WORLD HEALTH ORGANIZATION

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS

ON THE

EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS

Polynuclear Aromatic Compounds, Part 2, Carbon Blacks, Mineral Oils and Some Nitroarenes

VOLUME 33

IARC, LYON, FRANCE
April 1984

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Polynuclear Aromatic Hydrocarbons, Part 2, Carbon Blacks, Mineral Oils (Lubricant Base Oils and Derived Products) and Some Nitroarenes

VOLUME 33

This publication represents the views and expert opinions of an IARC Working Group on the Evaluation of the Carcinogenic Risk of Chemicals to Humans which met in Lyon

7-14 June 1983

April 1984

INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC MONOGRAPHS

In 1971, the International Agency for Research on Cancer (IARC) initiated a programme on the evaluation of the carcinogenic risk of chemicals to humans involving the production of critically evaluated monographs on individual chemicals. In 1980, the programme was expanded to include the evaluation of the carcinogenic risk associated with employment in specific occupations.

The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for chemicals and complex mixtures to which humans are known to be exposed, and on specific occupational exposures, to evaluate these data in terms of human risk with the help of international working groups of experts in chemical carcinogenesis and related fields, and to indicate where additional research efforts are needed.

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Lyon, 7-14 June 1983

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NOTE TO THE READER

The term 'carcinogenic risk' in the *IARC Monographs* series is taken to mean the probability that exposure to the chemical will lead to cancer in humans.

Inclusion of a chemical in the monographs does not imply that it is a carcinogen, only that the published data have been examined. Equally, the fact that a chemical has not yet been evaluated in a monograph does not mean that it is not carcinogenic.

Anyone who is aware of published data that may alter the evaluation of the carcinogenic risk of a chemical to humans is encouraged to make this information available to the Unit of Carcinogen Identification and Evaluation, International Agency for Research on Cancer, 150 cours Albert Thomas, 69372 Lyon Cedex 08, France, in order that the chemical may be considered for re-evaluation by a future Working Group.

Although every effort is made to prepare the monographs as accurately as possible, mistakes may occur. Readers are requested to communicate any errors to the Unit of Carcinogen Identification and Evaluation, so that corrections can be reported in future volumes.

IARC MONOGRAPH PROGRAMME ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS[1]

PREAMBLE

1. BACKGROUND

In 1969, the International Agency for Research on Cancer (IARC) initiated a programme to evaluate the carcinogenic risk of chemicals to humans and to produce monographs on individual chemicals. Following the recommendations of an ad-hoc Working Group, which met in Lyon in 1979 to prepare criteria to select chemicals for *IARC Monographs*(1), the *Monographs* programme was expanded to include consideration of exposures to complex mixtures which occur, for example, in many occupations.

The criteria established in 1971 to evaluate carcinogenic risk to humans were adopted by all the working groups whose deliberations resulted in the first 16 volumes of the *IARC Monographs* series. This preamble reflects subsequent re-evaluation of those criteria by working groups which met in 1977(2), 1978(3), 1982(4) and 1983(5).

2. OBJECTIVE AND SCOPE

The objective of the programme is to elaborate and publish in the form of monographs critical reviews of data on carcinogenicity for chemicals, groups of chemicals and industrial processes to which humans are known to be exposed, to evaluate the data in terms of human risk with the help of international working groups of experts, and to indicate where additional research efforts are needed. These evaluations are intended to assist national and international authorities in formulating decisions concerning preventive measures. No recommendation is given concerning legislation, since this depends on risk-benefit evaluations, which seem best made by individual governments and/or other international agencies.

The *IARC Monographs* are recognized as an authoritative source of information on the carcinogenicity of environmental and other chemicals. A users' survey, made in 1976, indicated that the monographs are consulted routinely by various agencies in 24 countries. As of April 1984, 34 volumes of the *Monographs* had been published or were in press. Four supplements have been published: two summaries of evaluations of chemicals associated with human cancer, an evaluation of screening assays for carcinogens, and a cross index of synonyms and trade names of chemicals evaluated in the series(6).

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[1] This project is supported by PHS Grant No. 1 U01 CA33193-01 awarded by the US National Cancer Institute, Department of Health and Human Services.

3. SELECTION OF CHEMICALS AND COMPLEX EXPOSURES FOR MONOGRAPHS

The chemicals (natural and synthetic, including those which occur as mixtures and in manuaacturing processes) and complex exposures are selected for evaluation on the basis of two main criteria: (a) there is evidence of human exposure, and (b) there is some experimental evidence of carcinogenicity and/or there is some evidence or suspicion of a risk to humans. In certain instances, chemical analogues are also considered. The scientific literature is surveyed for published data relevant to the *Monographs* programme; and the IARC *Survey of Chemicals Being Tested for Carcinogenicity*(7) often indicates those chemicals that may be scheduled for future meetings.

As new data on chemicals for which monographs have already been prepared become available, re-evaluations are made at subsequent meetings, and revised monographs are published.

4. WORKING PROCEDURES

Approximately one year in advance of a meeting of a working group, a list of the substances to be considered is prepared by IARC staff in consultation with other experts. Subsequently, all relevant biological data are collected by IARC; recognized sources of information on chemical carcinogenesis and systems such as CANCERLINE, MEDLINE and TOXLINE are used in conjunction with US Public Health Service Publication No. 149(8) . The major collection of data and the preparation of first drafts for the sections on chemical and physical properties, on production and use, on occurrence, and on analysis are carried out by SRI International, Stanford, CA, USA, under a separate contract with the US National Cancer Institute. Most of the data so obtained refer to the USA and Japan; IARC supplements this information with that from other sources in Europe. Bibliographical sources for data on mutagenicity and teratogenicity are the Environmental Mutagen Information Center and the Environmental Teratology Information Center, both located at the Oak Ridge National Laboratory, TN, USA.

Six months before the meeting, reprints of articles containing relevant biological data are sent to an expert(s), or are used by IARC staff, to prepare first drafts of monographs. These drafts are then compiled by IARC staff and sent, prior to the meeting, to all participants of the Working Group for their comments.

The Working Group then meets in Lyon for seven to eight days to discuss and finalize the texts of the monographs and to formulate the evaluations. After the meeting, the master copy of each monograph is verified by consulting the original literature, then edited by a professional editor and prepared for reproduction. The aim is to publish monographs within nine months of the Working Group meeting. Each volume of monographs is printed in 4000 copies for distribution to governments, regulatory agencies and interested scientists. The monographs are also available *via* the WHO Distribution and Sales Service.

5. DATA FOR EVALUATIONS

With regard to biological data, only reports that have been published or accepted for publication are reviewed by the working groups, although a few exceptions have been made: in certain instances, reports from government agencies that have undergone peer review and

are widely available are considered. The monographs do not cite all of the literature on a particular chemical: only those data considered by the Working Group to be relevant to the evaluation of the carcinogenic risk of the chemical to humans are included.

Anyone who is aware of data that have been published or are in press which are relevant to the evaluations of the carcinogenic risk to humans of chemicals for which monographs have appeared is asked to make them available to the Unit of Carcinogen Identification and Evaluation, Division of Environmental Carcinogenesis, International Agency for Research on Cancer, Lyon, France.

6. THE WORKING GROUP

The tasks of the Working Group are five-fold: (a) to ascertain that all data have been collected; (b) to select the data relevant for evaluation; (c) to ensure that the summaries of the data enable the reader to follow the reasoning of the Working Group; (d) to judge the significance of the results of experimental and epidemiological studies; and (e) to make an evaluation of the carcinogenicity of the chemical.

Working Group participants who contributed to the consideration and evaluation of chemicals within a particular volume are listed, with their addresses, at the beginning of each publication. Each member serves as an individual scientist and not as a representative of any organization or government. In addition, observers are often invited from national and international agencies and industrial associations.

7. GENERAL PRINCIPLES APPLIED BY THE WORKING GROUP IN EVALUATING CARCINOGENIC RISK OF CHEMICALS

The widely accepted meaning of the term 'chemical carcinogenesis', and that used in these monographs, is the induction by chemicals of neoplasms that are not usually observed, the earlier induction of neoplasms that are commonly observed, and/or the induction of more neoplasms than are usually found - although fundamentally different mechanisms may be involved in these three situations. Etymologically, the term 'carcinogenesis' means the induction of cancer, that is, of malignant neoplasms; however, the commonly accepted meaning is the induction of various types of neoplasms or of a combination of malignant and benign tumours. In the monographs, the words 'tumour' and 'neoplasm' are used interchangeably. (In the scientific literature, the terms 'tumorigen', 'oncogen' and 'blastomogen' have all been used synonymously with 'carcinogen', although occasionally 'tumorigen' has been used specifically to denote a substance that induces benign tumours.)

(a) *Experimental Evidence*

(i) *Evidence for carcinogenicity in experimental animals*

The Working Group considers various aspects of the experimental evidence reported in the literature and formulates an evaluation of that evidence.

Qualitative aspects: Both the interpretation and evaluation of a particular study as well as the overall assessment of the carcinogenic activity of a chemical involve several considerations

of qualitative importance, including: (a) the experimental parameters under which the chemical was tested, including route of administration and exposure, species, strain, sex, age, etc.; (b) the consistency with which the chemical has been shown to be carcinogenic, e.g., in how many species and at which target organ(s); (c) the spectrum of neoplastic response, from benign neoplasm to multiple malignant tumours; (d) the stage of tumour formation in which a chemical may be involved: some chemicals act as complete carcinogens and have initiating and promoting activity, while others may have promoting activity only; and (e) the possible role of modifying factors.

There are problems not only of differential survival but of differential toxicity, which may be manifested by unequal growth and weight gain in treated and control animals. These complexities are also considered in the interpretation of data.

Many chemicals induce both benign and malignant tumours. Among chemicals that have been studied extensively, there are few instances in which the neoplasms induced are only benign. Benign tumours may represent a stage in the evolution of a malignant neoplasm or they may be 'end-points' that do not readily undergo transition to malignancy. If a substance is found to induce only benign tumours in experimental animals, it should nevertheless be suspected of being a carcinogen, and it requires further investigation.

Hormonal carcinogenesis: Hormonal carcinogenesis presents certain distinctive features: the chemicals involved occur both endogenously and exogenously; in many instances, long exposure is required; and tumours occur in the target tissue in association with a stimulation of non-neoplastic growth, although in some cases hormones promote the proliferation of tumour cells in a target organ. For hormones that occur in excessive amounts, for hormone-mimetic agents and for agents that cause hyperactivity or imbalance in the endocrine system, evaluative methods comparable with those used to identify chemical carcinogens may be required; particular emphasis must be laid on quantitative aspects and duration of exposure. Some chemical carcinogens have significant side effects on the endocrine system, which may also result in hormonal carcinogenesis. Synthetic hormones and anti-hormones can be expected to possess other pharmacological and toxicological actions in addition to those on the endocrine system, and in this respect they must be treated like any other chemical with regard to intrinsic carcinogenic potential.

Quantitative aspects: Dose-response studies are important in the evaluation of carcinogenesis: the confidence with which a carcinogenic effect can be established is strengthened by the observation of an increasing incidence of neoplasms with increasing exposure.

The assessment of carcinogenicity in animals is frequently complicated by recognized differences among the test animals (species, strain, sex, age) and route and schedule of administration; often, the target organs at which a cancer occurs and its histological type may vary with these parameters. Nevertheless, indices of carcinogenic potency in particular experimental systems (for instance, the dose-rate required under continuous exposure to halve the probability of the animals remaining tumourless(9)) have been formulated in the hope that, at least among categories of fairly similar agents, such indices may be of some predictive value in other species, including humans.

Chemical carcinogens share many common biological properties, which include metabolism to reactive (electrophilic(10-11)) intermediates capable of interacting with DNA. However, they may differ widely in the dose required to produce a given level of tumour induction. The reason for this variation in dose-response is not understood, but it may be due to differences in

metabolic activation and detoxification processes, in different DNA repair capacities among various organs and species or to the operation of qualitatively distinct mechanisms.

Statistical analysis of animal studies: It is possible that an animal may die prematurely from unrelated causes, so that tumours that would have arisen had the animal lived longer may not be observed; this possibility must be allowed for. Various analytical techniques have been developed which use the assumption of independence of competing risks to allow for the effects of intercurrent mortality on the final numbers of tumour-bearing animals in particular treatment groups.

For externally visible tumours and for neoplasms that cause death, methods such as Kaplan-Meier (i.e., 'life-table', 'product-limit' or 'actuarial') estimates(9), with associated significance tests(12,13), have been recommended. For internal neoplasms that are discovered 'incidentally'(12) at autopsy but that did not cause the death of the host, different estimates(14) and significance tests(12,13) may be necessary for the unbiased study of the numbers of tumour-bearing animals.

The design and statistical analysis of long-term carcinogenicity experiments were reviewed in Supplement 2 to the *Monographs* series(15). That review outlined the way in which the context of observation of a given tumour (fatal or incidental) could be included in an analysis yielding a single combined result. This method requires information on time to death for each animal and is therefore comparable to only a limited extent with analyses which include global proportions of tumour-bearing animals.

Evaluation of carcinogenicity studies in experimental animals: The evidence of carcinogenicity in experimental animals is assessed by the Working Group and judged to fall into one of four groups, defined as follows:

(1) *Sufficient evidence* of carcinogenicity is provided when there is an increased incidence of malignant tumours: (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 on dose-response effects.

(2) *Limited evidence* of carcinogenicity is available when the data suggest a carcinogenic effect but are limited because: (a) the studies involve a single species, strain or experiment; or (b) the experiments are restricted by inadequate dosage levels, inadequate duration of exposure to the agent, inadequate period of follow-up, poor survival, too few animals, or inadequate reporting; or (c) the neoplasms produced often occur spontaneously and, in the past, have been difficult to classify as malignant by histological criteria alone (e.g., lung adenomas and adenocarcinomas and liver tumours in certain strains of mice).

(3) *Inadequate evidence* is available when, because of major qualitative or quantitative limitations, the studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect.

(4) *No evidence* applies when several adequate studies are available which show that, within the limits of the tests used, the chemical is not carcinogenic.

It should be noted that the categories *sufficient evidence* and *limited evidence* refer only to the strength of the experimental evidence that these chemicals are carcinogenic and not to

the extent of their carcinogenic activity nor to the mechanism involved. The classification of any chemical may change as new information becomes available.

(ii) *Evidence for activity in short-term tests*[1]

Many short-term tests bearing on postulated mechanisms of carcinogenesis or on the properties of known carcinogens have been developed in recent years. The induction of cancer is thought to proceed by a series of steps, some of which have been distinguished experimentally (16-20). The first step - initiation - is thought to involve damage to DNA, resulting in heritable alterations in or rearrangements of genetic information. Most short-term tests in common use today are designed to evaluate the genetic activity of a substance. Data from these assays are useful for identifying potential carcinogenic hazards, in identifying active metabolites of known carcinogens in human or animal body fluids, and in helping to elucidate mechanisms of carcinogenesis. Short-term tests to detect agents with tumour-promoting activity, are at this time, insufficiently developed.

Because of the large number of short-term tests, it is difficult to establish rigid criteria for adequacy that would be applicable to all studies. General considerations relevant to all tests, however, include (a) that the test system be valid with respect to known animal carcinogens and noncarcinogens; (b) that the experimental parameters under which the chemical was tested include a sufficiently wide dose range and duration of exposure to the compound and an appropriate metabolic system; (c) that appropriate controls be used; and (d) that the purity of the compound tested be specified. Confidence in positive results is increased if a dose-response relationship is demonstrated and if this effect has been reported in two or more independent studies.

Most established short-term tests employ as end-points well-defined genetic markers in prokaryotes and lower eukaryotes and in mammalian cell lines. The tests can be grouped according to the end-point detected:

Tests of *DNA damage.* These include tests for covalent binding to DNA, induction of DNA breakage or repair, induction of prophage in bacteria and differential survival of DNA repair-proficient/-deficient strains of bacteria.

Tests of *mutation* (measurement of heritable alterations in phenotype and/or genotype). These include tests for detection of the loss or alteration of a gene product, and change of function through forward or reverse mutation, recombination and gene conversion; they may involve the nuclear genome, the mitochondrial genome and resident viral or plasmid genomes.

Tests of *chromosomal effects.* These include tests for detection of changes in chromosome number (aneuploidy), structural chromosomal aberrations, sister chromatid exchanges, micronuclei and dominant-lethal events. This classification does not imply that some chromosomal effects are not mutational events.

Tests for *cell transformation*, which monitor the production of preneoplastic or neoplastic cells in culture, are also of importance because they attempt to simulate essential steps in

[1] Based on the recommendations of a working group which met in 1983(5)

cellular carcinogenesis. These assays are not grouped with those listed above since the mechanisms by which chemicals induce cell transformation may not necessarily be the result of a genetic change.

The selection of specific tests and end-points for consideration remains flexible and should reflect the most advanced state of knowledge in this field.

The data from short-term tests are summarized by the Working Group and the test results tabulated according to the end-points detected and the biological complexities of the test systems. The format of the table used is shown below. In these tables, a '+' indicates that the compound was judged by the Working Group to be significantly positive in one or more assays for the specific end-point and level of biological complexity; '-' indicates that it was judged to be negative in one or more assays; and '?' indicates that there were contradictory results from different laboratories or in different biological systems, or that the result was judged to be equivocal. These judgements reflect the assessment by the Working Group of the quality of the data (including such factors as the purity of the test compound, problems of metabolic activation and appropriateness of the test system) and the relative significance of the component tests.

Overall assessment of data from short-term tests

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes				
Fungi/green plants				
Insects				
Mammalian cells (*in vitro*)				
Mammals (*in vivo*)				
Humans (*in vivo*)				

An overall assessment of the evidence for *genetic activity* is then made on the basis of the entries in the table, and the evidence is judged to fall into one of four categories, defined as follows:

(i) *Sufficient evidence* is provided by at least three positive entries, one of which must involve mammalian cells *in vitro* or *in vivo* and which must include at least two of three end-points - DNA damage, mutation and chromosomal effects.

(ii) *Limited evidence* is provided by at least two positive entries.

(iii) *Inadequate evidence* is available when there is only one positive entry or when there are too few data to permit an evaluation of an absence of genetic activity or when there are unexplained, inconsistent findings in different test systems.

(iv) *No evidence* applies when there are only negative entries; these must include entries for at least two end-points and two levels of biological complexity, one of which must involve mammalian cells *in vitro* or *in vivo*.

It is emphasized that the above definitions are operational, and that the assignment of a chemical into one of these categories is thus arbitrary.

In general, emphasis is placed on positive results; however, in view of the limitations of current knowledge about mechanisms of carcinogenesis, certain cautions should be respected: (i) At present, short-term tests should not be used by themselves to conclude whether or not an agent is carcinogenic, nor can they predict reliably the relative potencies of compounds as carcinogens in intact animals. (ii) Since the currently available tests do not detect all classes of agents that are active in the carcinogenic process (e.g., hormones), one must be cautious in utilizing these tests as the sole criterion for setting priorities in carcinogenesis research and in selecting compounds for animal bioassays. (iii) Negative results from short-term tests cannot be considered as evidence to rule out carcinogenicity, nor does lack of demonstrable genetic activity attribute an epigenetic or any other property to a substance (5).

(*b*) *Evaluation of Carcinogenicity in Humans*

Evidence of carcinogenicity can be derived from case reports, descriptive epidemiological studies and analytical epidemiological studies.

An analytical study that shows a positive association between an agent and a cancer may be interpreted as implying causality to a greater or lesser extent, on the basis of the following criteria: (a) There is no identifiable positive bias. (By 'positive bias' is meant the operation of factors in study design or execution that lead erroneously to a more strongly positive association between an agent and disease than in fact exists. Examples of positive bias include, in case-control studies, better documentation of exposure to the agent for cases than for controls, and, in cohort studies, the use of better means of detecting cancer in individuals exposed to the agent than in individuals not exposed.) (b) The possibility of positive confounding has been considered. (By 'positive confounding' is meant a situation in which the relationship between an agent and a disease is rendered more strongly positive than it truly is as a result of an association between that agent and another agent which either causes or prevents the disease. An example of positive confounding is the association between coffee consumption and lung cancer, which results from their joint association with cigarette smoking.) (c) The association is unlikely to be due to chance alone. (d) The association is strong. (e) There is a dose-response relationship.

In some instances, a single epidemiological study may be strongly indicative of a cause-effect relationship; however, the most convincing evidence of causality comes when several independent studies done under different circumstances result in 'positive' findings.

Analytical epidemiological studies that show no association between an agent and a cancer ('negative' studies) should be interpreted according to criteria analogous to those listed above: (a) there is no identifiable negative bias; (b) the possibility of negative confounding has been considered; and (c) the possible effects of misclassification of exposure or outcome have been weighed. In addition, it must be recognized that the probability that a given study can detect a certain effect is limited by its size. This can be perceived from the confidence limits around the estimate of association or relative risk. In a study regarded as 'negative', the upper confidence limit may indicate a relative risk substantially greater than unity; in that case, the study excludes only relative risks that are above the upper limit. This usually means that a 'negative' study must be large to be convincing. Confidence in a 'negative' result is increased when several independent studies carried out under different circumstances are in agreement. Finally, a 'negative' study may be considered to be relevant only to dose levels within or below the range of those observed in the study and is pertinent only if sufficient time has elapsed

since first human exposure to the agent. Experience with human cancers of known etiology suggests that the period from first exposure to a chemical carcinogen to development of clinically observed cancer is usually measured in decades and may be in excess of 30 years.

