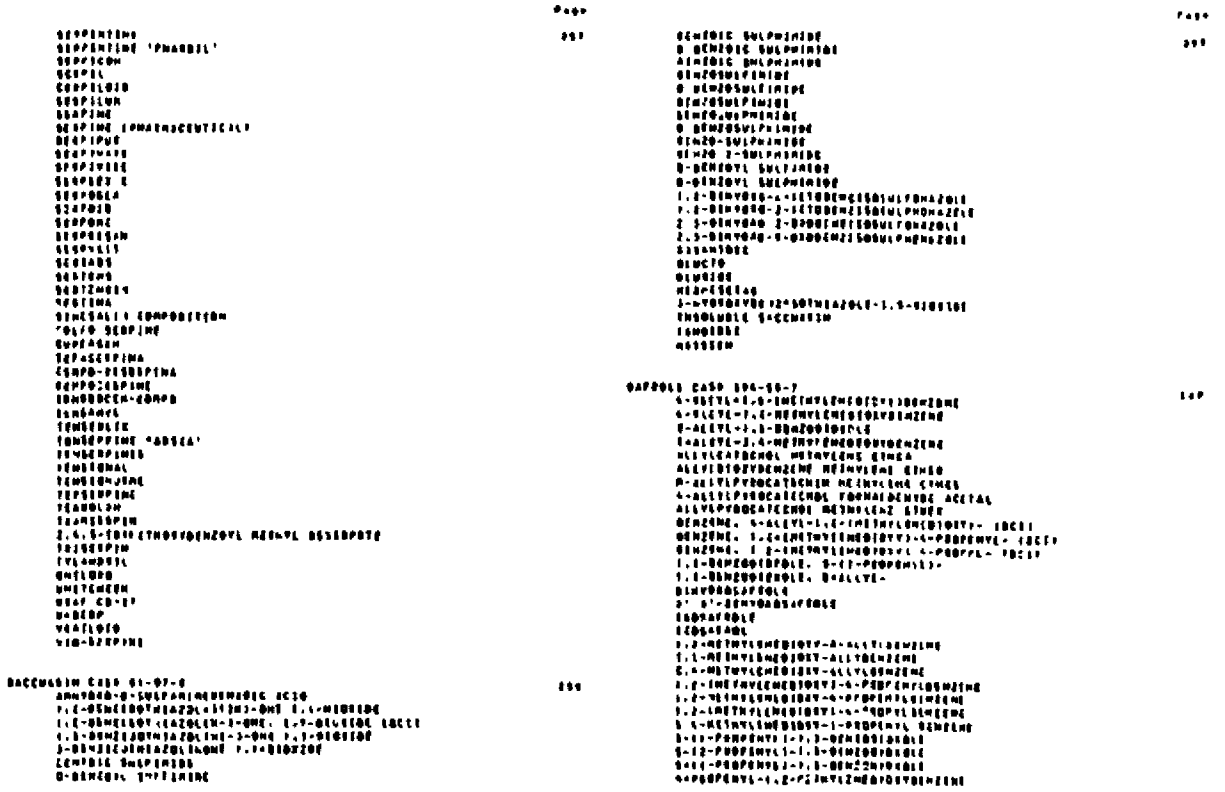

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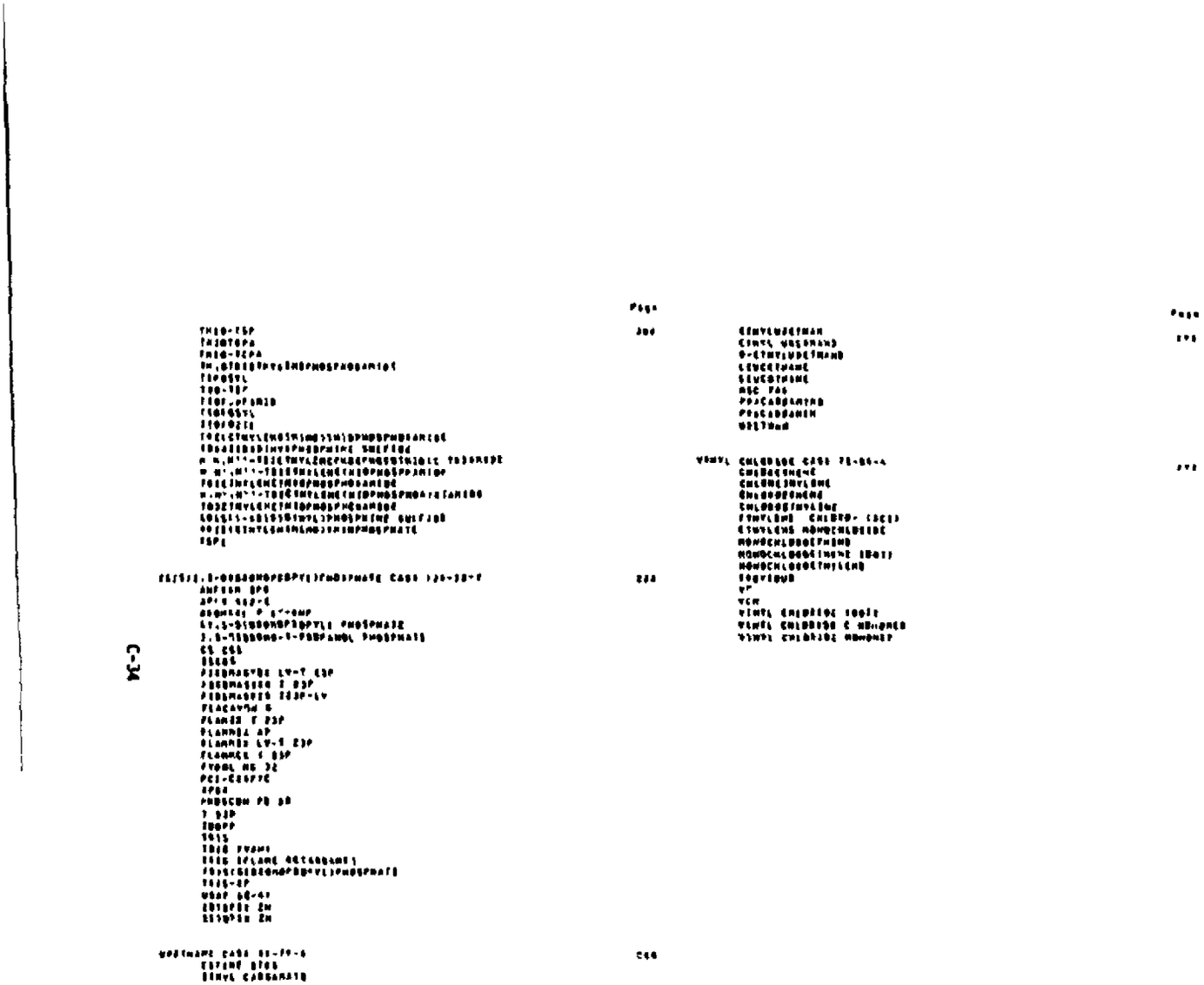

D. List of Participants

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Support to the National Toxicology Program for the preparation of the Third Annual Report on Carcinogens was provided by GEOMET Technologies, Inc., through NCI Contract Number NO1-CP-05616.

* Member, NTP Working Group for the Annual Reports on Carcinogens (NTP/WG ARC)

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• U.S. GOVERNMENT PRINTING OFFICE: 1983-381-111 3196

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