The evidence for carcinogenicity from studies in humans is assessed by the Working Group and judged to fall into one of four groups, defined as follows:

1. *Sufficient evidence* of carcinogenicity indicates that there is a causal relationship between the agent and human cancer.

2. *Limited evidence* of carcinogenicity indicates that a causal interpretation is credible, but that alternative explanations, such as chance, bias or confounding, could not adequately be excluded.

3. *Inadequate evidence*, which applies to both positive and negative evidence, indicates that one of two conditions prevailed: (a) there are few pertinent data; or (b) the available studies, while showing evidence of association, do not exclude chance, bias or confounding.

4. *No evidence* applies when several adequate studies are available which do not show evidence of carcinogenicity.

(c) *Relevance of Experimental Data to the Evaluation of Carcinogenic Risk to Humans*

Information compiled from the first 30 volumes of the *IARC Monographs*(4,21,22) shows that, of the chemicals or groups of chemicals now generally accepted to cause or probably to cause cancer in humans, all (with the possible exception of arsenic) of those that have been tested appropriately produce cancer in at least one animal species. For several of the chemicals (e.g., aflatoxins, 4-aminobiphenyl, diethylstilboestrol, melphalan, mustard gas and vinyl chloride), evidence of carcinogenicity in experimental animals preceded evidence obtained from epidemiological studies or case reports.

For many of the chemicals evaluated in the *IARC Monographs* for which there is *sufficient evidence* of carcinogenicity in animals, data relating to carcinogenicity for humans are either insufficient or nonexistent. **In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard chemicals for which there is sufficient evidence of carcinogenicity in animals as if they presented a carcinogenic risk to humans.** The use of the expressions 'for practical purposes' and 'as if they presented a carcinogenic risk' indicates that, at the present time, a correlation between carcinogenicity in animals and possible human risk cannot be made on a purely scientific basis, but only pragmatically. Such a pragmatical correlation may be useful to regulatory agencies in making decisions related to the primary prevention of cancer.

In the present state of knowledge, it would be difficult to define a predictable relationship between the dose (mg/kg bw per day) of a particular chemical required to produce cancer in test animals and the dose that would produce a similar incidence of cancer in humans. Some data, however, suggest that such a relationship may exist(23,24), at least for certain classes of carcinogenic chemicals, although no acceptable method is currently available for quantifying the possible errors that may be involved in such an extrapolation procedure.

8. EXPLANATORY NOTES ON THE MONOGRAPH CONTENTS

(a) *Chemical and Physical Data (Section 1)*

The Chemical Abstracts Services Registry Number, the latest Chemical Abstracts Primary Name (9th Collective Index)(25) and the IUPAC Systematic Name(26) are recorded in section 1. Other synonyms and trade names are given, but no comprehensive list is provided. Some of the trade names are those of mixtures in which the compound being evaluated is only one of the ingredients.

The structural and molecular formulae, molecular weight and chemical and physical properties are given. The properties listed refer to the pure substance, unless otherwise specified, and include, in particular, data that might be relevant to carcinogenicity (e.g., lipid solubility) and those that concern identification.

A separate description of the composition of technical products includes available information on impurities and formulated products.

(b) *Production, Use, Occurrence and Analysis (Section 2)*

The purpose of section 2 is to provide indications of the extent of past and present human exposure to the chemical.

(i) *Synthesis*

Since cancer is a delayed toxic effect, the dates of first synthesis and of first commercial production of the chemical are provided. This information allows a reasonable estimate to be made of the date before which no human exposure could have occurred. In addition, methods of synthesis used in past and present commercial production are described.

(ii) *Production*

Since Europe, Japan and the USA are reasonably representative industrialized areas of the world, most data on production, foreign trade and uses are obtained from those countries. It should not, however, be inferred that those areas or nations are the sole or even the major sources or users of any individual chemical.

Production and foreign trade data are obtained from both governmental and trade publications by chemical economists in the three geographical areas. In some cases, separate production data on organic chemicals manufactured in the USA are not available because their publication could disclose confidential information. In such cases, an indication of the minimum quantity produced can be inferred from the number of companies reporting commercial production. Each company is required to report on individual chemicals if the sales value or the weight of the annual production exceeds a specified minimum level. These levels vary for chemicals classified for different uses, e.g., medicinals and plastics; in fact, the minimal annual sales value is between $1000 and $50 000, and the minimal annual weight of production is between 450 and 22 700 kg. Data on production in some European countries are obtained by means of general questionnaires sent to companies thought to produce the compounds being evaluated. Information from the completed questionnaires is compiled, by country, and the resulting estimates of production are included in the individual monographs.

(iii) *Use*

Information on uses is meant to serve as a guide only and is not complete. It is usually obtained from published data but is often complemented by direct contact with manufacturers of the chemical. In the case of drugs, mention of their therapeutic uses does not necessarily represent current practice nor does it imply judgement as to their clinical efficacy.

Statements concerning regulations and standards (e.g., pesticide registrations, maximum levels permitted in foods, occupational standards and allowable limits) in specific countries are mentioned as examples only. They may not reflect the most recent situation, since such legislation is in a constant state of change; nor should it be taken to imply that other countries do not have similar regulations.

(iv) *Occurrence*

Information on the occurrence of a chemical in the environment is obtained from published data, including that derived from the monitoring and surveillance of levels of the chemical in occupational environments, air, water, soil, foods and tissues of animals and humans. When no published data are available to the Working Group, unpublished reports, deemed appropriate, may be considered. When available, data on the generation, persistence and bioaccumulation of a chemical are also included.

(v) *Analysis*

The purpose of the section on analysis is to give the reader an indication, rather than a complete review, of methods cited in the literature. No attempt is made to evaluate critically or to recommend any of the methods.

(c) Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans (Section 3)

In general, the data recorded in section 3 are summarized as given by the author; however, comments made by the Working Group on certain shortcomings of reporting, of statistical analysis or of experimental design are given in square brackets. The nature and extent of impurities/contaminants in the chemicals being tested are given when available.

(i) *Carcinogenicity studies in animals*

The monographs are not intended to cover all reported studies. Some studies are purposely omitted (a) because they are inadequate, as judged from previously described criteria(27-30) (e.g., too short a duration, too few animals, poor survival); (b) because they only confirm findings that have already been fully described; or (c) because they are judged irrelevant for the purpose of the evaluation. In certain cases, however, such studies are mentioned briefly, particularly when the information is considered to be a useful supplement to other reports or when it is the only data available. Their inclusion does not, however, imply acceptance of the adequacy of their experimental design or of the analysis and interpretation of their results.

Mention is made of all routes of administration by which the compound has been adequately tested and of all species in which relevant tests have been done(30). In most cases, animal strains are given. Quantitative data are given to indicate the order of magnitude of the effective carcinogenic doses. In general, the doses and schedules are indicated as they appear in the

original; sometimes units have been converted for easier comparison. Experiments in which the compound was administered in conjunction with known carcinogens and experiments on factors that modify the carcinogenic effect are also reported. Experiments on the carcinogenicity of known metabolites and derivatives are also included.

(ii) *Other relevant biological data*

LD50 data are given when available, and other data on toxicity are included when considered relevant.

Data on effects on reproduction, teratogenicity and feto- and embryotoxicity and on placental transfer, from studies in experimental animals and from observations in humans, are also included.

Information is given on absorption, distribution and excretion. Data on metabolism are usually restricted to studies that show the metabolic fate of the chemical in experimental animals and humans, and comparisons of data from animals and humans are made when possible.

Data from short-term tests are also included. In addition to the tests for genetic activity and cell transformation described previously (see pages 16-17), data from studies of related effects, but for which the relevance to the carcinogenic process is less well established, may also be mentioned.

The criteria used for considering short-term tests and for evaluating their results have been described (see pages 16-17). In general, the authors' results are given as reported. An assessment of the data by the Working Group which differs from that of the authors, and comments concerning aspects of the study that might affect its interpretation are given in square brackets. Reports of studies in which few or no experimental details are given, or in which the data on which a reported positive or negative result is based are not available for examination, are cited, but are identified as 'abstract' or 'details not given' and are not considered in the summary tables or in making the overall evaluation of genetic activity.

For several recent reviews on short-term tests, see IARC(30), Montesano *et al.*(31), de Serres and Ashby(32), Sugimura *et al.*(33), Bartsch *et al.*(34) and Hollstein *et al.*(35).

(iii) *Case reports and epidemiological studies of carcinogenicity to humans*

Observations in humans are summarized in this section. These include case reports, descriptive epidemiological studies (which correlate cancer incidence in space or time to exposure to an agent) and analytical epidemiological studies of the case-control or cohort type. In principle, a comprehensive coverage is made of observations in humans; however, reports are excluded when judged to be clearly not pertinent. This applies in particular to case reports, in which either the clinico-pathological description of the tumours or the exposure history, or both, are poorly described; and to published routine statistics, for example, of cancer mortality by occupational category, when the categories are so broadly defined as to contribute virtually no specific information on the possible relation between cancer occurrence and a given agent. Results of studies are assessed on the basis of the data and analyses that are presented in the published papers. Some additional analyses of the published data may be performed by the Working Group to gain better insight into the relation between cancer occurrence and

exposure to the agent under consideration. The Working Group may use these analyses in its assessment of the evidence or may actually include them in the text to summarize a study; in such cases, the results of the supplementary analyses are given in square brackets. Any comments by the Working Group are also reported in square brackets; however, these are kept to a minimum, being restricted to those instances in which it is felt that an important aspect of a study, directly impinging on its interpretation, should be brought to the attention of the reader.

(*d*) *Summary of Data Reported and Evaluation (Section 4)*

Section 4 summarizes the relevant data from animals and humans and gives the critical views of the Working Group on those data.

(i) *Experimental data*

Data relevant to the evaluation of the carcinogenicity of the chemical in animals are summarized in this section. The animal species mentioned are those in which the carcinogenicity of the substance was clearly demonstrated. Tumour sites are also indicated. If the substance has produced tumours after prenatal exposure or in single-dose experiments, this is indicated. Dose-response data are given when available.

Significant findings on effects on reproduction and prenatal toxicity, and results from short-term tests for genetic activity and cell transformation assays are summarized, and the latter are presented in tables. An evaluation is made of the degree of evidence for genetic activity in short-term tests.

(ii) *Human data*

Human exposure to the chemical is summarized on the basis of data on production, use and occurrence. Case reports and epidemiological studies that are considered to be pertinent to an assessment of human carcinogenicity are described. Other biological data that are considered to be relevant are also mentioned.

(iii) *Evaluation*

This section comprises evaluations by the Working Group of the degrees of evidence for carcinogenicity of the exposure to experimental animals and to humans. An overall evaluation is then made of the carcinogenic risk of the chemical, complex mixture or occupational exposure to humans. This section should be read in conjunction with pages 15 and 19 of this Preamble for definitions of degrees of evidence. When no data are available from epidemiological studies, but there is *sufficient evidence* that the exposure is carcinogenic to animals, a footnote is included, reading: 'In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard chemicals for which there is *sufficient evidence* of carcinogenicity in animals as if they presented a carcinogenic risk to humans.'

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   Volume 3 (1973) Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds (17 monographs), 271 pages

   Volume 4 (1974) Some Aromatic Amines, Hydrazine and Related Substances, *N*-Nitroso Compounds and Miscellaneous Alkylating Agents (28 monographs), 286 pages

   Volume 5 (1974) Some Organochlorine Pesticides (12 monographs), 241 pages

   Volume 6 (1974) Sex Hormones (15 monographs), 243 pages

   Volume 7 (1974) Some Anti-thyroid and Related Substances, Nitrofurans and Industrial Chemicals (23 monographs), 326 pages

   Volume 8 (1975) Some Aromatic Azo Compounds (32 monographs), 357 pages

   Volume 9 (1975) Some Aziridines, *N*-, *S*- and *O*-Mustards and Selenium (24 monographs), 268 pages

   Volume 10 (1976) Some Naturally Occurring Substances (22 monographs), 353 pages

   Volume 11 (1976) Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics (24 monographs), 306 pages

   Volume 12 (1976) Some Carbamates, Thiocarbamates and Carbazides (24 monographs), 282 pages

Volume 13 (1977) Some Miscellaneous Pharmaceutical Substances (17 monographs), 255 pages

Volume 14 (1977) Asbestos (1 monograph), 106 pages

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Volume 16 (1978) Some Aromatic Amines and Related Nitro Compounds - Hair Dyes, Colouring Agents, and Miscellaneous Industrial Chemicals (32 monographs), 400 pages

Volume 17 (1978) Some *N*-Nitroso Compounds (17 monographs), 365 pages

Volume 18 (1978) Polychlorinated Biphenyls and Polybrominated Biphenyls (2 monographs), 140 pages

Volume 19 (1979) Some Monomers, Plastics and Synthetic Elastomers, and Acrolein (17 monographs), 513 pages

Volume 20 (1979) Some Halogenated Hydrocarbons (25 monographs), 609 pages

Volume 21 (1979) Sex Hormones (II) (22 monographs), 583 pages

Volume 22 (1980) Some Non-Nutritive Sweetening Agents (2 monographs), 208 pages

Volume 23 (1980) Some Metals and Metallic Compounds (4 monographs), 438 pages

Volume 24 (1980) Some Pharmaceutical Drugs (16 monographs), 337 pages

Volume 25 (1981) Wood, Leather and Some Associated Industries (7 monographs), 412 pages

Volume 26 (1981) Some Antineoplastic and Immunosuppressive Agents (18 monographs), 411 pages

Volume 27 (1981) Some Aromatic Amines, Anthraquinones and Nitroso Compounds, and Inorganic Fluorides Used in Drinking-Water and Dental Preparations (18 monographs), 344 pages

Volume 28 (1982) The Rubber Manufacturing Industry (1 monograph), 486 pages

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GENERAL REMARKS ON THE SUBSTANCES CONSIDERED

In this thirty-third volume of *IARC Monographs*, carbon blacks, mineral oils and some nitroarenes are considered. It is the second of four volumes in which the carcinogenicity of polynuclear aromatic compounds and complex mixtures containing polynuclear aromatic compounds is evaluated. In February 1983, an IARC Working Group evaluated the available data on experimental carcinogenicity of 48 polynuclear aromatic compounds (IARC, 1983) (Table 1). In October 1983, a further working group considered some industrial situations in which exposure to polynuclear aromatic compounds occurs - aluminium production plants, coal gasification plants, coke-oven plants and iron and steel foundries. A group to meet in February 1984 will consider soots and some products of the processing of petroleum, coal and shale: bitumens (asphalts), coal tars and derived products (pitches and creosotes) and shale oils.

Table 1. Chemicals evaluated by an IARC Working Group in February 1983 (Volume 32 of the *IARC Monographs*)

Chemical	Degree of evidence of carcinogenicity for experimental animals
Anthanthrene	Limited
Anthracene	No evidence
Benz[*a*]acridine	Inadequate
Benz[*c*]acridine	Limited
Benz[*a*]anthracene	Sufficient
Benzo[*b*]fluoranthene	Sufficient
Benzo[*j*]fluoranthene	Sufficient
Benzo[*k*]fluoranthene	Sufficient
Benzo[*ghi*]fluoranthene	Inadequate
Benzo[*a*]fluorene	Inadequate
Benzo[*b*]fluorene	Inadequate
Benzo[*c*]fluorene	Inadequate
Benzo[*ghi*]perylene	Inadequate
Benzo[*c*]phenanthrene	Inadequate
Benzo[*a*]pyrene	Sufficient
Benzo[*e*]pyrene	Inadequate
Carbazole	Limited
Chrysene	Limited
Coronene	Inadequate
Cyclopenta[*cd*]pyrene	Limited
Dibenz[*a*,*h*]acridine	Sufficient
Dibenz[*a*,*j*]acridine	Sufficient
Dibenz[*a*,*c*]anthracene	Limited
Dibenz[*a*,*h*]anthracene	Sufficient
Dibenz[*a*,*j*]anthracene	Limited
7H-Dibenzo[*c*,*g*]carbazole	Sufficient

Chemical	Degree of evidence of carcinogenicity for experimental animals
Dibenzo[*a*,*e*]fluoranthene	Limited
Dibenzo[*a*,*e*]pyrene	Sufficient
Dibenzo[*a*,*h*]pyrene	Sufficient
Dibenzo[*a*,*i*]pyrene	Sufficient
Dibenzo[*a*,*l*]pyrene	Sufficient
1,4-Dimethylphenanthrene	Inadequate
Fluoranthene	No evidence
Fluorene	Inadequate
Indeno[1,2,3-*cd*]pyrene	Sufficient
5-Methylchrysene	Sufficient
2-, 3-, 4- and 6-Methylchrysenes	Limited
1-Methylchrysene	Inadequate
2-Methylfluoranthene	Limited
3-Methylfluoranthene	Inadequate
1-Methylphenanthrene	Inadequate
Perylene	Inadequate
Phenanthrene	Inadequate
Pyrene	No evidence
Triphenylene	Inadequate

The specific carcinogenic potential in experimental animals of individual polynuclear aromatic compounds was considered by the IARC Working Group in February 1983. Few epidemiological studies are available, however, since they are limited by the fact that humans are exposed to complex mixtures containing polynuclear aromatic compounds and not to individual compounds; in such cases, the detection of a carcinogenic risk due specifically to a certain chemical in a mixture can be particularly difficult, if at all possible. Nevertheless, epidemiological investigations can produce data on groups of individuals exposed to varying mixtures of polynuclear aromatic compounds under real exposure conditions. An added difficulty, however, is the frequent lack of information regarding factors such as other exposures at work sites or smoking, which might also pertain to morbidity either independently or by interacting with the exposure under investigation.

Carbon blacks are used mainly in the production of rubber. A small percentage is after-treated and used in printing inks, paints and plastics, and in photocopying toners. An issue of great importance for assessing the cancer risk of carbon blacks is whether or not the polynuclear aromatic compounds and other carcinogens adsorbed on them are bioavailable. This issue has been addressed in the introduction to section 3.1 of the monograph on carbon blacks.

Mineral oils, a group of petroleum-derived products, include lubricant base oils and derived products with widely different characteristics, depending on the crude source, the degree of refining and the additives present. In view of the complexity of mineral oils and the processes used to make them, the Working Group found it useful to adopt a scheme for classifying them. This classification is given in the monograph on mineral oils, p. 90. The published studies on biological effects are cited following this classification to aid in understanding the data.

Most of the epidemiological studies of exposure to mineral oils do not specify the nature of the oil, the presence or absence of additives or the composition of any impurities. Those occupations for which epidemiological data were considered include, primarily, mulespinners,

metal workers, printing pressmen and jute workers. Epidemiological studies of exposures during oil refining were not considered, but monographs on these and other exposures may be prepared in the future.

Newspaper printing pressmen have been exposed to ink mist consisting primarily of extracts that are by-products of solvent treatment of mineral oils, which are rich in polynuclear aromatic compounds and in which carbon blacks are also present.

Cutting fluids are used to reduce temperature and provide lubrication of metal surfaces during metal cutting and grinding operations. Various formulations are available to suit particular requirements. Carcinogenic *N*-nitrosamines have been found in emulsifiable, semi-synthetic, and water-based, synthetic, cutting fluids, resulting from reactions between nitrates and amines. They have not been found in straight oils (Spiegelhalder, 1980). The majority of reports on the presence of *N*-nitrosamines refer to the water-based synthetic products, which are not covered in these monographs as they do not contain any oil. *N*-Nitrosodiethanolamine has been reported at levels of 0-30 000 mg/l in concentrates (prior to dilution with water) of water-based synthetic cutting fluids. *N*-Nitrosomorpholine, *N*-nitrosodimethylamine and *N*-nitrosodibutylamine have also been identified in these products (Zingmark & Rappe, 1977; Loeppky *et al.*, 1980; Spiegelhalder, 1980).

The semisynthetic and synthetic products have been available commercially for only 10-15 years. They are known to produce dermatitis, but they were introduced too recently for epidemiological evaluation to be made of possible human carcinogenicity.

The Working Group noted that many published reports of animal studies on mineral oils lack adequate information on the nature, source and characterization of the test materials. It also noted that the bioassay protocols and the criteria used for diagnosing tumours induced are poorly described in many of these studies. Accurate definition of these parameters is particularly important in the evaluation of carcinogenesis of complex mixtures.

Six monographs were prepared on nitroarenes. These compounds are considered to be relatively stable thermally; and hey can undergo a variety of chemical reactions, including photochemical transformations. Nitroarenes occur in diesel exhaust particulates (exposures to diesel exhausts will be considered by a future IARC Working Group) and may also occur as trace contaminants in some after-treated carbon blacks.

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THE MONOGRAPHS

CARBON BLACKS

1. Chemical and Physical Data

1.1 Synonyms and trade names

Acetylene black

Chem. Abstr. Services Reg. No.: 1333-86-4

Chem. Abstr. Name: Carbon black, acetylene

IUPAC Systematic Name: Carbon black, acetylene

Synonyms: C.I. 77266; C.I. Pigment Black 7; explosion acetylene black; explosion black; thermal acetylene black

Trade Names: P68; P1250; Shawinigan Acetylene Black; Ucet

Channel black

Chem. Abstr. Services Reg. No.: 1333-86-4

Chem. Abstr. Name: Carbon black, channel

IUPAC Systematic Name: Carbon black, channel

Synonym: Impingement black

Trade Names: Aroflow; Arrow; Atlantic; Black Pearls; Carbolac; Carbomet; CK3; Collocarb; Conductex, Continental; Croflex; Crolac; Degussa; Dixie; Dixiecell; Dixiedensed; Elf; Excelsior; Farbruss; Fecto; Huber; Kosmink; Kosmobil; Kosmolak; Kosmos; Kosmovar; Micronex; Mogul; Monarch; Neo-Spectra; Peerless; Printex; Raven; Regent; Royal Spectra; Special Black IV & V; Spheron; Superba; Super-Carbovar; Super-Spectra; Texas; Triangle; United; Witco; Wyex

Furnace black

Chem. Abstr. Services Reg. No.: 1333-86-4

Chem. Abstr. Name: Carbon black, furnace

IUPAC Systematic Name: Carbon black, furnace

Synonyms: C.I. 77266; C.I. Pigment Black 7; gas-furnace black; oil-furnace black

Trade Names: Aro; Arogen; Aromex; Arovel; Arotone; Atlantic; Black Pearls; Carbodis; Collocarb; Conductex, Continex; Corax; Croflex; Dixie; Durex; Elftex; Essex; Furnal; Furnex; Gastex; Huber; Humenegro; Kosmos; Metanex; Modulex; Mogul; Molacco; Monarch; Neotex; Opal; Peerless; Pelletex; Philblack; Printex; Rebonex; Regal; Special Schwarz; Statex; Sterling; Texas; Ukarb; United; Vulcan

Lampblack

Chem. Abstr. Services Reg. No.: 1333-86-4

Chem. Abstr. Name: Carbon black, lamp

IUPAC Systematic Name: Carbon black, lamp

Synonyms: C.I. 77266; C.I. Pigment Black 6

Trade Names: Carbon Black BV and V; Durex; Eagle Germantown; Flamruss; Magecol; Tinolite; Torch Brand

Thermal black

Chemical Abstr. Services Reg. No.: 1333-86-4

Chem. Abstr. Name: Carbon black, thermal

IUPAC Systematic Name: Carbon black, thermal

Synonyms: C.I. 77266; C.I. Pigment Black 7; therma-atomic black

Trade Names: Atlantic; Cancarb; Croflex; Dixitherm; Huber; Kosmotherm; Miike 20; P-33; Sevacarb; Seval; Shell Carbon; Statex; Sterling; Thermatomic; Thermax; Thermblack; Velvetex

1.2 Description

Carbon blacks are sometimes confused with soots but they are widely different materials (Medalia *et al.*, 1981). Carbon blacks are powdered forms of elemental carbon manufactured by the controlled vapour phase pyrolysis of hydrocarbons. They have small particle sizes, high

surface areas per unit mass, quite low contents of ash and toluene-extractable materials and varying degrees of particle aggregation. A carbon black with a high degree of aggregation is said to have a high 'structure'. Structure is determined by the size and shape of the aggregated particles, the number of particles per aggregate and their average mass.

In contrast, soots are black materials of varying and often unknown composition, which are unwanted by-products of the incomplete combustion of any kind of carbon-containing material, such as waste oil, coal, paper, rubber, plastic, garbage, etc, or from fuel oil or gasoline. Soots have a low available carbon surface area owing to their large particle size and small carbon component. They contain quite large quantities of dichloromethane- and toluene-extractable materials, and their ash content can be over 50% (European Committee for Biological Effects of Carbon Black, 1982).

Acetylene black

Acetylene black is characterized by high purity, low oxygen content, and an extremely high degree of aggregation or structure. X-ray analysis indicates that acetylene blacks are the most crystalline or graphitic of the commercial blacks. Contents of ash and benzene extract are very low, and acetylene black is not readily wetted by water since the surface is saturated with hydrogen atoms.

Channel black

Channel blacks made in the past were characterized by small particle size, a low degree of aggregation or structure, and a relatively high content of oxygen complexes on their surface, as well as an acidic pH. Since natural gas was used as the feedstock and water was not required for quenching the reaction, they had a very low ash content. The volatile content of these channel blacks was about 5% but could be increased to as much as 17% by after-treatments. The surface of these channel blacks reportedly contained hydroxyl, carbonyl and carboxylic acid groups (Garret, 1973; Claassen, 1978).

Carbon blacks made in the Federal Republic of Germany by an impingement process from aromatic hydrocarbon-containing coal-tar residues and coke-oven gases are said to have similar properties to those of older channel blacks (Claassen, 1978).

Furnace black

Furnace blacks consist of irregularly shaped aggregate structures of spherical particles. They are now produced almost entirely by the oil-furnace process, which was preceded by the gas-furnace process. The gas-furnace blacks were characterized by low structure levels and properties that led to a low-to-medium reinforcing performance. Oil-furnace blacks have substantially higher aggregate structures and are now available with a wide range of characteristics depending on the desired product performance. The quality of furnace blacks is controlled by variations of the raw materials, operating temperatures and atmosphere turbulence, and by alteration of furnace design.

Lampblack

Lampblack is considered to be the forerunner of all carbon blacks. Essential and typical properties of lampblack are its high degree of aggregation or structure and low surface area.

Formerly, lampblacks were oily products sold in the fluffy state or partially compressed; however, recent grades are essentially oil-free and sold in pelleted form.

Thermal black

Thermal blacks exhibit the lowest surface area, the lowest degree of aggregation or structure, and the largest particle size of the commercial carbon blacks. They are also characterized by low oxygen content. They are virtually structureless, consisting of discrete spherical particles.

1.3 Chemical and physical properties

All commercially available carbon blacks are insoluble in water and organic solvents, but differ in other chemical and physical properties. The properties of four typical commercially available carbon blacks are summarized in Table 1.

Table 1. Typical ranges of properties for four types of carbon black pigment[a]

Property	Acetylene	Furnace	Lampblack	Thermal
Average particle diameter (nm)	35-50	17-70	50-100	150-500
Surface area, N_2[b] (m^2/g)	60-70	20-200	20-95[c] (17-25)[d]	6-15
Oil absorption (cm^3/g)	3.0-3.5	0.67-1.95	1.05-1.65	0.30-0.46
pH	5-7	5-9.5	3-7	7-8
Volatile matter (%)	0.4	0.3-2.8	0.4-9.0[c] (0.5-1.5)[d]	0.10-0.50
Hydrogen (%)	0.05-0.10	0.45-0.71	--	0.3-0.5
Oxygen (%)	0.10-0.15	0.19-1.2	--	0.00-0.12
Benzene extract (%)	0.1	0.01-0.18	0.00-0.14	0.02-1.7
Ash (%)	0.00	0.1-1.0	0.00-0.16	0.02-0.38
Sulphur (%)	0.02	0.05-1.5	--	0.00-0.25
Density (g/cm^3)	--	1.80	1.77[e]	--

[a] Data from Garret (1973), unless otherwise specified

[b] Surface area calculated by the nitrogen adsorption method

[c] Value in USA

[d] Value in Europe (data provided by European carbon black manufacturers)

[e] From Weast (1981)

1.4 Technical products and impurities

Analyses of samples of the four carbon blacks produced commercially in the USA and Europe are given in Table 2, and those of the three carbon black types produced in Japan are given in Table 3.

Table 2. Analyses of samples of the four carbon blacks produced commercially in the USA and Europe[a]

Property	Acetylene	Furnace (high abrasion)	Lamblack		Thermal	
			USA	Europe[b]	Medium	Fine
Average particle diameter (nm)	40	28	65	95	500	180
Surface area (BET)[c] (m^2/g)	65	75	22	20	47	13
DBPA[d] (ml/100 g)	250	103	130	115	36	33
Tinting strength[e] (%) SRF[f]	108	210	90	80	35	65
Benzene extract (%)	0.1	0.06	0.2	0.1	0.3	0.8
pH	4.8	7.5	3.0	7.0	8.5	9.0
Volatile material (%)	0.3	1.0	1.5	1.0	0.5	0.5
Ash (%)	0.0	0.4	0.02	0.05	0.3	0.1
Composition (%)						
carbon	99.7	97.9	98	98	99.3	99.2
hydrogen	0.1	0.4	0.2	0.4	0.3	0.5
sulphur	0.02	0.6	0.8	0.6	0.01	0.01
oxygen	0.2	0.7	0.8	0.4	0.1	0.3

[a] Property parameters and data from Dannenberg (1978), unless otherwise specified

[b] Data provided by European carbon black manufacturers

[c] BET, the Brunauer, Emmett and Teller procedure for calculating surface area

[d] DBPA, the dibutyl phthalate absorption method, a standard procedure for measuring void volume, a characteristic related to structure

[e] A measure of particle size or 'the ability of a carbon black to hide a white pigment such as zinc oxide' (from Garret, 1973)

[f] SRF, semi-reinforcing furnace (from Garret, 1973)

Table 3. Typical analyses of three types of carbon black commercially available in Japan

Property	Acetylene	Furnace	Thermal
Average particle diameter (nm)	40	21	90
Iodine adsorption (mg/g)[a]	105	119	26
DBPA[b] (ml/100 g)	125	115	27
pH	7.5	7.7	8.5
Volatile material (%)	0.2	1.4	0.5
Ash (%)	0.1	0.25	0.4

[a] Iodine adsorption is reported as the milligrams of iodine adsorbed per gram of carbon black under specified conditions established by the American Society for Testing and Materials (American Society for Testing and Materials, 1983) and has been used to approximate the surface area of carbon blacks (Johnson & Eberline, 1978)

[b] DBPA, the dibutyl phthalate absorption method, a standard procedure for measuring void volume, a characteristic related to structure

Acetylene black

Acetylene black available in the USA contains a minimum of 99.5% carbon and has an average particle size of 30 nm (Gulf Oil Chemicals Company, 1982).

Typical analyses of the acetylene black made by the manufacturer in the Federal Republic of Germany are as follows: particle diameter (arithmetic mean), approximately 35 nm; surface area (calculated by the procedure of Brunauer, Emmett and Teller), approximately 70 m^2/g; pH, 7; volatile matter, 0.05% maximum; ash, 0.05% maximum; benzene extract, 0.05% maximum; carbon, 99.8% minimum; hydrogen, oxygen and nitrogen, 0.05% maximum for each; and sulphur, 0.005% maximum (Hoechst Aktiengesellschaft, 1979).

Channel black

This black, when manufactured, was available as a dry chemical in either powder or pelleted form. Three types were available for reinforcing rubber - easy, medium and hard processing. These varied slightly in particle diameter, that with the largest particle diameter (approximately 29 nm) being known as easy-processing channel (EPC) and that with the smallest (approximately 22 nm) as hard-processing channel (HPC). The average diameters of the channel blacks used for colour and ink applications were as shown in Table 4.

Table 4. Average diameters of channel blacks used in colours and inks

Channel black	Symbol	Average diameter (nm)
High-colour channel	HCC	12
Medium-colour channel	MCC	16
Regular colour channel	RCC	25
Medium-flow channel	MFC	25
Long-flow channel	LFC	25

The MFC and LFC blacks received an after-treatment with hot air to increase their volatile contents and thereby the 'flow' of the lithographic inks in which they were used.

It was reported in 1952 that no polynuclear aromatic compound could be eluted from channel blacks with benzene (Falk & Steiner, 1952a). However, a combination of gas chromatography and mass spectroscopy was used in 1978 to analyse the material obtained by Soxhlet extraction of two highly oxidized channel blacks using benzene and naphthalene as extractants. Several compounds were identified in mg/kg quantities with both the benzene extractant - 1-nitronaphthalene (10.0), 9-fluorenone (8.1), phenanthrene/anthracene (7.6), anthraquinone (3.0) and 1,8-naphthalenedicarboxylic anhydride (8.4) - and the naphthalene extractant - 9-fluorenone (1.0), anthraquinone (7.7), xanthone (1.8), 1,8-naphthalenedicarboxylic anhydride (29.4), 9,10-phenanthrenequinone (6.9), and several binaphthyls and dinaphthofurans that were probably formed by reaction of naphthalene with impurities or surface groups of the carbon blacks. In addition, low concentrations of several ketones, quinones, anhydrides and nitro derivatives of polynuclear aromatic hydrocarbons were found (Fitch *et al.*, 1978).

Fitch and Smith (1979) reported the results of Soxhlet extraction of seven channel black grades with benzene/methanol for 20 hours and subsequent analysis by gas chromatography/mass spectroscopy. Two carbon black grades had no detectable extract. Phenanthrene concentrations in the range of 12-470 mg/kg and 1,8-naphthalenedicarboxylic anhydride concentrations in the range of 62-161 mg/kg were found in the extracts of the other five channel blacks. The following compounds were identified in at least two extracts: dibenzofuran (11-190 mg/kg), 1-nitronaphthalene (15-46 mg/kg), 9-fluorenone (21-218 mg/kg) and anthraquinone (23-63 mg/kg). The channel blacks strongly adsorbed benzo[*a*]pyrene, and presumably

other polynuclear aromatic hydrocarbons as well. The oxidized hydrocarbons appeared to be more readily extracted. There seemed to be a shift to more oxidized polynuclear aromatic hydrocarbons with increasing carbon oxidation, and the authors suggested that the nitro aromatics probably resulted from nitration of adsorbed polynuclear aromatic hydrocarbons during the oxidative after-treatment with nitric acid.

According to the results of Cole and Sanders as reported by Rivin and Smith (1982), the Soxhlet toluene extracts from two channel blacks contained the following polynuclear aromatic hydrocarbons: fluoranthene (0.24 and 0.5 mg/kg), pyrene (0.34 and 0.26 mg/kg), benzo[*a*]pyrene (0.12 and 0.11 mg/kg), benzo[*e*]pyrene (0.14 and 0.19 mg/kg), indeno[1,2,3-*cd*]pyrene (<0.03 and 0.08 mg/kg), benzo[*ghi*]perylene (0.66 and 0.53 mg/kg) and coronene (0.55 and 0.44 mg/kg).

Furnace black

Furnace blacks are available in a wide variety of grades. Those used in rubber products have been classified by the American Society for Testing and Materials (ASTM) according to a standard four-character nomenclature system. In this system, the letter N indicates that the product gives a normal curing rate, while the letter S indicates that it reduces the rate of cure. The first digit is used to designate the typical average particle size (e.g., 1 indicates 11-19 nm and 9 indicates 201-500 nm), and the last two digits are assigned arbitrarily.

Table 5 provides the ASTM designations for furnace blacks used in rubber, a description of their types, the symbols used to designate the types, as well as typical data on three measures of surface area (iodine adsorption, cetyl trimethyl ammonium bromide (CTAB) adsorption and nitrogen adsorption), on one measure of the degree of aggregation (dibutyl phthalate absorption (DBPA)), and on one rough measure of particle size (tinting strength). Table 6 provides similar information for furnace blacks used in inks, paints and plastics.

Table 5. Typical properties of currently available furnace blacks for rubber[a,b]

ASTM designation	Type of black[c]	Symbol	Iodine adsorption No. D 1510[f] (g/kg)	CTAB[d] D 3765[f] (m^2/g)	Nitrogen adsorption D 3037[f] (m^2/g)	DPBA[e] No. D 2414[f] (cm^3/100 g)	Tinting strength D 3265[f]
N110	Super-abrasion furnace	SAF	145	126	143	113	124
N121	Super-abrasion[g] furnace, high structure	SAF-HS	120	121	132	130	121
S212	Intermediate[h] super-abrasion furnace, low structure, slow cure	--	117[i]	119	117	86	115
N219	Intermediate super-abrasion furnace, low structure	ISAF-LS	118	107	116	78	123
N220	Intermediate super-abrasion furnace	ISAF	121	111	119	114	115
N231	Intermediate super-abrasion furnace, low modulus	ISAF-LM	125	108	117	91	117
N234	Improved intermediate super-abrasion furnace, high structure	--	118	119	126	125	124

ASTM designation	Type of black[c]	Symbol	Iodine adsorption No. D 1510[f] (g/kg)	CTAB[d] D 3765[f] (m^2/g)	Nitrogen adsorption D 3037[f] (m^2/g)	DPBA[e] No. D 2414[f] (cm^3/100 g)	Tinting strength D 3265[f]
N242	Intermediate super-abrasion furnace, high structure	ISAF-HS	123	111	125	126	116
N293	Conductive furnace	CF	145	114	130	100	117
N299	Unspecified furnace	--	108	104	108	124	113
S315	High-abrasion furnace, low structure, slow curing	HAF-LS-SC	86[i]	95	88	79	--
N326	High-abrasion furnace, low structure	HAF-LS	82	83	84	71	112
N330	High-abrasion furnace	HAF	82	83	83	102	103
N332	Improved high[j]-abrasion furnace	--	84	--	--	102	118
N339	Improved high[h]-abrasion furnace, high structure	--	90	95	96	120	110
N341	Unspecified furnace[j]	--	67	72	73	112	100
N347	High-abrasion furnace, high structure	HAF-HS	90	88	90	124	103
N351	Unspecified furnace[j]	--	67	74	73	120	100
N356	Super-processing furnace, high structure	SPF-HS	90	93	90	160	104
N358	Super-processing furnace	SPF	84	88	87	150	99
N375	Improved high-abrasion furnace	--	90	98	100	114	115
N472	Extra-conductive furnace	ECF or XCF[f]	270	145	270	178	--
N539	Fast-extruding[h] furnace, low structure	FEF-LS	42	41	41	109	--
N550	Fast-extruding furnace	FEF	43	42	42	121	--
N568	Fast-extruding furnace, high structure	FEF-HS	45	41	41	132	--
N630	General-purpose furnace, low structure	GPF-LS	36	38	38	78	--
N642	General-purpose furnace, very low structure	--	36	37	37	64	--
N650	General-purpose[g] furnace, high structure	GPF-HS	36	38	38	125	--
N660	General-purpose furnace	GPF	36	35	35	91	--
N683	All-purpose furnace	APF	30	39	37	132	--
N754	Semi-reinforcing[j] furnace, low structure	SRF-LS	25	29	-	58	--
N762	Semi-reinforcing furnace, low modulus	SRF-LM	26	29	28	62	--
N765	Semi-reinforcing furnace, high structure	SRF-HS	31	33	31	111	--

ASTM designation	Type of black[c]	Symbol	Iodine adsorption No. D 1510[f] (g/kg)	CTAB[d] D 3765[f] (m^2/g)	Nitrogen adsorption D 3037[f] (m^2/g)	DPBA[e] No. D 2414[f] ($cm^3/100$ g)	Tinting strength D 3265[f]
N774	Semi-reinforcing furnace, high modulus	SRF-HM	27	29	29	70	--
N785	Medium-processing furnace	MPF	25	36	-	126	--
N787	Semi-reinforcing[j] furnace, high modulus	SRF-HM	31	32	30	81	--

[a] The values given are often averages of typical values supplied by several manufacturers

[b] From American Society for Testing and Materials (1983), unless otherwise specified

[c] From Garret (1973)

[d] CTAB, cetyl trimethyl ammonium bromide measurement of surface area

[e] DBPA, dibutyl phthalate absorption

[f] ASTM standard methods of test for the various properties

[g] From Dannenberg (1978)

[h] From Ford & Lyon (1973)

[i] Gaseous adsorption surface area

[j] From Smith (1982)

Table 6. Typical properties of furnace process carbon blacks for inks, paints and plastics[a]

Furnace black	Nigrometer index[b]	Surface area (BET)[c] (m^2/g)	Particle size (nm)	Oil (DBPA)[d] (ml/100 g) (pellets)	Tinting strength index	Volatile content (%)	Toluene extract (%)
High-colour							
HCF-1	64	560	13	105	100	9.5	0.08
HCF-2	65	240	14	50	115	2.0	0.08
HCF-3	69	230	15	65	120	2.0	0.08
Medium-colour							
MCF-1	74	220	16	110	122	1.5	0.08
MCF-2	74	210	17	68	120	1.5	0.08
MCF-3	78	200	18	117	118	1.0	0.08
Long-flow	83	138	24	55	112	5.0	0.10
Medium-flow	84	96	25	70	112	2.5	0.10
Conductive	87	254	30	178	82	2.0	0.10
Regular-colour							
RCF-1	84	140	19	114	114	1.5	0.10
RCF-2	83	112	24	60	116	1.0	0.10
RCF-3	83	86	25		112	1.0	0.30
RCF-4	84	94	25	70	110	1.0	0.10
RCF-5	87	80	27	72	104	1.0	0.10
RCF-6	90	46	36	60	92	1.0	0.10
RCF-6A	90	85	27		100	1.0	0.10
RCF-7	93	45	37		73	1.0	0.10
Low-colour							
LCF-1	94	30	60	64	59	1.0	0.10
LCF-2	95	42	41	120	61	1.0	0.10
LCF-3	96	35	50	91	49	1.0	0.10
LCF-4	99	25	75	70	49	1.0	0.10

[a] From Dannenberg (1978)

[b] A method for measuring the diffuse reflectance from a black paste with a black tile standard. The low numbers represent the jettest or most intense black grades

[c] As calculated by the Brunauer, Emmett and Teller (BET) procedure

[d] DBPA, dibutyl phthalate absorption

A very small percentage of the total quantity of furnace blacks is subjected to after-treatment by various oxidation processes for particular applications.

Falk and Steiner (1952a) studied the polynuclear aromatic hydrocarbon (PAH) content of 17 brands of commercial furnace blacks by ultraviolet spectrophotometry of benzene extracts. In one sample no PAH was found, but in most of the samples the following seven PAHs were found: anthanthrene, benzo[*ghi*]perylene, benzo[*a*]pyrene, benzo[*e*]pyrene, coronene, fluoranthene and pyrene. Gabor *et al.* (1969) found benzo[*a*]pyrene and chrysene at average concentrations of 80 mg/kg and 28 mg/kg, respectively, in one furnace carbon black sample.

In a study using thin-layer chromatographic methods to separate the individual PAHs, Soxhlet benzene extracts from ten samples of different types of furnace blacks were analysed. These extracts were found to be free of anthracene, benz[*a*]anthracene, chrysene, dibenz[*a,h*]anthracene and methylated PAHs by methods reported to be capable of detecting 10 μg/kg. Specific PAHs that were found included benzo[*a*]pyrene (at 0.8-6.7 mg/kg by weight) and cyclopenta[*cd*]pyrene (Renes, 1975).

In a study of the PAH and neutral polar components of the 100-hour dichloromethane Soxhlet extract of an oil-furnace black (not further identified), the PAH fraction was found to contain acenaphthylene, benzo[*ghi*]fluoranthene, cyclopenta[*cd*]pyrene, fluoranthene, naphthalene, phenanthrene and pyrene. The neutral polar compounds included an unidentified anhydride, 6*H*-benzo[*cd*]pyren-6-one, 4*H*-cyclopenta[*def*]phenanthren-4-one and phenalenone (Gold, 1975).

One commercial grade of furnace black (N339 oil-furnace black) was found to contain 23 mg/kg benzo[*a*]pyrene and 92 mg/kg coronene; and another (N774 oil-furnace black) contained trace amounts of phenols (0.6 mg/kg), lead (2.7 mg/kg), antimony, arsenic, barium, bismuth, chromium, molybdenum, selenium, thallium and vanadium (less than 0.5 mg/kg), and beryllium, cadmium, cobalt, cyanides and mercury (less than 0.05 mg/kg) (Collyer, 1975).

A study was made (Lee & Hites, 1976) of the PAHs and sulphur-containing polycyclic compounds in furnace blacks. Three of the four commercial products studied had been produced from aromatic feedstocks containing a considerable amount of organic sulphur (1.2-3.1%). Soxhlet dichloromethane extraction gave 0.01-0.2% PAHs; gas chromatography and mass spectrophotometry permitted the identification of 28 compounds, seven of which were polycyclic compounds of the benzothiophene type.

In a study of five types of furnace black used in tyre manufacture, it was found that 250 hours of extraction with hot benzene were necessary to obtain exhaustive extraction of the PAHs present (Table 7) (95% extraction was obtained after 150 hours). The extractables after 250 hours constituted from 252-1417 mg/kg (mean values) of carbon black. When dry carbon black was injected directly into the mass spectrograph, no PAH was detected (Locati *et al.*, 1979).

Table 7. Polynuclear aromatic hydrocarbons in benzene extracts of furnace blacks after 150-250 hours of extraction[a]

Polynuclear aromatic hydrocarbon	Amount (mg/kg)
Anthanthrene	< 0.5 - 108
Benzacridine derivative	< 0.5
Benzo[*def*]dibenzothiophene + benzo[*e*]acenaphthylene	< 0.5
Benzofluoranthenes (total)	< 0.5 - 17
Benzo[*ghi*]fluoranthene	20 - 161
Benzo[*ghi*]perylene	23 - 336
Benzopyrenes (total)	2 - 40
Cyclopenta[*cd*]pyrene	< 0.5 - 264
Coronene and isomer	13 - 366
Dimethylcyclopentapyrene and/or dimethylbenzofluoranthene	2 - 57
Fluoranthene	10 - 100
Indeno[1,2,3-*cd*]pyrene	1 - 59
Phenanthrene and/or anthracene	< 0.5 - 5
Pyrene	46 - 432

[a] From Locati *et al.* (1979)

Taylor *et al.* (1980), using toluene to extract adsorbates on five rubber-grade oil-furnace blacks, found the percentages of total extractables and benzo[*a*]pyrene concentrations shown in Table 8.

Table 8. Benzo[*a*]pyrene concentrations in toluene extracts of five furnace blacks[a]

ASTM[b] designation	Surface area (m^2/g)	Total extract (mg/kg)	Benzo[*a*]pyrene concentration (mg/kg)
N220	118	330	0.55
N234	128	830	1.64
N339	90	860	1.50
N351	70	970	5.06
N375	101	1320	3.15

[a] From Taylor *et al.* (1980)

[b] American Society for Testing and Materials

A long-flow furnace black used as a component of one photocopy toner was shown to contain nitropyrenes among other impurities. The occurrence of nitropyrenes in this carbon black (which was first used in photocopy toner in 1967) appears plausible, since the method of manufacture for this carbon black involves an oxidation-nitration step. Although high-performance liquid chromatography indicated the presence of more than 50 compounds in the toluene extracts of this carbon black, only very low concentrations of PAHs were found. Benzo[*a*]pyrene, said to be present typically at about 1 mg/kg in ordinary carbon black, was found at only 0.001 mg/kg. The concentration of pyrene, said to be usually a major component of such extracts, was 0.06 mg/kg. Changes in the production technique of this carbon black reduced the total extractable nitropyrene content from an uncontrolled 5-100 mg/kg to below 0.3 mg/kg (Rosenkranz *et al.*, 1980; Sanders, 1981; Butler *et al.*, 1983). Toners produced using this carbon black after 1980 have contained no detectable levels of mutagenicity and, hence, of nitropyrenes (Rosenkranz *et al.*, 1980; Butler *et al.*, 1983).

Soxhlet toluene extraction of a pre-1979 production lot of a furnace black that had been after-treated by an oxidation-nitration process gave an extract that was 0.3% of the carbon weight (considerably higher than most furnace black extracts). Reverse-phase high-performance liquid chromatography revealed that it was an unusual carbon black extract in that the characteristic PAHs (benzo[*ghi*]perylene, coronene and pyrene) were almost absent. The extract contained 1,8-dinitropyrene 23.4 mg/kg, 1,6-dinitropyrene 21.0 mg/kg, 1,3,6-trinitropyrene 13.4 mg/kg, 1,3-dinitropyrene 6.3 mg/kg and 1-nitropyrene 2.9 mg/kg. In a 1980 production lot of the carbon black (presumably made by a different process), the content of 1,8- plus 1,6-dinitropyrenes was less than 2 mg/kg (Sanders, 1981).

When a sample of a commercial furnace black (not produced since 1980) was subjected to Soxhlet extraction with toluene (Ramdahl & Urdal, 1982), the following nitro compounds were identified in the extracted materials, using a gas chromatography/mass spectroscopic method sensitive to a detection limit of 1 pg: 1,3-dinitropyrene, 1,6-dinitropyrene, 1,8-dinitropyrene, 9-nitroanthracene, nitrocyclopenta[*cd*]pyrene or other isomer, 1- and 2-nitrophthalene, 1-nitropyrene, 1,3,6-trinitropyrene, an unknown dinitro compound and three unknown mononitro compounds.

Lampblack

Lampblack is available as a dry pigment and as a paste in oil. The American Society for Testing and Materials (ASTM) specifications for the dry pigment are: 3.0% maximum moisture and other volatile matter; 2.0% maximum acetone extract; 1.0% maximum ash; and 1.0% maximum coarse particles (residue on a No. 325 sieve). It must give a clear blue-grey tone when diluted with zinc oxide. Specifications for the paste in oil are 25% minimum pigment; 75% maximum linseed oil; 1.0% maximum coarse particles (residue on a No. 325 sieve); and 0.7% maximum moisture and other volatile matter. The colour and tone as well as the tinting strength must be equal to that of a reference sample (American Society for Testing and Materials, 1978).

No information was available on the specifications for lampblack used in rubber processing (the major use for lampblack).

A sample of commercial lampblack subjected to Soxhlet extraction with benzene or naphthalene had the following properties: particle size 44 nm; pH 7; and content: 96.7% carbon, 1.5% sulphur, 0.9% oxygen, 0.6% hydrogen, and 0.0% nitrogen. The following compounds were identified in the extracted materials: benzo[*def*]dibenzothiophene, benzo[*ghi*]fluoranthene, benzo[*j* or *k*]fluoranthene, benzo[*ghi*]perylene/anthanthrene, 6-*H*-benzo[*cd*]pyren-6-one[1], coronene, 4-*H*-cyclopenta[*def*]phenanthren-4-one[1], cyclopenta[*cd*]pyrene, fluoranthene, indeno-[1,2,3-*cd*]pyrene, a naphtho[*def*]dibenzothiophene[1], 1,8-naphthalenedicarboxylic anhydride, perylene/benzo[*a*]pyrene, phenanthrene/anthracene, pyrene, a sulphur-bridged hexacyclic compound[1] and a sulphur-bridged pentacyclyclic compound[1] (Fitch *et al.*, 1978).

[1] Identification is tentative.

Thermal black

Thermal black is available in several grades. Table 9 provides information on the American Society for Testing and Materials (ASTM) classification of these compounds, according to the system described above for *Furnace black*.

Table 9. American Society for Testing and Materials (ASTM) standard grades of thermal black[a]

ASTM designation	Type of black	Symbol	Iodine adsorption No., D 1510[c] (g/kg)	CTAB[b] adsorption D 3765[c] (m^2/g)	Nitrogen adsorption D 3037[c] (m^2/g)
N907	Medium thermal, non-staining, free flowing	MT-NS-FF	--	--	11
N908	Medium thermal, non-staining	MT-NS	--	--	--
N990	Medium thermal, free flowing	MT-FF	--	9	9
N991	Medium thermal	MT	10	8	7

[a] From Dannenberg (1978) and American Society for Testing and Materials (1982)

[b] CTAB, cetyl trimethyl ammonium bromide

[c] ASTM standard methods of test for the various properties

One thermal carbon black sample had the following average concentrations: benzo[*a*]pyrene 345 mg/kg, dibenz[*a,h*]anthracene 331 mg/kg, chrysene 510 mg/kg and benzo[*j*]fluoranthene 1200 mg/kg (Gabor *et al.*, 1969). Analysis of an N990-type medium thermal black by an unspecified extraction procedure showed the presence of benzo[*a*]pyrene at a concentration of 192 mg/kg and coronene at 472 mg/kg (Collyer, 1975). Total Soxhlet benzene extract (24 hours) of an N990-type thermal black was 0.4% of the carbon weight. The individual PAHs found included: benzo[*ghi*]perylene, 1217 mg/kg; coronene, 800 mg/kg; pyrene, 603 mg/kg; anthanthrene, 299 mg/kg; fluoranthene, 197 mg/kg; benzo[*a*]pyrene, 186 mg/kg; and benzo[*e*]pyrene, 145 mg/kg (De Wiest, 1980).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

Carbon blacks - General

The early Chinese and Hindus employed a simple lampblack process to produce the black used in their inks and lacquers. Developments of the lampblack process supplied the needs of the pigmenting industry until the channel process was established on the basis of the natural-gas fields of the USA in 1872. At that time, annual world consumption of carbon blacks was less than 1 million kg. Consumption increased rapidly following the discovery in 1904 of its usefulness in the reinforcement of rubber; and the needs of the growing world rubber industry were met by supplies of channel black and lampblack from the USA. In 1922, the gas-furnace process was introduced in the USA. The increasing cost of natural gas led to a switch to the oil-furnace process in the early 1940s, and to the final closure of channel black

manufacture in the USA in 1976. Since oil feedstock is readily transported, the oil-furnace process could be located close to the consuming industry; and the period following the end of the Second World War has seen the establishment of carbon black manufacture in many industrialized countries (Table 10).

Table 10. Carbon black manufacturing locations

North America	
	Canada, USA
South and Central America	
	Argentina, Brazil, Colombia, Mexico, Peru, Venezuela
Western Europe	
	Federal Republic of Germany, France, Italy, The Netherlands, Spain, Sweden, United Kingdom
Eastern Europe	
	Poland, Romania, USSR, Yugoslavia
Middle East	
	Iran, Israel, Turkey
Africa	
	South Africa
Australia and South-East Asia	
	Australia, India, Indonesia, Japan, Malaysia, Philippines, Republic of Korea, Taiwan, Thailand

A total of about 90 plants produce carbon blacks in countries other than those of the COMECON. The annual capacity of a single furnace black plant is normally in the range of 20-150 million kg, whereas lampblack plants are smaller and many have annual capacities as low as 1 million kg. An estimated 40% is manufactured in the USA, 30% in western Europe and 15% in Japan.

Acetylene black

The dissociation of acetylene into carbon and hydrogen was known as early as 1861, and the first commercial process was based on partial combustion of acetylene (Bean, 1964). Subsequently, a process based on explosion by an electric arc was developed in Germany. The process in current use, continuous thermal decomposition, is covered by a series of patents going back to 1938 (Bean, 1964; Claassen, 1978), and was reported in 1964 to have been in commercial use for some years in continental Europe, Asia and Canada (Bean, 1964).

In the continuous thermal decomposition process for acetylene black, the reaction is initiated by burning the acetylene feedstock with a controlled amount of air. When the reaction temperature is sufficiently high (e.g., 800°C), the air supply is shut off, oxidation ceases, and an exothermic self-sustained dissociation of acetylene to form hydrogen and acetylene black occurs at temperatures up to 1000°C.

Acetylene black was first made commercially in the Federal Republic of Germany in 1928. In Canada, a plant using the continuous thermal decomposition process started operation in the 1930s. A US plant started in 1964 and was subsequently closed, but a similar plant was started up in Puerto Rico. In 1979, another plant was started in the USA, which replaced the Canadian plant. It was first produced commercially in Japan in 1942.

No data are available on the quantity of acetylene black produced in the USA in recent years. However, the two US plants are estimated to have had annual production capacities of 3.6 and 9 million kg in 1981. Canadian production of acetylene black in 1963 has been reported to have been 9 million kg (Burgess *et al.*, 1965). It is believed to be produced by one company in France (annual capacity 12 million kg) and one company in the Federal Republic of Germany (annual capacity 10 million kg). Total production by the two Japanese manufacturers in 1981 is estimated to have been 20 million kg, and acetylene black is believed to have comprised a significant part of both imports (estimated at 10 million kg) and exports (estimated at 11 million kg) of all carbon blacks by Japan in that year.

Channel black

The channel process for making carbon blacks was first used commercially in the USA in 1872. However, rising natural gas prices, smoke-pollution, low yield and the rapid development of the furnace-process grades of carbon black have been cited as reasons for abandonment of this process in 1976 (Dannenberg, 1978).

In the channel or impingement process, small natural-gas flames were impinged on channel irons that collected the deposited carbon blacks (Garret, 1973). This process gave only very low yields (5%); however, a plant making carbon blacks by an impingement process in the Federal Republic of Germany is reported to give yields of above 60%, using coal-tar residues containing naphthalene or anthracene as the carbon-black feedstock. The molten material is evaporated by a stream of hot coke-oven gas and heated to about 370°C prior to reaching the burners. The flames are directed to revolving water-cooled pipes, and the formed carbon blacks are continuously scraped from the pipes. For the production of finer-particle blacks for use as pigments, the amount of oil carried by the gas is decreased and the vapours to the burner are diluted with air (Claassen, 1978).

The channel process was the most important method for making carbon blacks in the past. US production reached a peak of 307 million kg in 1948; but it had fallen to 132 million kg by 1960 and showed a steady decline until production stopped in 1976. The quantity of carbon blacks made by the manufacturer in the Federal Republic of Germany using the impingement process is believed to constitute less than 1% of total world production of carbon blacks.

Furnace black

The gas-furnace process for making carbon blacks was first introduced in the USA in 1922, and the oil-furnace process in 1943 (Garret, 1973). The gas-furnace process, which is based on the partial combustion of natural gas, was carried out using refractory-lined retorts or furnaces at a temperature of 1200-1500°C. This process was characterized by low yields of carbon blacks and has not been used in the USA since the 1960s (Dannenberg, 1978). In the oil-furnace process, which now is used to produce about 97% of total world production, a heavy aromatic feedstock from a petroleum refinery or petrochemical operation is injected by atomization into a high-velocity stream of combustion gases produced by the complete burning

of an auxiliary fuel (such as natural gas) with excess air. Although some of the feedstock is burned at 1200-1700°C, most is converted to hydrogen and carbon black with high yields. Downstream, the reaction gases are cooled by spraying with water. The carbon black particles are then separated from the gases, densified and pelletized. A very small percentage of furnace black is subjected to after-treatment by various oxidation processes, some of which have involved nitration.

In late 1981, seven US companies were manufacturing furnace blacks at a total of 24 plants, with a combined production capacity of approximately 1500 million kg per year. Estimated US production levels for the major types of furnace black in 1980 are given in Table 11. Separate data on US imports of furnace black are not available; however, total imports of all carbon blacks amounted to 16 million kg in 1982, over 75% of which came from Canada, 19% from Mexico, and 3% from the Federal Republic of Germany (US Bureau of the Census, 1983a). Total US exports of all carbon blacks amounted to 34.1 million kg in 1982 - over 25% to Canada, 16% to Japan, and 9% to Mexico (US Bureau of the Census, 1983b).

Table 11. Estimated US production levels for the major types of furnace black in 1980

ASTM[a] designation	Type	Production (million kg)
N330	High abrasion (HAF)	483
N660	General purpose (GPF)	269
N220	Intermediate super abrasion (ISAF)	137
N762	Semi-reinforcing (SRF)	133
N550	Fast extruding (FEF)	114
N110	Super abrasion (SAF)	19
	Total	1155

[a] ASTM, American Society for Testing and Materials

Furnace black is believed to be produced by three companies in France (total annual capacity, 236 million kg), four companies in the Federal Republic of Germany (395 million kg), three companies in Italy (175 million kg), two companies in the Netherlands (110 million kg), three companies in Spain (91 million kg), one company in Sweden (33 million kg), and two companies in the United Kingdom (approximately 200 million kg).

Furnace black was first produced commercially in Japan around 1950. Total production by the seven Japanese manufacturers in 1981 is estimated to have been 529 million kg in 1981; little was imported but it probably represented a significant part of the exports of all carbon blacks (estimated at 11 million kg).

Lampblack

Lampblack was first produced commercially in the USA in the 1840s (Patterson, 1980). It is made principally by burning aromatic petroleum oils and coal-tar products such as creosote and anthracene oils in open, shallow pans using a restricted air supply (Smith, 1964), at lower temperatures than other carbon black processes. The lampblack is separated from the tail gas, densified and pelletized.

Separate data are not available on the quantity of lampblack produced in the USA in recent years. However, total combined US production of bone black and lampblack in 1977 amounted to 6.04 million kg, up from 1.14 million kg in 1972 (US Bureau of the Census, 1980), most of which was lampblack. The two US lampblack plants are estimated to have had annual production capacities of 5 million kg and less than 1 million kg, respectively, in 1981. US imports of lampblack in 1982 totalled 311 thousand kg (US Bureau of the Census, 1983a), and total combined exports of bone black and lampblack amounted to 4.26 million kg (US Bureau of the Census, 1983b), most of which was lampblack.

Lampblack is produced on a small scale in the Federal Republic of Germany and the United Kingdom; total production is believed to constitute less than 1% of total world production of carbon black.

Lampblack is not produced in Japan.

Thermal black

In the thermal process, a chamber filled with chequered brickwork is heated to about 1300°C by injecting a burning mixture of gas and air. When the required temperature has been reached, the flow of burning gas is stopped and the hydrocarbon feedstock (usually gas) is injected. Contact with the hot bricks causes the feedstock to crack, forming carbon black and hydrogen. This process is run cyclically using two chambers, one being heated while the other is producing carbon black. In one plant in the United Kingdom, medium thermal black is produced from oil rather than natural gas as the raw material (Johnson & Eberline, 1978).

US production of thermal black in 1976 amounted to 70 million kg (US Bureau of Mines, 1977), and that in 1980 is estimated to have been 53 million kg. Separate data on US imports of thermal black are not available; however, total US imports in 1982 of all carbon blacks amounted to 16 million kg, over 75% of which came from Canada, 19% from Mexico, and 3% from the Federal Republic of Germany (US Bureau of the Census, 1983a). Total US exports of all carbon blacks in 1982 amounted to 34.1 million, over 25% of which went to Canada, 16% to Japan and 9% to Mexico (US Bureau of the Census, 1983b).

One company in Canada, one in the Federal Republic of Germany and one in the United Kingdom are believed to produce thermal black. It was first produced commercially in Japan around 1950; production by the only Japanese manufacturer in 1981 is estimated to have been 7 million kg.

Total production of thermal black is estimated to be about 2% of total carbon black production in North America, western Europe and Japan.

(*b*) *Use*

Information on the quantities of carbon blacks used in various applications is very seldom presented so as to provide separate data on the individual types of carbon black. However, it can be inferred that the major use is of furnace black, since this is the predominant item of commerce, and that thermal black follows furnace black in a distant second place; minor quantities of the other three carbon blacks are used in highly specialized applications.

Carbon blacks are powerful black pigments, but their principal industrial use today is based on their ability to reinforce natural and synthetic rubbers. (See IARC, 1982, for a description

of the rubber manufacturing processes in which carbon blacks are used.) Addition of carbon blacks in quantities in the range 10-150 parts per 100 parts by weight of rubber polymer results in very marked improvements in the properties of vulcanized rubbers, particularly in resistance to abrasion, tear strength, tensile strength, stiffness and hardness. Addition of carbon blacks in these proportions also changes the properties of rubbers in the unvulcanized condition, so improving handling and shaping in the manufacture of all types of rubber products. Carbon blacks are unique in their ability to reinforce rubber. The world rubber industry is thus dependent on the use of carbon blacks.

The most important product of the rubber industry is the pneumatic tyre, and this represents the single largest application of carbon blacks: For every 100 parts by weight of rubber used in the manufacture of a tyre, there are about 60 parts by weight of carbon blacks. Since tyres also contain steel and textile materials, carbon blacks represent about 25% of the total weight of a finished pneumatic tyre.

For more than a thousand years before the discovery in 1904 of their reinforcing effect in rubber, carbon blacks had been used as pigments. Today, pigmenting represents less than 10% of the total usage - in inks, paints, lacquers, cements, paper, coatings and in plastics, where they are also used as ultraviolet absorbers.

Annual usage of carbon blacks in countries other than those of the COMECON is estimated to be about 4 thousand million kg, about 97% of which is furnace black. The approximate percentage usage of carbon blacks is as follows: rubber - tyres, 65; rubber - non-tyres, 25; ink, paint, plastics, 9; others (e.g., paper), 1.

Many of the non-tyre applications of carbon blacks in rubber are also for the automotive industry - for example, hoses, weatherstrip, sponge seals, engine mountings. Overall, about 80% of total carbon black consumption is for automotive applications.

In 1980, the estimated use pattern for all carbon blacks in the USA was: 61% for automotive tyres, tubes and treads; 18% for non-automotive rubber products; 12% for automotive belts, hose and miscellaneous products; and 9% for non-rubber uses. The estimated quantities used in the major end-use markets were: 1056 million kg in elastomers; 36 million kg in printing ink; 34 million kg in plastics; 8 million kg in paint; 1 million kg in paper; and 25 million kg in other uses.

Western European carbon black consumption in 1980 was an estimated 931 million kg. Approximately 60% was used in tyres, 30% in other non-tyre rubber uses, and 10% in miscellaneous applications. The major countries using carbon blacks were: France (25% of the total); the Federal Republic of Germany (19%); Italy and the United Kingdom (16% each); and Spain (10%).

Total use of all carbon blacks in Japan in 1981 is estimated to have been approximately 550 million kg. An estimated 73% was used in automotive tyres, 22% in other rubber products, and 5% in non-rubber uses (e.g., paint, paper, plastics and batteries).

Acetylene black

Acetylene black is used primarily because of its high liquid absorption properties and its high thermal and electrical conductivity, in the construction of dry-cell batteries and in the production of conductive rubber and plastic products. Because of its ability to soak up large

quantities of electrolyte, acetylene black imparts greater capacity, longer shelf life, and lower resistance to dry cells than any other filler. In rubber products, acetylene black provides high modulus and good thermal and electrical conductivity. Its electrical conductivity properties are used in the manufacture of resistors and thermal insulators and its antistatic properties are used in aircraft tyres, belt drives, cable sheathing, conductive tapes, conveyor belts, heater pads and panels, hoses, and shoe soles. In plastic products, acetylene black is used for its antistatic properties in cable sheathing, conductive coatings, flooring materials (e.g., for operating rooms) and heat-cured adhesives. Miscellaneous uses for acetylene black include applications in catalysts (as a carrier), clothing, electronic and electrical equipment, greases, inks, lubricants, metallic carbides, polishing powders, and television picture tubes (Bean, 1964; Union Carbide Corp., 1964; Claassen, 1978; Gulf Oil Chemicals Company, 1982).

In western Europe, an estimated 95% of acetylene black is used for dry-cell batteries and the remainder in rubber and plastics. In Japan, acetylene black is used principally in the construction of dry-cell batteries.

Channel black

Channel black was used for both rubber reinforcing and as a pigment. In rubber reinforcing, it was reported to yield products with high tensile strength, high elongation and high tear resistance. The complete absence of oily material made it a nonbleeding pigment when a black rubber stock was used adjacent to a light-coloured stock. The smaller particle-size channel blacks used as pigments gave high colour intensity when used in paint, ink and plastics. The carbon blacks made by the impingement process in the Federal Republic of Germany reportedly also find use in rubber reinforcing and pigment applications (Claassen, 1978).

Furnace black

Approximately 98% of the carbon black used in the rubber industry is produced by the furnace process, and furnace black is also used in printing inks, plastics and paints. For these different purposes, a wide variety of specially tailored grades possessing the necessary properties are available (for example, different grades are used in tyre sidewalls than in tyre treads).

In rubber applications, furnace black is used in proportions ranging from 10 to 150% of the weight of the elastomer, depending upon the performance requirements. It contributes to reinforcement and to resistance to tear, abrasion, flex and fatigue, as well as improving the processing characteristics of many elastomers. The major use is in the manufacture of tyres, retread rubber and inner tubes. Other automotive elastomer uses include belts, hose, motor mounts, O-rings and wire and cable covers. Non-automotive elastomer uses include coated fabrics, conveyor belts, floor mats, footwear, gaskets, gloves, hard rubber products, hose, packaging, pontoons, toys and wire and cable covers.

The estimated use pattern for all carbon blacks (principally furnace black) in the USA in 1980 in printing-inks was: 50% for newspaper inks, 16% for lithographic/offset inks, 11% each for gravure and letterpress inks, and 6% each for flexographic and other inks (e.g., typewriter ribbon inks). It is also used as a colourant in alkyd and acrylic enamels, industrial finishes, lacquers and a variety of other paints.

Furnace black is used in plastics principally for the following purposes: antistatic agent, colourant, filler (sometimes to impart strength), ultraviolet light stabilizer, and as an additive

to increase or decrease electrical conductivity. End uses include appliances, automotive accessories, extrusion and calendered coatings, film, housewares, phonograph records, pipe and conduit, and wire and cable.

The quantities of all carbon blacks (principally furnace black) used in other applications in the USA in 1980 are as follows: paper (e.g., for album, letterboard, wrapping and bag papers, backing paper for photographic film, and highly conductive and electrosensitive papers), 1 million kg; carbon paper, 7 million kg; dispersions (e.g., as a colourant in paints, plastics, water colours and other products), 7 million kg; magnetic tape, 1 million kg; photocopy toners, 1 million kg; electric motor brushes, 1 million kg; and other miscellaneous uses (including adhesives, cement, ceramics, electronics, mortar, textiles and other uses), 3 million kg.

Four producers manufactured about 18 million kg of after-treated carbon blacks by various processes in 1982. This amount represents 0.5% of the 3500 million kg of carbon black produced in the USA, western Europe and Japan. More than half of this quantity was used in printing inks; other applications include enamels and photocopying toners.

Lampblack

Lampblack is used primarily in rubber and to a lesser extent as a colourant. When used in rubber, it combines low cost with certain desirable performance characteristics; as a colourant, it is used for tinting and shading cosmetics, enamels, inks, lacquers, paints and plastics. It is readily dispersible and has little tendency to float in paint or ink formulations (Claassen, 1978). The principal use of lampblack in the pigmentation of artists' paints is in water colours, and it has minor use in oil colours (Levison, 1973).

The physical and electrical properties of lampblack make it useful in the production of arc carbons, brushes and resistors. Its high tinting strength and hiding power has led to its use in blackboards, cement, crayons and leather (Garret, 1973).

Thermal black

Thermal blacks are used principally in rubber and to a lesser extent as colourants in paints and plastics (Dannenberg, 1978). Thermal blacks are used in non-tyre rubber when low reinforcement is required, and they are used in specialty polymers and in neoprene, nitrile and ethylene-propylene elastomers (Patterson, 1980). End-product applications include belts, footwear, gaskets, hose, mechanical goods, O-rings, sealants, tyre innerliners and wire insulation (Dannenberg, 1978).

(*c*) *Examples of legislation concerning carbon blacks*

Eight countries have been reported to limit exposure to carbon blacks by regulation or recommended guidelines. Their standards are listed in Table 12. A comprehensive list of regulations covering use of carbon blacks in products in contact with food is given in Table 13 (Rivin & Smith, 1982), and, when these regulations apply to heavy metal content, the maximum permissible metal contents are shown in Table 14.

Table 12. National occupational exposure limits for carbon blacks[a]

Country	Year	Concentration (mg/m^3)	Interpretation[b]	Status
Australia	1978	3.5	TWA	Guideline
Belgium	1978	3.5	TWA	Regulation
Federal Republic of Germany[c]	-	6	TWA	Guideline
Finland[d]	1981	3.5 7	TWA STEL	Guideline
Italy	1978	3.5	TWA	Guideline
The Netherlands	1978	3.5	TWA	Guideline
Sweden[e]	1981	3	TWA	Regulation
Switzerland	1978	20 total airborne dust 8 fine (respirable) dust	TWA	Regulation
United Kingdom[f]		3.5 7	TWA STEL	Guidelines
USA				
OSHA	1982	3.5	TWA	Regulation
ACGIH	1982	3.5	TWA	Guideline
NIOSH	1978	7	STEL	
		3.5 (with PAH $\leq$ 0.1 %)[g]	TWA	Guideline

[a] From National Institute for Occupational Safety & Health (NIOSH) (1978); International Labour Office (1980); American Conference of Governmental Industrial Hygienists (ACGIH) (1982); US Occupational Safety & Health Administration (OSHA) (1982)

[b] TWA, time-weighted average; STEL, short-term exposure limit

[c] Senatskommission zur Prufung gesundheitsschaldlicher Arbeitstoffe (1983)

[d] From National Board of Labour Protection, Finland (1981)

[e] From National Board of Occupational Safety & Health, Sweden (1981)

[f] Anon. (1982)

[g] PAH, polynuclear aromatic hydrocarbons

Table 13. Legislation on carbon blacks in materials in contact with food[a]

Country	Publication	Date	Details[b]
Austria	61 Farben-verordnung	1975	Limits on extraction of metals by 0.1N HCl. Regulations of FRG also apply.
Belgium	Arrêté Royal (published in *Moniteur Belge* 24.9.76)	25.8.76	Aromatic amines <500 mg/kg. Limits on extraction of metals by 0.1N HCl. Optical transmission of benzene or toluene extract at 390 nm must be 70% min.
Canada	B.23.001	8.1.81	No specific regulation, general health safety requirement.
Czechoslovakia	Instruction 49/1978	1978	Benzo[*a*]pyrene content 0.1 mg/kg max. Limits on extraction of metals by 0.1N HCl (this applies to pigments and fillers for use in plastics)
Denmark			No government regulation.
Federal Republic of Germany	B.Gesundh., B1.15, 268	1.7.72	Toluene extract (DIN 53553), 0.15% max. UV absorption of cyclohexane extract, extinction at 386 nm 0.1 max.
	B.Gesundh., B1.21, 330	1.7.78	Recommended max. carbon black content, 2.5%, except in polyolefin fittings (3% max.) and rubber articles in contact with milk (30% max.) (Recommendations III, IV, XXXII, XXXVIII and XLVI). No limit in flexible containers for solid powders, etc. (Recommendation XXXI).

Country	Publication	Date	Details[b]
Finland			No government regulation.
France	Circular No. 176	1.12.80	Benzene extract, 0.1% max. No benzo[*a*]pyrene must be detectable. Aromatic amines <500 mg/kg. Limits on extraction of metals by 0.1N HCl (applies to pigments and fillers for use in plastics).
Italy	Ministerial Decree (*Gazetta Ufficiale* 104)	20.4.73	Benzene extract, 0.1% max. UV absorption of extract (1 cm cell), 0.15 max. at 280-289 nm; 0.12 max. at 290-299 nm; 0.08 max. at 300-359 nm; and 0.02 max. at 360-400 nm. Aromatic amines must not exceed 500 mg/kg. Limits on extraction of metals by 0.1N HCl.
The Netherlands	Exec. Reg. CIII-55		Toluene extract, 0.15% max. after 8 h. Aromatic amines, <500 mg/kg. Limits of extraction of metals by 0.1N HCl (for use in packaging materials).
Norway			No government regulation.
Spain	8223 Resolución Anexo 3 amended by 13795 Resolución	28.1.77	Optical transmission of benzene or toluene extract at 390 nm, 70% min. Primary aromatic amines <500 mg/kg. Limits on extraction of metals by 0.1N HCl (applies to plastics, cellulose ethers and esters only).
Sweden			No government regulation. Metal content must be nil from July 1982.
Switzerland			Regulations of FRG followed.
United Kingdom			No government regulation. US or FRG regulations used. EEC directives enforced by Statutory Instruments.
	Statutory Inst. No. 1927 (EEC Directive 893)	1978	Materials and articles in contact with food must be made by good manufacturing practice so that they do not transfer their constituents to food in such a way as to endanger health or deteriorate the food.
	BS 4991 BS 1972 Toy (Safety) Reg.1367 BPF Code of Practice	1974 1967 1974 1978	For use in pipes for drinking water; toluene extract, 0.1% max., volatiles (950°C., 7 min.), 9% max.; particle size, 10-25 nm. Limits on certain metal contents using 0.07N HCl. For plastics in contact with food. Carbon black, 5% max. and of high purity.
USA	FDA Regulations, Title 21 175.300 175.320		Resinous and polymeric coatings in contact with food. Only channel black to be used.
	176.170 176.180		Paper and paper board in contact with food. Only channel black to be used.
	177.1460		Melamine-formaldehyde resins for moulded articles. Only channel black to be used.
	177.1210		Closures with sealing gaskets for food containers. Only channel black to be used.
	177.2410		Phenolic resins and moulded articles. Only channel black to be used.
	177.2600		Rubber articles for repeated use in contact with food. Allows up to 50 wt % furnace or channel black (10% max. furnace black for use in contact with milk or edible oils.)
	175.105		Substances for use only as components of adhesives. Only channel black to be used.
European Economic Community	Directive 76/893/EEC	19.11.76	General requirement for materials and articles for contact with foodstuffs (no reference to Carbon black).

[a] From Rivin & Smith (1982)
[b] For metal extraction limits, see Table 14.

Table 14. Maximum metal content (mg/kg) of carbon blacks extracted by 0.1N HCl[a]

Country	Antimony	Arsenic	Barium	Cadmium	Chromium	Copper	Lead	Mercury	Nickel	Selenium	Silver	Tin	Uranium	Zinc
Austria	2000	200	4000	4000	-	4000	2000	400	-	-	-	4000	4000	4000
Belgium	2000	50	100	2000	1000	-	100	50	-	100	-	-	-	-
Czechoslo-vakia	-	50	100	100	100	-	1000	50	-	100	-	-	-	2000
France	-	50[b]	100	1000	-	-	100[b]	50	-	100	-	-	-	2000
Italy	-	50[b]	100	2000	-	-	100[b]	50	-	100	-	-	-	2000
The Netherlands	2000	100	100	1000	1000	-	100	50	100	100	-	-	-	-
Spain	2000	100	100	2000	1000	-	100	50	-	100	-	-	-	2000
Sweden	-	-	-	Nil[c]	-	-	-	-	-	-	-	-	-	-
United Kingdom[d]	250	250	500	100	250	-	2500	100	-	-	-	-	-	-
USA	-	100	2000	20	100	-	100	4	-	20	100	-	-	-

[a] From Rivin & Smith (1982)

[b] By ash analysis

[c] From July 1982

[d] Toy (Safety) Reg. 1367 (uses 0.07N HCl)

In the past, only channel black was approved by the US Food and Drug Administration for direct use in food, drugs and cosmetics; however, this use was banned in 1976 (US Food & Drug Administration, 1976). Because of the possibility that traces of oil feedstocks can appear in the wastes, the US Environmental Protection Agency (1982) has banned the discharge of process waste-water pollutants into navigable waters by carbon black manufacturers utilizing any of the following processes: channel, furnace, lamp and/or thermal.

2.2 Occurrence

(*a*) *Natural occurrence*

Carbon blacks are not known to occur as natural products.

(*b*) *Occupational exposure*

Occupational exposure to carbon blacks, by inhalation and dermal contact, has been reduced in the last 20-25 years by the introduction of bulk shipping and handling equipment, together with improved industrial hygiene. Well over half of all carbon black shipments are handled by these means.

The US literature on occupational exposure to carbon blacks has been reviewed by the US National Institute for Occupational Safety and Health (1978) and by Rivin and Smith (1982). A summary of further data is given below.

Sands and Benitez (1961) reported concentrations of carbon blacks (measured as total dust) at three rubber factories ranging from 0.14-38.9 mg/m^3: 1.77-38.9 mg/m^3 in areas where Banbury mixers were loaded; 1.41-21.2 mg/m^3 during milling; and 0.14-4.24 mg/m^3 in the general air of milling rooms.

Between July 1972 and January 1977, the US Occupational Safety and Health Administration (OSHA) (1977) conducted 85 surveys with regard to carbon black to determine compliance with the occupational exposure limit of 3.5 mg/m^3. Approximately 20% of the workplaces inspected were in violation of the standard, and levels in about 60% of these were 1-2 times above the standard.

A study by Smith and Musch (1982) involving the collection of 1951 samples from different areas of employment within 24 different carbon black plants in the USA showed that all summary geometric mean time-weighted average values (GM-TWA) by area of employment and by job category were well within the US (OSHA) permissible exposure limit (PEL) of 3.5 mg/m^3; the values ranged from 0.01-1.45 mg/m^3 for various employment areas. Respirable dust levels ranged from 0.00-0.35 mg/m^3 (GM-TWA). Employees involved in both filling and stacking bags of carbon blacks were exposed to the highest levels of total dust (GM-TWA, 2.2 mg/m^3); the bagging operation involved the highest levels of respirable dust (GM-TWA, 0.48 mg/m^3).

In the rubber industry, employees are exposed to carbon blacks mainly in the compounding and Banbury mixing areas. It has been reported that for total dust (in which carbon blacks were one component) the median of levels in 14 US tyre and tube manufacturing plants was 1.7 mg/m^3 (individual plant means ranged up to 3.9 mg/m^3) for the compounding area samples and 1.3 mg/m^3 (the highest plant mean was 4.2 mg/m^3) for the Banbury mixing area samples. The values for the personnel samples were 3.1 mg/m^3 (highest plant mean, 5.0 mg/m^3) for the compounding area and 1.9 mg/m^3 (highest plant mean, 5.8 mg/m^3) for the Banbury area (Williams *et al.*, 1980). Additional data on occupational exposure to dusts in rubber processing are given in IARC (1982).

Carbon blacks were detected by the US National Institute for Occupational Safety and Health (NIOSH) in the workroom air of two US factories during 1979. Total dust concentrations at the first plant, which produced titanium diboride from titanium dioxide, boron carbide, and carbon blacks, were in the range of 0.15-17.9 mg/m^3. The maximum amount of carbon blacks in the total dust was estimated to be 0.02-4.8 mg/m^3 (Hollett, 1980). At the second plant, total dust levels in the range of 0.15-3.33 mg/m^3 were found during rubber compounding operations; the maximum level of carbon blacks was estimated at 0.11-2.59 mg/m^3 (Salisbury, 1980). Oleru *et al.* (1983) found dust levels of 10-31 mg/m^3 in a factory producing dry-cell batteries using carbon blacks. Carbon blacks were not detected in 1979 at a plant which used them in the manufacture of vinyl coving and floor covering (limit of detection, 0.5 mg/m^3) (Belanger & Elesh, 1979).

Since carbon blacks are used in various printing inks, at levels ranging from 5-22% (Dannenberg, 1978), there is possible occupational exposure to carbon blacks particularly in newspaper pressrooms. Details of studies of exposure to oil mists containing carbon blacks are given in the monograph on mineral oils and related products in this volume.

On the basis of the 1974 National Occupational Hazard Survey, the US National Institute for Occupational Safety and Health (1980, 1981) projected that 217 000 US workers were exposed to C.I. Pigment Black 7 (acetylene black, furnace black, and thermal black), and 1400 workers were exposed to C.I. Pigment Black 6 (lampblack). Actual exposure to these two pigments was observed in 159 and 10 industries, respectively, using Standard Industrial Classification categories.

(c) *Air*

In 1978, an estimated 1.24 million kg of carbon blacks were emitted during carbon black manufacture in the USA (Rawlings & Hughes, 1979). Table 15 summarizes typical particulate carbon black emissions to the air during various stages of their manufacture by the oil-furnace process. The particulate matter was reported to comprise carbon blacks (McBath, 1979).

Table 15. Typical particulate emissions during the manufacture of carbon blacks by the oil-furnace process[a]

Source	Range (kg/thousand kg)	Average (kg/thousand kg)
Main process vent (uncontrolled)	0.1-5	3.27
Flare	1.2-1.5	1.35
Carbon monoxide boiler and incinerator	-	1.04
Dryer vent:		
uncontrolled	0.05-0.40	0.23
bag filter	0.01-0.40	0.12
scrubber	0.01-0.70	0.36
Pneumatic system vent:		
bag filter	0.06-0.70	0.29
Vacuum clean-up system vent:		
bag filter	0.01-0.05	0.03
Fugitive emissions	-	0.10
Solid waste incinerator (where used)	-	0.12

[a] From McBath (1979)

Rivin and Smith (1982) reviewed the literature on emissions of carbon blacks to the atmosphere during their manufacture. Modern carbon black plants generally employ bag filters to reduce emissions; discharge from a bag filter in good condition during this process (under normal conditions) reportedly contains carbon blacks (wet basis) at less than 50 mg/m^3, a concentration that is not visible (Johnson & Eberline, 1978).

Tyre dust, of which carbon blacks are a component, was estimated, in a 1969 study, to account for approximately 0.8% of the aerosol above an urban area in California. An estimated 0.2% of the particulates in the aerosol consisted of elemental carbon contributed by tyre dust (Friedlander, 1973).

Carbon blacks were not detected in the atmosphere around a factory in the Federal Republic of Germany where they were manufactured (Deimel & Dulson, 1980).

2.3 Analysis

In addition to a discussion of methods of analysis to detect the presence of carbon blacks in various matrices, this section includes a discussion of the methods used to isolate and analyse the compounds adsorbed on carbon blacks.

(a) *Carbon blacks in various matrices*

Levels of carbon blacks in the atmosphere are generally determined by gravimetric methods. Free carbon has been determined by predigestion of a sample with nitric acid to destroy

organic matter followed by weighing of the residue and ignition between 140 and 700°C. The amount of free carbon is determined by the loss of weight upon ignition (National Institute for Occupational Safety & Health, 1978).

Because of the difficulty of separating carbon blacks from other airborne particulates, total dust in the occupational environment is usually measured as an indication of carbon black airborne contamination. Both membrane-filter sampling and high-volume sampling techniques are used in collecting carbon blacks in the work environment, followed by gravimetric analysis to arrive at the total dust concentration. The gravimetric method of the US National Institute for Occupational Safety and Health (NIOSH) for determining total dust has an estimated detection range of 1.5-10 mg/m^3 for a 200-litre sample. It is validated over the range of 1.86-7.7 mg/m^3 for a 200-litre sample and 7.8-27.7 mg/m^3 for a 100-litre sample. A preselector, which removes particles [smaller than about 5 μm in diameter], can be used to determine the level of respirable dust (National Institute for Occupational Safety & Health, 1978; Rivin & Smith, 1982).

The American Society for Testing and Materials (ASTM) (1983) has published methods for the analysis of carbon blacks in several natural and synthetic rubbers. The methods are of two types: (1) nitric acid digestion followed by pyrolysis and (2) thermogravimetric analysis. It has been reported that thermogravimetric analysis is more rapid and that this method is accurate for determining the carbon black content of rubbers in the range 0.1-30% (Charsley & Dunn, 1981).

Carbon blacks in olefin plastics (i.e., polyethylene, polypropylene and polybutylene) can be determined gravimetrically by pyrolysis of the sample at 500-700°C under an inert atmosphere. Because the polymer is lost during pyrolysis, leaving a carbon black residue, this method cannot be used for compositions containing nonvolatile pigments or fillers other than carbon black (American Society of Testing and Materials, 1979).

(*b*) *Adsorbates on carbon blacks*

Several studies have been made in which the Soxhlet extraction properties of various organic solvents in removing adsorbates from carbon blacks were compared (the compositions of carbon black extracts are given in Section 1.4 of this monograph). The efficiency of the extraction depends on the extraction time and solvent, the type of carbon black, the relationship between sample weight/solvent volume and the amount of extractable material. Some solvents may react with the surface groups of carbon blacks and form artefacts during the extraction (Fitch *et al.*, 1978).

Locati *et al.* (1979) found that a Soxhlet extraction time of 150 hours was necessary to remove 95% of the benzene-extractable matter in five furnace blacks studied, and 250 hours for exhaustive extraction. They observed also that the lower the molecular weight, the shorter was the time necessary to obtain extraction.

Taylor *et al.* (1980) examined the solvent efficiency of three solvents (24-hour Soxhlet) as measured by benzo[*a*]pyrene extractability from five furnace blacks. They found that toluene and benzene had quite similar efficiencies, but that cyclohexane could not remove more than 10% of the benzene-extractable benzo[*a*]pyrene from any of the furnace blacks. Toluene was, however, clearly the best extractant when the adsorbate content of the carbon black was low (less than 1 mg/kg).

Sanders (1981) found that nitropyrenes were not efficiently removed from an after-treated carbon black (115 m^2/g, 0.3% extract, total nitropyrenes 67 mg/kg) by suspending it in solvents (150 mg/ml, 30°C, overnight with agitation), but that there was a marked difference between solvents. The percentage of 1,6-dinitropyrene removed was: 0.1 with dimethyl sulphoxide, 0.2 with dichloromethane, 0.7 with toluene, and 12 with *ortho*-dichlorobenzene. While *ortho*-dichlorobenzene and toluene Soxhlet extractions of 1,6- and 1,8-dinitropyrene were nearly complete in 16 (*ortho*-dichlorobenzene) and 48 (toluene) hours, dichloromethane-Soxhlet extraction removed 10% of these dinitropyrenes from an after-treated carbon black in 72 hours.

Giammarise *et al.* (1982) found that benzene, toluene, monochlorobenzene and *ortho*-dichlorobenzene were all effective extraction solvents for nitropyrenes from an obsolete carbon black with a high level of nitropyrene impurities (approximately 70 mg/kg). Monochlorobenzene was the best extractant. When a current carbon black with only traces of nitropyrene impurities (approximately 0.5 mg/kg) was extracted, monochlorobenzene removed more than 90% of the nitropyrenes in 24 hours, while toluene extracted only 60% in that time.

A summary of the analytical methods used to determine the components of the carbon black extracts produced by Soxhlet extraction of carbon blacks with various solvents has been published (Jacob & Grimmer, 1979).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

3.1 Carcinogenicity studies in animals

A review of the carcinogenicity of carbon blacks in experimental animals has been published (National Institute for Occupational Safety & Health, 1978).

Bioavailability of polynuclear aromatic hydrocarbons adsorbed on carbon blacks

Since it has been demonstrated that carcinogens are adsorbed onto carbon particles, an evaluation of the possible risks of carbon black exposure must take into consideration the efficiency with which biological fluids remove these chemicals. The bioavailability of organic materials adsorbed onto other carbonaceous particles has already been examined, particularly with regard to diesel exhaust particles (King *et al.*, 1981; Holmberg & Ahlborg, 1983).

The available evidence (Falk & Steiner, 1952b; Steiner, 1954; Nau *et al.*, 1960; Neal *et al.*, 1962; Kutscher *et al.*, 1967; Lakowicz & Bevan, 1979; De Wiest, 1980; Taylor *et al.*, 1980; Buddingh *et al.*, 1981) showed that when carbon blacks are exposed to biological material, including human albumin, some elution of polynuclear aromatic hydrocarbons may occur. The extent of this elution depends on the relation between the amount of adsorbed material and the available adsorptive surface.

(a) Oral administration

Mouse: [A series of feeding studies was conducted (Nau *et al.*, 1958a) over several years on samples of carbon blacks said to be representative of material produced at the time (see Table 16). The details of each experiment are not clearly described, and positive data are presented only on one carbon black sample and on positive controls. Negative data are either not included or inadequately reported. The anatomical and histological descriptions are generally inadequate.]

Table 16. Types and properties of carbon blacks used in various studies[a]

Supplier no.	Product no.	Type	Parent material	Iodine surface area, average (m^2/g)[b]	Benzene extract, average (%)	pH, average	Volatile, average (%)	Grade of black[c]
1	2	Oil furnace	Oil residue	52.7	0.374	9.09	3.53	HAF
1	1	Oil furnace	Oil residue	184.5	0.15	8.86	3.17	CF
2	9	Gas furnace	Gas	21.5	0.06	9.69	0.60	HMF
2	10	Furnace	Gas-oil	28.4	0.07	8.85	1.42	FEF or MAF
2	11	Furnace	Gas-oil	61.7	0.05	9.22	1.29	HAF
2	12	Furnace	Gas-oil	99.3	0.05	9.02	2.34	ISAF
3	3	Oil furnace	Oils	76.0	0.053	9.58	4.51	HAF
3	4	Oil furnace	Oils	35.5	0.125	9.53	2.05	FEF
4	13	Channel	Gas	108.0	0.00	4.99	5.08	MPC
4	14	Channel special	Gas	126.0	0.02	9.00	2.50	STC
5	5	Oil furnace	Oils	35.5	0.17	9.08	1.96	FEF
5	8	Therma combustion	Gas	11.5	1.04	7.47	1.04	MT
5	6	Oil furnace	Heavy aromatic tar plus natural gas	67.7	0.246	9.70	2.46	HAF
5	7	Gas furnace	Gas	21.7	0.118	9.83	0.69	SRF
5	15	Oil furnace	Oil	62.4	0.26	6.72	3.01	HAF
5	16	Gas furnace	Gas	111.0	0.08	5.81	5.15	Ink black

[a] From Nau *et al.* (1958a)

[b] Iodine surface area levels are lower than nitrogen surface area levels

[c] HAF, high-abrasion furnace; CF, conducting furnace; HMF, high-modulus furnace; FEF, fast-extruding furnace; MAF, medium-abrasion furnace; ISAF, intermediate super-abrasion furnace; MPC, medium-processing channel; STC, special thermal channel; MT, medium thermal; SRF, semi-reinforcing furnace

Groups of 10-50 male and female CFW white and C3H brown mice, six to ten weeks old, were fed diets containing (1) 10% whole carbon black; (2) benzene-extracted carbon black; (3) benzene extract from carbon black; (4) 3-methylcholanthrene (MCA) or MCA adsorbed to flour; or (5) MCA adsorbed to benzene-extracted carbon black (estimated total dose: (1) not specified; (2) 180-240 g carbon black/mouse; (3) 0.26-1.43 g benzene extract/mouse; (4) 0.20-0.34 g MCA/mouse; and (5) 0.25-0.43 g MCA/mouse, respectively). The diets were prepared as an 'oil-based' mixture or as a 'water-based' mixture and administered as pellets for 12-18 months, after which time all mice were killed and all organs were examined histologically. Groups of control mice received pelleted basal diets either with or without 5% cottonseed oil or 1% carboxymethylcellulose (CMC). 'No significant changes from normal'

[details not given] were reported in mice fed unextracted carbon black and in controls. Of the 130 male animals receiving benzene-extracted carbon black (supplier No. 5, product No. 5, furnace black FEF; see Table 16), nine had various types of skin tumours and one a subcutaneous lymphoma. Of the 153 animals fed diets containing benzene extracts from carbon blacks adsorbed to or mixed with flour, cottonseed oil or CMC, nine animals developed various types of gastrointestinal tract malignancies. The highest tumour incidence occurred in a group of 22 male C3H mice, fed approximately 1.2 g/mouse with benzene extract from carbon black (supplier No. 5, product No. 5; see Table 16) adsorbed to flour and incorporated into the 'oil-based' mixture: four animals developed squamous-cell carcinoma of the stomach. Of the 190 mice fed diets containing 0.02% MCA, 51 developed adenocarcinomas or squamous-cell carcinomas of the gastrointestinal tract, two mesenteric fibrosarcomas and four pancreatic malignancies. In contrast, one out of 190 mice fed diets containing similar quantities of MCA adsorbed to extracted carbon black had one fibrosarcoma of the gastrointestinal tract (Nau *et al.*, 1958a).

Groups of 24 Swiss mice [sex and age unspecified] received for 15 months rice diets containing 0.06% *para*-dimethylaminoazobenzene, or 0.06% *para*-dimethylaminoazobenzene adsorbed onto various carbon blacks by incubation for 2 hours in cyclohexane solution. Further groups of mice received rice diets containing similar concentrations of the carbon blacks alone (two furnace and one channel: Philblack O, 12%; Micronex, 18%; and Kosmos 60, 9%, respectively). In the group receiving *para*-dimethylaminoazobenzene alone, 14/24 (58%) of the mice developed liver tumours; in the three groups receiving *para*-dimethylaminoazobenzene adsorbed onto carbon blacks, only 1/72 mice developed a hepatoma; and no tumour was reported in 72 mice receiving carbon blacks alone (von Haam *et al.*, 1958).

(*b*) *Skin application*

Mouse: In cocarcinogenesis experiments, groups of Swiss mice [number, sex and age unspecified] received weekly skin paintings of 1% test substance (three types of carbon black: two furnace blacks and 'black kosmos 33' [sic], and 14 extracts [characteristics, source and methods of extraction unspecified]) in acetone together with a known cocarcinogen, croton oil (0.5%) on the shaved back skin for life. A group of 20 positive controls received applications of 1% benzo[*a*]pyrene, and 20 negative controls received 0.5% croton oil in acetone only. The experiment lasted 315 days; 148/204 mice given the test substance were still alive at the end of the experiment. In the groups receiving applications of carbon black extracts, six mice developed squamous-cell carcinomas of the skin and 11 developed skin papillomas. The six skin carcinomas occurred among 48 mice treated with four of the extracts. In positive controls, 11 carcinomas occurred in 15 animals that survived. Eight of the 14 extracts produced either papillomas and/or carcinomas. None of the three 'crude' carbon blacks produced skin carcinomas, but one produced skin papillomas in two of the eight surviving mice. No papilloma or carcinoma was reported in the 20 negative control animals (von Haam & Mallette, 1952).

In a series of experiments by Nau *et al.* (1958b), groups of CFW white and C3H brown mice [sex unspecified], six to ten weeks old, received thrice-weekly skin applications by brush of 10% or 20% 'whole' carbon blacks suspended in a 1% carboxymethylcellulose (CMC) solution or in cottonseed or mineral oil, 20% extracted carbon blacks, benzene extracts from various carbon blacks, 3-methylcholanthrene, 3-methylcholanthrene adsorbed to carbon black, benzo[*a*]pyrene or benzo[*a*]pyrene adsorbed to carbon black. Tests were conducted on carbon blacks said to be representative of materials used at that time (see Table 16).

A total of 240 CFW white and C3H brown mice [sex unspecified], six to ten weeks old, received thrice-weekly skin applications by brush of 10% or 20% 'whole' carbon black (supplier

No. 5, products No. 5 and 8, furnace and thermal blacks; supplier No. 4, product No. 13, channel black; see Table 16) containing 0-1% benzene-extractable material in cottonseed or mineral oil or 1% CMC on the shaved back for 12-18 months (estimated total dose, 3.6-12.8 g/mouse). No skin tumour was reported, but five tumours occurred in other organs in channel black-painted mice. Another 130 animals received treatment with a benzene-extracted carbon black (supplier No. 5, product No. 5, furnace black; see Table 16) (estimated total dose, 6.3-23.4 g/mouse); no skin tumour was observed, but two lymphosarcomas were reported (Nau *et al.*, 1958b).

Groups of male C3H and CFW mice [numbers and age unspecified] received thrice-weekly skin applications of materials obtained by hot benzene extraction from eight different carbon blacks for up to 12 months. All but one of the extracts showed moderate to strong carcinogenicity (see Table 17) (Nau *et al.*, 1958b).

Table 17. Skin tumour induction with various carbon black extracts in mice treated for at least 12 months[a]

Type of material used[b]	Total dose of benzene extract (mg)	Final tumour index (%)
Supplier No. 1	12.7	0
Type HAF	45.0	15.0
(furnace black)	51.4	16.0
	201.7	82.0
Supplier No.3	12.6	0
Type HAF	20.0	0
(furnace black)	24.3	0
	147.4	33.0
Supplier No. 5	12.6	0
Type HAF	16.5	0
(furnace black)	32.5	24.0
	36.5	52.0
	170.0	85.0
Supplier No. 3	10.8	0
Type FEF	21.8	7.0
(furnace black)	26.6	9.0
	135.0	44.0
Supplier No. 5	27.0	33.0
Type FEF	32.9	25.0
(furnace black)	129.0	25.0
	201.0	74.0
Supplier No. 5	6.3	0
Type SRF	7.9	14.0
(furnace black)	8.9	0
	15.4	0
	18.0	0
	24.0	0
	132.6	73.0
Supplier No. 1	17.9	0
Type CF	21.5	0
(furnace black)	136.6	0
Supplier No. 5 Type MT (thermal black)	117.1	85.0

[a] From Nau *et al.* (1958b)

[b] See also Table 16

[c] Defined by the authors as the percentage of animals, not dying from other causes, developing tumours during the treatment period

Groups of positive controls (162 mice) received [presumably] thrice-weekly skin applications of 3-methylcholanthrene (MCA) (estimated total dose, 7-24 mg/mouse) or benzo[*a*]pyrene (26-27 mg/mouse) in water, oil or benzene for 6-18 months. Further groups of mice (170) received preparations of carbon black to which either MCA or benzo[*a*]pyrene had been adsorbed. Water or oil was used as the vehicle, and applications were carried out for 12-18 months (estimated total doses, 9-24 mg MCA; 30 mg benzo[*a*]pyrene). The tumour indices defined by the authors as the percentage of animals, not dying from other causes, developing tumours during the treatment period, were 74-92% for MCA and 58-69% for benzo[*a*]pyrene in the positive-control groups. When the carcinogens were adsorbed to two different carbon blacks (supplier No. 5, products No. 5 and 8; see Table 16) before application, their tumorigenic activity appeared to be reduced: a total dose of 9.5, 13 or 16.5 mg MCA adsorbed to the carbon blacks (2 mg MCA/g carbon black), suspended in water and applied over 12-18 months to the skin of 90 mice produced tumour indices of 0, 20 and 44%, respectively, in three experimental groups, as compared to a tumour index of 83% with 24 mg unadsorbed MCA. Skin application to groups of 20 mice of 24 mg MCA adsorbed to carbon black and suspended in cooking oil produced a tumour index of 59% compared to that of 92% obtained with applications of 20 mg unadsorbed MCA. The application of 13 mg MCA adsorbed to carbon black and suspended in mineral oil to 40 mice over a 12-month period produced a skin tumour index of 4%; a comparable control group had a tumour index of 90%. Application of 30 mg benzo[*a*]pyrene adsorbed to carbon black and suspended in water to 20 mice over a period of 12 months produced no skin tumour, whereas application of 26 mg unadsorbed benzo[*a*]pyrene to 18 mice over the same period of time produced a tumour index of 69%. Negative-control groups of more than 15 mice receiving applications of benzene or the various suspension media developed no skin tumour, and a group of 943 untreated controls had a skin tumour index of 0.07% (Nau *et al.*, 1958b). [The Working Group noted several deficiencies in these experiments, namely, inadequacies in reporting, and in experimental design.] A similar reduction in the tumorigenic response was obtained with benzo[*a*]pyrene using three carbon blacks (two furnace and one channel) (von Haam *et al.*, 1958).

Monkey: Two rhesus monkeys, weighing 2-3 kg, received thrice-weekly skin applications of a channel black (same material as above) with no benzene extractable material (estimated total dose, 327-948 g/animal) on both armpits and groins for a period of 17.5 or 30 months; no skin tumour developed. Another rhesus monkey received skin applications of a 20% benzene-extracted furnace carbon black (supplier No. 5, product No. 5; see Table 16) under similar conditions. A sarcoma of the chest wall was reported (Nau *et al.*, 1958b). [The Working Group noted the inadequate number of monkeys used and the short observation period.]

(*c*) *Inhalation and/or intratracheal administration*

Mouse: A total of 280 C3H brown and CFW white male mice, 10 weeks of age, were exposed by inhalation to furnace black with 0.28% hot benzene-extractable material at a concentration of 1.6 [56][1] mg/m^3 and channel black with little or no benzene-extractable material at 2.4 [85][1] mg/m^3 for seven hours per day, on five days per week for 200-3000 hours; no malignancy attributable to the treatment was observed (Nau *et al.*, 1962). [The Working Group noted that the extent of particle deposition in the lungs of exposed animals is difficult to assess because of inadequate physical characterization of the suspended particles. Inadequate reporting of the experiment was also noted.]

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[1] In a report by the National Institute for Occupational Safety & Health (NIOSH) (1978), it is stated that 'The senior author has subsequently stated that the exposure concentrations reported in his article' [namely, in the Nau *et al.* (1962) article] 'are incorrect....' The corrected exposure concentrations are 56 mg/m^3 for furnace black and 85 mg/m^3 for channel black, according to the NIOSH report.

Rat: Rats instilled intratracheally with a total dose of 0.6 mg benzo[*a*]pyrene [dose schedule unspecified] developed no lung tumour, while rats receiving two types of carbon black mixed with benzo[*a*]pyrene (six injections of 0.1 mg benzo[*a*]pyrene on 10 mg carbon black) developed a high lung tumour incidence (12/50, thermal and 21/52, channel black) (Shabad *et al.*, 1972). [The Working Group noted the absence of some important experimental detail.]

Other species: Groups of *hamsters*, *guinea-pigs* and *monkeys* [details not given] were exposed by inhalation to furnace black containing 0.28% benzene-extractable material at a concentration of 1.6 [56][1] mg/m^3 and channel black containing little or no benzene-extractable material at 2.4 [85][1] mg/m^3 for seven hours per day, on five days per week for an unspecified period (hamsters, guinea-pigs) or for more than 13 000 hours (monkeys); no malignancy was observed (Nau *et al.*, 1962). [The Working Group noted the inadequacy of the reporting.]

(*d*) *Subcutaneous and/or intramuscular administration*

Mouse: Groups of 50 C57BL mice of both sexes, 5-5.5 months of age, received s.c. injections of: 300 mg furnace black (surface area, 15 m^2/g) containing a calculated amount of 300 mg/kg benzo[*a*]pyrene, either suspended in tricaprylin or as a pellet; 300 mg 'non-benzo[*a*]pyrene-extractable' channel black (surface area, 380 m^2/g) in tricaprylin or as a pellet; 300 mg channel black plus 0.09 mg benzo[*a*]pyrene in tricaprylin or as a pellet; material extracted by benzene from 300 mg furnace black, in tricaprylin; the residue from the 300 mg furnace black after benzene extraction, in tricaprylin; 300 mg furnace black treated for three hours in hot chromic acid and suspended in tricaprylin; and 600 mg of a mixture of furnace and channel blacks in tricaprylin. Further groups of mice received injections of 1.0 ml tricaprylin (vehicle controls) or 0.09 mg benzo[*a*]pyrene in tricaprylin (positive controls). Nearly one-third of the animals were still alive 20 months after injection of the test materials, at which time the experiment was terminated. All questionable tumours found *post mortem* were examined microscopically. Tumour incidence was calculated as a percentage, based on the number of animals alive five months after the start of the study, at which time the first deaths from tumours occurred. In six of the nine groups (treated and controls) in which no or few sarcomas were induced, 70% of the animals were still alive 12 months after the start of the experiment; in the other three, 52-66% of the mice were still alive at this time. When compared with tricaprylin controls, a significantly increased incidence of subcutaneous sarcomas, a few of which metastasized, was observed in animals treated with the carbon black containing benzo[*a*]pyrene (furnace black); the incidences of lymphomas, hepatomas, lung tumours, angiomas, angiosarcomas and uterine sarcoma were similar in both treated and control animals. The incidence of subcutaneous sarcomas induced by the injection of test materials and the 'average fatal time' (i.e., time to death from subcutaneous sarcoma) are summarized in Table 18. High incidences of sarcoma (18/46) were observed in mice receiving furnace black with extractable benzo[*a*]pyrene administered in tricaprylin, in those receiving the extract from furnace black containing benzo[*a*]pyrene (22/45) and in positive controls (39/41). It should be noted that administration of furnace black containing benzo[*a*]pyrene in pellet form in the absence of tricaprylin induced an incidence of sarcomas of 2/47 and that of non-benzo[*a*]pyrene-extractable channel black in pellet form an incidence of 1/47. Residues from furnace black after benzene extraction induced one sarcoma in 37 animals; no subcutaneous sarcoma developed in any of the other groups. It was found that mixing non-benzo[*a*]pyrene-extractable carbon black with benzo[*a*]pyrene-extractable carbon black (furnace and channel blacks) resulted in a loss of carcinogenicity of the latter (Steiner, 1954).

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[1] In a report by the National Institute for Occupational Safety & Health (NIOSH) (1978), it is stated that 'The senior author has subsequently stated that the exposure concentrations reported in his article' [namely, in the Nau *et al.* (1962) article] 'are incorrect....' The corrected exposure concentrations are 56 mg/m^3 for furnace black and 85 mg/m^3 for channel black, according to the NIOSH report.

Table 18. Carcinogenicity of carbon blacks[a]

Materials tested[b]	Tumours/ survivors at 5 months	Tumour yield (%)	Average fatal time (days)
BP[b]-containing carbon black[c], tricaprylin	18/46	39.1	363
BP-containing carbon black[c], pellets	2/47	4.3	411
Non BP-extractable carbon black[d], tricaprylin	0/48	0.0	-
Non BP-extractable carbon black[d], pellets	1/47	2.1	524
Non BP-extractable carbon black[d] plus BP, tricaprylin	0/43	0.0	-
Non BP-extractable carbon black[d] plus BP, pellets	0/48	0.0	-
Benzene extract of BP-containing carbon black[c], tricaprylin	22/45	48.9	295
Carbon black[c] residue, tricaprylin	1/37	2.7	405
BP-containing carbon black[c] treated with chromic acid, tricaprylin	0/47	0.0	-
BP-containing carbon black[c] plus non BP-extractable carbon black[d], tricaprylin	0/41	0.0	-
Tricaprylin, 1.0 ml	0/43	0.0	-
BP, 0.09 mg, tricaprylin	39/41	95.1	233

[a] From Steiner, 1954

[b] BP, benzo[*a*]pyrene

[c] Furnace black from which benzo[*a*]pyrene and six other polynuclear aromatic hydrocarbons can be extracted with benzene

[d] 'Nonbenzo[*a*]pyrene-extractable' channel black

A series of 21 groups of 10-20 male or female C3H brown or CFW white mice (total number, 344), eight to ten weeks old, received as one or two s.c. injections 17-300 mg 'whole' carbon black suspended in cooking oil, in 1% carboxymethylcellulose in water, or in tricaprylin, and were observed for 20 months. The author reported an 8-13% tumour index in three groups receiving s.c. injections of carbon black (products No. 4,7 and 8, two furnace and one thermal blacks; see Table 16) in cooking oil. The tumour index was defined by the author as 'the percent of tumours occurring in animals excluding those found dead of causes unknown'. The tumours were described as 'subcutaneous mixed tumours' (Nau *et al.*, 1960).

Three groups of 20 male or female C3H mice alone or with CFW mice received two s.c. injections of 0.14-150 mg of an oil-furnace black (product No. 4; see Table 16) (after extraction in hot benzene for 24 hours) in cooking oil or 1% CMC in water, and the mice were observed for 20 months. No tumour occurred at the injection site among 19 mice killed at the end of the experiment or in animals dying during the course of the experiment (Nau *et al.*, 1960).

Groups of 10-20 male or female C3H and CFW mice, eight to ten weeks old, received as one or two s.c. injections 0.01-6.5 mg of a benzene extract of various carbon blacks in cooking oil (products No. 1,2,3,4,5,6,7,8,9,10,15,16 and 17; see Table 16). In 31/36 groups, tumour indices of 15-100% were reported, 22 of which had an index of >50%. No subcutaneous tumour was observed in five groups. Further groups given s.c. injections of 0.2-3.25 mg benzene extracts of carbon blacks (products No. 1,5,6 and 7; see Table 16) in methanol or 1% CMC in water were reported to have a nil tumour index. Similar groups of C3H mice received one or two s.c. injections of 0.1-0.2 mg extracted material readsorbed to carbon black (product No. 5; see Table 16) in oil or in CMC in water; a nil tumour index was again reported. Further groups of 19-20 C3H mice received as one or two s.c. injections 0.5-1.0 ml of cooking

oil, incubated with carbon black (product No. 5; see Table 16) for 1-6 months then centrifuged to remove the carbon black; the subcutaneous tumour index in these animals was 17-92% (Nau *et al.*, 1960).

As a positive control, 14 groups of 10-20 CFW and/or C3H mice, eight to ten weeks of age, received as one or two s.c injections 0.002-1.0 mg 3-methylcholanthrene (MCA) in oil; the reported tumour indices ranged from 25-100%. When four groups of C3H mice received as one or two s.c. injections 0.05-0.25 mg of MCA in water, reported tumour indices ranged from 12-95%, whereas a nil tumour index was reported for five groups of 12 female C3H mice receiving 0.002-0.01 mg MCA. A further 11 groups of 15-21 male or female C3H mice received single s.c. injections of 0.01-0.2 mg MCA adsorbed to different carbon blacks (products No. 1,5,6,7,13 and 18; see Table 16) in cooking oil. In three of these groups (products No. 1,7 and 13; see Table 16), the reported tumour indices were 5, 5 and 7%; in the other groups the tumour index was nil. Four groups of 10-22 C3H mice received the same amount of test material adsorbed to carbon blacks (products No. 5 and 14; see Table 16) in water; the reported tumour index was nil. Two groups of 20 C3H mice injected with 0.1 mg benzo[*a*]pyrene alone or adsorbed to carbon black (product No. 5; see Table 16) in water were reported to have tumour indices of 56 and 0%, respectively. Four groups of 20-31 C3H mice were injected with 0.5-1.0 ml tricaprylin or cooking oil, and the tumour indices ranged from 0 to 5%. Of a total of 943 untreated CFW and C3H controls, six were reported to have malignant skin neoplasms, one a malignant neoplasm of the liver and one a malignant neoplasm of the spleen. No detail as to the histology of these tumours was available. No animal developed a subcutaneous sarcoma (Nau *et al.*, 1960). [The Working Group noted deficiencies in experimental design and reporting in the above experiments; in particular, difficulty was experienced in interpreting the data presented in tabular form.]

(*e*) *Intraperitoneal administration*

Mouse: A group of 31 female C3H brown mice received one i.p. injection of approximately 200 mg of two different carbon blacks (products No. 5 and 18, one channel and one furnace black; see Table 16) in an aqueous CMC suspension. No tumour was observed with either material (Nau *et al.*, 1960.

3.2 Other relevant biological data

(*a*) *Experimental systems*

Toxic effects

Comprehensive reviews of the toxicity of carbon blacks to experimental animals are available (National Institute for Occupational Safety & Health, 1978; Rivin & Smith, 1982).

Rabbits exposed by inhalation to carbon black [dose and type unspecified] for one hour per day for up to 14 months developed inflammatory foci; carbon black-filled macrophages were seen in alveoli, bronchi and the secondary lymph nodes (Borchardt, 1929).

CFW and C3H male mice given diets containing 10% furnace black for 12-18 months showed no significant change in the normal status of organs and tissues [details of histopathology not given] (Nau *et al.*, 1958a).

Channel and furnace blacks were studied in chronic inhalation experiments with mice, hamsters, guinea-pigs, rabbits and monkeys. Animals were exposed for seven hours per day, five days per week to 56 mg/m^3 furnace black or to 85 mg/m^3 channel black[1]. Carbon deposition with little or no fibrotic change was observed in the lungs of exposed mice and monkeys. Studies in mice indicated that more channel black than furnace black was stored in the lungs. Right atrial and right ventricular strain were reported to have been detected by electrocardiography in monkeys. Bronchopneumonia, particularly with furnace black, was observed in mice. Skin reactions (epidermal atrophy or hyperplasia and/or dermal fibrosis) were seen in exposed mice. In some mice, Kupffer cells contained carbon black particles, and exposed mice showed an increased frequency of liver amyloidosis. Particles were found in phagocytic cells in the proximal convoluted tubules and glomeruli of the kidneys in mice, together with amyloidosis and renal fibrosis (Nau *et al.*, 1962). It was later reported that carbon black particles also accumulated in the lungs of exposed monkeys (total duration of exposure, 5784 hours) and caused perifocal emphysema; ventricular and septal hypertrophy were also seen (Nau *et al.*, 1976).

In mice and rats exposed to carbon black [type unspecified; details of exposure not reported], accumulations in the oral mucosa, with development of epithelial atrophy, hyperkeratosis, desquamation of keratinous masses and inflammatory reactions, were observed. Carbon black particles were found in the endothelium and lumen of blood vessels (Smolyar & Granin, 1971).

In rats exposed by inhalation to channel black (50% of the particles with a mass median diameter of 2.2 μm) at a concentration of 4 mg/m^3 continuously for 16 days, alveolar deposition of particles was observed. No effect on the biological properties of surfactant material was observed, but signs of alveolar damage (thickening, atelectasis, distension and rupture) were reported (Rhoades, 1972).

Three months following intratracheal instillation to rats of 50 mg of various types of carbon blacks (five furnace blacks, PM-15, PM-50, PGM-33, PM-70 and PM-100; and two channel blacks, DGM-80 and DG-100), thickened interalveolar septa, emphysematous alveoli and accumulation of histiocytes, fibroblasts and collagen fibres were observed in the particle-containing areas of the lungs. Emphysematous and fibrotic changes became more pronounced by six to nine months, and channel blacks caused a more intense reaction than furnace blacks of the same particle size. Similar observations were reported in a parallel inhalation study using PM-50 only at 240 mg/m^3 (Troitskaya *et al.*, 1975).

In mice exposed by inhalation for three hours per day, on five days per week to thermal black at a concentration of 1.5 mg/m^3, an increased number of sloughing squamous cells was observed in the nasal cavity after 12 weeks. Small but statistically significant variations in immunoglobulin levels were seen after exposures of up to 20 weeks. [The significance of these variations was not clear.] A reduction in lung bactericidal capacity was also observed (Fenters *et al.*, 1979).

When golden hamsters were exposed by inhalation to 'furnace thermal' black (particle diameter, 150-200 nm) at a concentration of 56 mg/m^3 for six hours per day on five days per

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[1] In a report by the National Institute for Occupational Safety & Health (NIOSH) (1978), it is stated that 'The senior author has subsequently stated that the exposure concentrations reported in his article' [namely, in the Nau *et al.* (1962) article] 'are incorrect....' The corrected exposure concentrations are 56 mg/m^3 for furnace black and 85 mg/m^3 for channel black, according to the NIOSH report.

week for 236 days or 108 mg/m^3 for 53 and 172 days, no change in the histology of the upper respiratory tract was observed in high-dose animals. Five of 17 low-dose animals exposed for 236 days showed oedema of the lamina propria of the thyroarytenoid fold and presence of eosinophilic material in the subglottic and tracheal glands (Snow, 1970).

No data were available to the Working Group on effects on reproduction and prenatal toxicity.

Absorption, distribution, excretion and metabolism

Uptake and retention of carbon black particles in lung macrophages have been observed following inhalation (see studies above), as well as following injection into the cerebral ventricles of rats (Bertheussen *et al.*, 1978) or into the bladder wall of rats (Bertheussen & Melchior Nissen, 1976). Carbon black particles perfused into the abdominal aorta of rabbits were observed in the endothelial cells of the vessel (Hoff & Gottlob, 1967).

Mutagenicity and other short-term tests

The activity of carbon black particles and of their corresponding solvent extracts in short-term assays must be considered separately. When carbon black particles are tested, results may be influenced by such experimental conditions as the presence of serum, the concentration of dimethyl sulphoxide (DMSO) or other solvents and the duration of exposure. In addition, these assays may underestimate in-vivo exposure owing to the short duration of the experiments. Conversely, the amount of chemicals eluted by solvent extracts of carbon blacks may be greater than that which would be eluted by biological fluids (Buddingh *et al.*, 1981). Additionally, the nature of the solvent and the temperature and duration of the Soxhlet extraction influence the final biological response (Sanders, 1981; Giammarise *et al.*, 1982; Butler *et al.*, 1983).

Only three different carbon blacks have been assayed in short-term tests: a rubber-grade black (N339), a nitric acid after-treated black (Black Pearls) and a third carbon black, of unspecified type. Extracts of the latter two were also examined. In addition, extracts of 20 other carbon black samples were tested.

In an extensive study, Kirwin *et al.* (1981) tested a rubber grade furnace black [N339, surface area 100 m^2/g; toluene extractables (48 hours), 0.15 wt%] in five short-term assays:

- Mutagenicity in *Salmonella typhimurium*: No mutagenic activity was observed in *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 or TA100 at concentrations of carbon black of up to 7.5 mg/plate in the presence or absence of an Aroclor-induced rat-liver supernatant (S9). [It was not reported whether the carbon black particles were suspended in DMSO prior to testing or, if so, the time interval between suspension and testing.]

- Sister chromatid exchange in Chinese hamster ovary cells: The carbon black was suspended in DMSO at 100 mg/ml [time and temperature unspecified] and then diluted in culture medium to give a final concentration range of 0.00032-1 mg/ml. Cells were exposed for 2 hours, both in the presence and absence of S9. Very small increases in the frequency of sister chromatid exchanges as compared to the control values were observed for several concentrations, but these were not dose related.

- L5178Y TK+/- mouse lymphoma mutagenicity assay: Cells were exposed for 4 hours [time extended for an unspecified time owing to difficulty in separating carbon black from cells] to concentrations of carbon black of 10-40 mg/ml in the absence of S9 and of 5-15 mg/ml in the presence of S9. Cell survival was <1% at the highest concentration. No mutagenicity was observed. [The Working Group noted the use of non-standard experimental procedures.]

- C3H/10T1/2 CL8 mouse embryo morphological cell transformation assay: Carbon black suspended in acetone was tested at four concentrations ranging from 2-16 mg/ml. No transformed focus was observed.

- Genetic activity in *Drosophila melanogaster*: Larvae were given diets containing 1% carbon black until pupation. Flies were scored for mosaics, Y chromosome loss, chromosomal aberrations and dominant lethal and sex-linked lethal mutations. No genetic effect was observed.

A nitric acid after-treated carbon black [Black Pearls, a furnace black; surface area of 115 m^2/g; toluene extractables (48 hours) of 0.3% (Sanders, 1981)] was tested for mutagenicity in *S. typhimurium*. Particles were first suspended in DMSO for five hours, and an aliquot containing 500 μg of carbon black was then tested in strain TA98. No mutagenic activity was observed (Rosenkranz *et al.*, 1980). An aliquot of a 48-hour Soxhlet toluene extract (solvent exchanged into DMSO) equivalent to 10 μg of this carbon black was, however, mutagenic in the same strain. This carbon black contained nitrated pyrenes at a level of 67 mg/kg (Sanders, 1981). More recent production lots of this grade of carbon black had a 200-fold reduction in nitrated pyrene content and yielded extracts for which the mutagenicity was reduced by the same order of magnitude (Rosenkranz *et al.*, 1980; Agurell & Löfroth, 1983; Butler *et al.*, 1983).

Liber *et al.* (1983) tested a carbon black [type unspecified], which had a high yield of extract (0.78%, methylene chloride), for mutagenicity in AHH-1 human diploid lymphoblasts. Cells were suspended in a medium supplemented with 10% fetal calf serum and allowed to incubate for five days either with suspended carbon black 0.05-1.0 mg/ml or the extract 0.01-1.0 μg/ml. Both carbon black and the extract induced mutations to 6-thioguanine-resistance at a frequency three to five times the background level.

Benzene or acetone extracts of 20 commercial carbon blacks were tested in the *Salmonella* mutagenicity assay. Of the 20 extracts (some of which required activation with rat liver S9), 15 were mutagenic to strains TA98 and/or TA100 and five were inactive (Agurell & Löfroth, 1983).

(*b*) *Humans*

Toxic effects

Comprehensive reviews of the toxicity of carbon blacks to humans are available (National Institute for Occupational Safety & Health, 1978; Rivin & Smith, 1982).

The most important reported effects of carbon blacks in humans are on lung function. Early reports of carbon black-induced lung disease were published by Töppner (1952), Gerasimov and Shatalova (1967) and Rosmanith *et al.* (1969).

In a study by Valić *et al.* (1975), respiratory function was measured in a group of 35 carbon-black workers examined in 1964 and again in 1971. Measurements of carbon-black

concentrations in the work environment showed that the respirable concentration (mean, less than 1 μm) was 7.2 mg/m^3 in 1964; similar concentrations were reported for 1971. By 1971, the average duration of exposure was 12.9 years and was more than 10 years for 26 out of 35 workers. Carbon-black workers who smoked exhibited a reduced forced vital capacity and a reduced forced expiratory volume, both compared with controls and with the predicted values. For carbon-black workers who did not smoke there was no significant difference compared with controls. For smoking and non-smoking carbon-black workers, however, the annual declines in these parameters were three- to four-fold greater than expected. Radiological lung changes, characterized by interstitial fibrosis, were found in 17.1% of the workers. Lung changes progressed between 1964 and 1971; in one case, initial signs of pneumoconiosis were seen in 1971 but not in 1964. In a follow-up study of 30 of the workers in 1978, further deterioration in pulmonary function effects were observed (Beritić-Stahuljak *et al.*, 1980). [The mechanisms for selecting exposed and non-exposed populations are unclear. It is stated that some of the controls lived in the neighbourhood of the plant and were exposed to carbon blacks.]

Lung function tests on 82 workers producing carbon blacks (Gabor *et al.*, 1969) showed alterations including a decrease in vital capacity and in forced expiratory volume in some 17% of all workers, the decrease in the latter test being most marked among thermal-black producers. Chest roentgenograms on 72 workers were reported to show that 13.9% of workers had radiological signs of pneumoconiosis, clinically diagnosed as anthracosis and that signs of possible early pneumoconiosis were found in an additional 7%. Radiological lesions were found more frequently in channel-black workers than in furnace- and thermal-black workers. Exposure levels to carbon black were not stated. Ambient concentrations of some polynuclear aromatic hydrocarbons were measured, and anthracene was noted to occur at levels of 1.2-2.1 mg/m^3 in excess of the then current US maximum allowable concentration of 0.1 mg/m^3. Similarly, Troitskaya *et al.* (1975) found a greater incidence of pneumoconiosis in channel-black workers than in furnace-black workers.

In another study on carbon-black (furnace) workers, Cocarla *et al.* (1976) found that 29 of 143 workers had pneumoconiosis, with generalized or limited emphysema. In the same subpopulation, an increase in levels of serum IgA and a decrease in IgM were observed.

In 125 Nigerian carbon black-exposed workers in dry-cell battery and tyre manufacture, a reduction in pulmonary function and an increase in respiratory symptoms were observed in comparison to controls. The largest reduction in pulmonary function was observed in the group that had exposure to the highest dust level (31 mg/m^3), which occurred with the shortest length of employment (1-3 years) at the dry-cell battery factory. The most common respiratory symptoms were cough with phlegm. Radiographs were reported to show no abnormality. No adjustment was made for smoking; however, only 12.8% of workers in the study group were smokers (Oleru *et al.*, 1983).

Four cases of Stage I pneumoconiosis and 15 cases of suspected pneumoconiosis were observed among 89 workers in a carbon-black (lampblack) plant in the USSR. Younger people were found to be more susceptible to effects on the respiratory tract. The degree of lung change was most marked among those who had worked for more than ten years. Measurements of carbon black levels were not reported (Kareva & Kollo, 1961).

Impaired respiratory function was also observed among Soviet carbon-black [type unspecified] workers. Six out of 25 workers with 10-16 years' exposure showed radiological evidence of early pneumoconiosis (Komarova & Rapis, 1968). [Interpretation of these data is difficult because: (1) sampling methods and methods used to ascertain examined workers are not

specified; (2) the sex distribution of the 6/25 workers with 10-16 years' exposure is not presented, although 64% of the total of 66 workers examined were women; (3) no information is given about other occupational exposures or about smoking history; (4) X-ray diagnostic criteria are not explained; and (5) carbon black levels are not reported.]

Among the other effects of exposure to carbon black (lampblack) that have been reported are dermatological lesions, such as the presence of carbon black 'tattoos' on hands and forearms, as well as follicular blackheads containing carbon black on uncovered skin surfaces (Capusan & Mauksch, 1969). An increase in keratosis and leukoplakia in the oral cavity of workers exposed to furnace black was reported by Smolyar and Granin (1971). [The Working Group noted major methodological limitations to this study.]

No data were available to the Working Group on effects on reproduction and prenatal toxicity, on absorption, distribution, excretion and metabolism or on mutagenicity and chromosomal effects.

3.3 Case reports and epidemiological studies of carcinogenicity to humans

(a) Case reports

Maisel *et al.* (1959) reported a case of epidermoid carcinoma of Stensen's duct in a 53-year-old male research chemist who had had heavy and unusual exposure to most commercial carbon blacks and to more than 170 different experimental carbon blacks made in his own carbon-black furnace. [This single case cannot be regarded as informative regarding the carcinogenicity of commercial carbon blacks to humans.]

(b) Epidemiological studies

Epidemiological studies in the rubber industry have been reviewed (IARC, 1982). The Working Group that undertook that review considered that there was *sufficient evidence* for excess occurrence in rubber workers of cancers of the bladder, stomach and lung and of leukaemia and limited evidence for excess occurrence in rubber workers of cancers of the skin, colon and prostate and of lymphoma. Excess occurrence was unevenly distributed among different jobs: in jobs entailing exposure to various dusts, containing varying amounts of carbon blacks, an excess of stomach cancer was noted (e.g., Blum *et al.*, 1979; Parkes *et al.*, 1982). There was no report that allowed evaluation of whether there is or is not a statistically significant association between exposure to carbon blacks *per se* and malignant disease.

Other exposures to carbon blacks occur chiefly in conjunction with exposure to mineral oils (see monograph, p. 87). Epidemiological studies of printing pressmen are summarized in section 3.3 of that monograph.

The cancer rates of employees at carbon-black production facilities in the USA have been followed for different periods since 1935 and described in three reports (Ingalls, 1950; Ingalls & Risquez-Iribarren, 1961; Robertson & Ingalls, 1980). The first two reports are based on male workers at the same group of plants of one company (estimated to provide one quarter of all US carbon black production). In 1949, there were 677 carbon-black workers (257 in plants producing channel black, 259 producing furnace black, 161 in both channel- and furnace-black production). In 1957, the channel-black plants employed 135 workers, the furnace-black plants

565 workers and the plants using both processes, 58 workers. The third study (Robertson & Ingalls, 1980) includes the same employees as those described above and adds information on workers from additional companies (average number of employees from all sources, 1250/year).

Ingalls (1950) reported the numbers of cancer deaths and incident cases among male workers employed by one US company in carbon-black production plants located in Texas, Oklahoma and Louisiana. Expected numbers of deaths were based on age-specific rates among US males in 1940; expected morbidity was based on that in a small local population (Oak Ridge, Tennessee). The incidence of cancer for the period 1 July 1944 to 30 June 1949 was ascertained from annual examinations and insurance claims. Three cases were observed (one of the stomach, the fatal case, and two basal-cell cancers of the skin) - all among employees in a channel-black plant - compared to 2.6 expected; three were observed (one of the lung and two of the skin - one melanoma, one basal cell) compared to 2.0 expected among other workers. Cancer deaths, ascertained from a retrospective cohort study for the period 1 July 1939 to 30 June 1949, were one observed (stomach cancer), 1.7 expected for carbon-black workers, and 1 observed (lung cancer), 1.5 expected for other workers.

Cancer morbidity and mortality of workers in the same carbon-black production plants were reported for the period 1 July 1949 to 31 December 1956 (Ingalls & Risquez-Iribarren, 1961). Expected numbers of deaths were based on age-specific rates among US males in 1950; expected morbidity was based on rates in urban and rural areas of New York State. One cancer death (cancer of the large intestine) was observed in a carbon-black worker and two (one melanoma of the skin, one lung cancer) in other workers. Cancer deaths (calculated on the basis of person-years during employment only) were 1 observed, 3.2 expected for carbon-black workers and 2 and 3.1 for other workers. Six incident cancer cases were observed in carbon-black workers (the fatal case in the large intestine, two of the skin - melanoma, two of the colon, one of the lip - carcinoma) and three in other workers (the fatal case of the lung[1], one of the skin - melanoma, one of the tongue). For all sites of cancer, there were 6 observed [7.2 expected] for carbon-black workers and 3 observed [6.6 expected] for others, neither being statistically significantly. [The expected numbers were calculated by the Working Group from the expected rates per 1000 work-years quoted by the authors, on the grounds that in this form they convey better the order of magnitude of the comparison.]

[The Working Group re-examined the data on deaths and incident cases of cancer reported in the first two papers (Ingalls, 1950; Ingalls & Risquez-Iribarren, 1961). These cases occurred in the period 1939-1956 and totalled 15. Of these, eight were skin cancers (three basal-cell, one squamous, four melanoma), three were cancers of the colon (or large intestine), two of the lung, one of the stomach, and one of the tongue. Of the skin cases, five occurred in carbon-black workers and three in others. The very high proportion (>50%) of skin cancers among cancers at all sites is striking; the fact that half (four) were melanomas (two each among carbon-black and other workers) is even more impressive. This is the only large-scale study known to the Working Group that deals exclusively with carbon-black exposure; there was known to be heavy atmospheric contamination in the earlier processes used in its manufacture, which might help to account for the high incidence among all plant workers.]

In a retrospective cohort mortality study of male employees aged 15 years and over with 12 months or more service during the years 1935-1974 at carbon-black plants of four US

[1] The fatal case of melanoma of the skin, which was detected prior to 1 July 1949, was counted in the morbidity study of Ingalls (1950).

producers, 29 cancer deaths were observed (95% confidence interval, 19.4-41.6) with 41.0 expected (Robertson & Ingalls, 1980). Expected numbers of deaths were calculated from state vital statistics, death rates for white males at five-year intervals starting in 1937 applied to annual employee censuses by age, in five-year groups. Observed (95% confidence interval) compared to expected deaths were 6 (2.2-13.1) to 9.6 for cancers of the digestive organs and the peritoneum and 13 (6.9-22.3) to 14.7 for cancer of the respiratory system. For all malignancies combined, there was no evidence of increasing mortality with increasing years of service, no significant excess in any of the eight five-year periods and no trend over time.

[The US studies are uninformative with regard to cancer incidence and/or mortality at older (post-retirement) ages. In the Robertson and Ingalls (1980) report, 34 049 of the 34 739 person years at risk were for carbon-black workers aged 15-64 years and 690 were for those aged 65 and over. No analysis is presented relating cancer mortality to years since (first) exposure or relating cancer mortality to level of exposure. Completeness of ascertainment of follow-up of vital status is not documented. Restricting studies predominantly to employed workers aged less than 65 years limits the observable latent period, decreases statistical power to detect excesses, if present, particularly of site-specific cancers, and possibly underestimates cancer morbidity and mortality by not following workers who left the plant before retirement. The very unusual distribution by site of the cancers reported is the only evidence suggesting an effect of the exposure, although ascertainment bias favouring more complete detection of skin cancers cannot be ruled out.]

A general excess risk of cancer was reported in workers in one carbon-black producing plant in the USSR (Troitskaya *et al.*, 1980). [However, neither absolute figures nor the method of calculating observed to expected ratios were given.]

4. Summary of Data Reported and Evaluation

4.1 Experimental data

In a series of feeding studies in mice, which had several deficiencies in design and reporting, carbon blacks were reported not to produce the gastrointestinal tumours seen after administration of solvent (benzene) extracts from one carbon black.

Skin-painting studies with carbon blacks showed them to have no tumorigenic activity in mice, while solvent (benzene) extracts induced benign and malignant skin tumours.

Inhalation studies in mice, hamsters, guinea-pigs and monkeys with carbon blacks did not demonstrate tumorigenic activity; the studies suffered from many inadequacies, including poor characterization of the carbon black aerosol.

Studies in mice showed that materials extracted from carbon blacks were carcinogenic, producing local tumours after subcutaneous injection. A carbon black containing demonstrable quantities of carcinogenic polynuclear aromatic compounds also produced local sarcomas when injected subcutaneously in tricaprylin. Administration of the same carbon black as pellets in the absence of that solvent produced a low incidence of subcutaneous tumours.

In studies in mice by feeding, skin application and subcutaneous injection, administration of polynuclear aromatic hydrocarbons with known carcinogenic activities in combination with carbon blacks resulted in a lower tumour response than did administration of the carcinogens alone.

A commercial rubber-grade carbon black was tested in *Salmonella typhimurium* and mouse lymphoma cells for mutagenicity, in Chinese hamster ovary cells for induction of sister chromatid exchange, in mouse embryo cells for transforming ability, and in *Drosophila melanogaster* for clastogenicity and mutagenicity. No genetic effect or transforming ability was observed.

A commercial nitric acid-treated carbon black and its extract were tested for mutagenicity in *S. typhimurium* strain TA98 in the absence of an exogenous metabolic system. The toluene extract, but not the carbon black, was mutagenic.

A carbon black [type unspecified] and its extract were tested for mutagenicity in human lymphoblasts. Both the particles and the extract were mutagenic.

Extracts of various commercial carbon blacks were mutagenic to *S. typhimurium* in the presence and/or absence of an exogenous metabolic system. They have not been tested in other short-term tests for genetic activity.

Overall assessment of data from short-term tests on carbon blacks

As only one sample of carbon black particles has been adequately tested, no evaluation of the genetic activity in short-term tests of carbon blacks, as a class, was attempted.

Overall assessment of data from short-term tests on extracts of commercial carbon blacks[a]

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes		+		
Fungi/ green plants				
Insects				
Mammalian cells (*in vitro*)				
Mammals (*in vivo*)				
Humans (*in vivo*)				
Degree of evidence in short-term tests for genetic activity : *Inadequate*				Cell transformation : No data

[a] The groups into which the table is divided and '+', '−' and '?' are defined on pp. 16-17 of the preamble; the degrees of evidence are defined on p. 17.

4.2 Human data

Carbon blacks have been produced commercially since 1872. They have been made by a number of processes, but the oil-furnace process, which was introduced in 1943, is now by far the predominant process used.

The principal use of carbon blacks is in the production of rubber products (approximately 90% of total usage), with inks, paints and plastics accounting for almost all of the remaining use. The production of carbon blacks, their use in the production of rubber and other products, and the use and disposal of these products are sources of occupational, consumer and environmental exposure.

The available epidemiological studies on workers in the carbon-black producing industry are largely uninformative. The cohort studies provide limited information because most of the workers were not followed past retirement and the power of the studies to detect an effect was limited. One study showed a high proportion of cancers of the skin, particularly melanomas, which were found in equal numbers in a cohort of carbon-black workers and in a comparison group; the comparison group in this study consisted of other workers in the same plants. The epidemiological studies of other industries, in which the populations were also exposed to other substances, cannot be evaluated with regard to the carcinogenicity of carbon blacks; however, excesses of stomach cancer were reported in workers in jobs entailing exposure to dusts that include carbon blacks.

4.3 Evaluation[1]

The available data on carbon blacks are *inadequate* to permit an evaluation of their carcinogenicity to experimental animals. There is *sufficient evidence*[2] that solvent (benzene) extracts of most of the carbon blacks tested are carcinogenic to experimental animals.

The available epidemiological data provide *inadequate evidence* to evaluate the carcinogenicity to humans of carbon blacks.

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[1] See preamble, pp. 15 and 19, for definitions of italicized terms.

[2] In the absence of adequate data on humans, it is reasonable, for practical purposes, to regard chemicals for which there is *sufficient evidence* of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans.

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MINERAL OILS[1]

(LUBRICANT BASE OILS AND DERIVED PRODUCTS)

1. Chemical and Physical Data

1.1 Synonyms and trade names

Mineral oils (general)

Chem. Abstr. Services Reg. No.: 8002-05-9

Chem. Abstr. Name: Petroleum

IUPAC Systematic Name: --

Synonym: Petroleum distillate

In view of problems of nomenclature and of the wide differences in the production, uses and chemical, physical and toxicological characteristics of petroleum refinery materials, a system for defining petroleum crude oil refinery process streams was adopted in 1978 under the US Toxic Substances Control Act (TSCA) and in 1981 under the Commission of the European Communities's Sixth Amendment to the Dangerous Substances Directive - European Inventory of Existing Commercial Chemical Substances (EINECS). Each stream is defined on the basis of petroleum crude oil type, viscosity and process, and is identified by a Chemical Abstract Services (CAS) Registry Number, which identifies its last refining process.

The important refinery streams (most of which are used as lubricant base oils) that are included on the inventories of chemical substances in the USA and Europe are given in Table 1.

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[1] A general term that has been used to describe not only material covered in this monograph but crude petroleum and virtually all materials derived from it (e.g., light naphtha, gasoline, kerosene, middle distillates and fuel oils). Within this monograph, the term 'lubricant base oils' is used to refer to the refinery streams and the term 'lubricating oil' to the end product, as marketed, which is sold for lubricating purposes and may or may not contain additives.

Table 1. Properties of lubricant refinery streams as defined by the TSCA Inventory[a]

Chem. Abstr. Name	CAS number[b]	Carbon number distribution	Crude oil type	Viscosity at 40 °C (mm^2/sec)	Boiling range (°C)	Remarks
Crude oil distillation streams						
Light paraffinic distillate	64741-50-0	C15-C30	Paraffinic	<19	-	Contains a large proportion of saturated aliphatic hydrocarbons
Heavy paraffinic distillate	64741-51-1	C20-C50	Paraffinic	≥ 19	-	Contains a large proportion of saturated aliphatic hydrocarbons
Light naphthenic distillate	64741-52-2	C15-C30	Naphthenic	<19	-	Contains few normal paraffins
Heavy naphthenic distillate	64741-53-3	C20-C50	Naphthenic	≥ 19	-	Contains few normal paraffins
Vacuum residuum	64741-49-7	C11-C25	-	-	205-400	
Acid-treating streams						
Acid-treated light paraffinic distillate	64742-21-8	C15-C30	Paraffinic	<19	-	Predominantly saturated hydrocarbons
Acid-treated heavy paraffinic distillate	64742-20-7	C20-C50	Paraffinic	≥ 19	-	Predominantly saturated hydrocarbons
Acid-treated light naphthenic distillate	64742-19-4	C15-C30	Naphthenic	<19	-	Contains relatively few normal paraffins
Acid-treated heavy naphthenic distillate	64742-18-3	C20-C50	Naphthenic	≥ 19	-	Contains relatively few normal paraffins
Acid-treated residual oil	64742-17-2	>C25	-	-	>400	
Chemically neutralized streams						
Chemically neutralized light paraffinic distillate	64742-28-5	C15-C30	Paraffinic	<19	-	
Chemically neutralized heavy paraffinic distillate	64742-27-4	C20-C50	Paraffinic	≥ 19	-	Contains a relatively large proportion of aliphatic hydrocarbons
Chemically neutralized light naphthenic distillate	64742-35-4	C15-C30	Naphthenic	<19	-	Contains relatively few normal paraffins
Chemically neutralized heavy naphthenic distillate	64742-34-3	C20-C50	Naphthenic	≥ 19	-	Contains relatively few normal paraffins
Clay-treating streams						
Clay-treated light paraffinic distillate	64742-37-6	C15-C30	Paraffinic	<19	-	Contains a relatively large proportion of saturated hydrocarbons
Clay-treated heavy paraffinic distillate	64742-36-5	C20-C50	Paraffinic	≥ 19	-	Contains a relatively large proportion of saturated hydrocarbons
Clay-treated light naphthenic distillate	64742-45-6	C15-C30	Naphthenic	<19	-	Contains relatively few normal paraffins
Clay-treated heavy naphthenic distillate	64742-44-5	C20-C50	Naphthenic	≥ 19	-	Contains relatively few normal paraffins
Clay-treated residual oil	64742-41-2	>C25	-	-	>400	
Solvent-refining streams						
Solvent-refined light paraffinic distillate	64741-89-5	C15-C30	Paraffinic	<19	-	Predominantly saturated hydrocarbons
Solvent-refined heavy paraffinic distillate	64741-88-4	C20-C50	Paraffinic	≥ 19	-	Predominantly saturated hydrocarbons
Solvent-refined light naphthenic distillate	64741-97-5	C15-C30	Naphthenic	<19	-	Contains few normal paraffins
Solvent-refined heavy	64741-96-4	C20-C50	Naphthe-	≥ 19	-	Contains few normal

Chem. Abstr. Name	CAS number[b]	Carbon number distribution	Crude oil type	Viscosity at 40 °C (mm^2/sec)	Boiling range (°C)	Remarks
naphthenic distillate			nic			paraffins
Solvent-deasphalted residual oil	64741-95-3	>C25	-	-	>400	Obtained as the solvent-soluble fraction from C3-C4 solvent deasphalting of a residuum
Solvent-refined residual oil	64742-01-4	>C25	-	-	>400	Obtained as the solvent-insoluble fraction from solvent refining of a residuum using a polar organic solvent such as phenol or furfural
Hydrotreating streams						
Hydrotreated light paraffinic distillate	64742-55-8	C15-C30	Paraffinic	<19	-	Contains a relatively large proportion of saturated hydrocarbons
Hydrotreated heavy paraffinic distillate	64742-54-7	C20-C50	Paraffinic	≥ 19	-	Contains a relatively large proportion of saturated hydrocarbons
Hydrotreated light naphthenic distillate	64742-53-6	C15-C30	Naphthenic	<19	-	Contains relatively few normal paraffins
Hydrotreated heavy naphthenic distillate	64742-52-5	C20-C50	Naphthenic	≥ 19	-	Contains relatively few normal paraffins
Hydrotreated residual oil	64742-57-0	>C25	-	-	>400	
White mineral oil (Liquid paraffin; pharmaceutical-grade white oils; food-quality oils; technical oils; technical white oils)	8042-47-5	C15-C50	-	-	-	Obtained by intensive treatment with sulphuric acid and oleum or by hydrogenation
Petrolatum	8009-03-8	>C25	Paraffinic	Semi-solid	-	Predominantly saturated crystalline and liquid hydrocarbons
Complex-dewaxing streams						
Complex-dewaxed light naphthenic oil	64742-76-3	C15-C30	Naphthenic	<19	-	Contains relatively few normal paraffins
Complex-dewaxed heavy naphthenic oil	64742-75-2	C20-C50	Naphthenic	≥ 19	-	Contains relatively few normal paraffins
Extracts						
Light paraffinic distillate solvent extract	64742-05-8	C15-C30	Paraffinic	-	-	Predominantly aromatic hydrocarbons
Heavy paraffinic distillate solvent extract	64742-04-7	C20-C50	Paraffinic	-	-	Predominantly aromatic hydrocarbons
Light naphthenic distillate solvent extract	64742-03-6	C15-C30	Naphthenic	-	-	Predominantly aromatic hydrocarbons
Heavy naphthenic distillate solvent extract	64742-11-6	C20-C50	Naphthenic	-	-	Predominantly aromatic hydrocarbons
Residual oil solvent extract	64742-10-5	>C25	-	-	-	Predominantly aromatic hydrocarbons
Solvent-dewaxing streams						
Solvent-dewaxed light paraffinic distillate	64742-56-9	C15-C30	Paraffinic	<19	-	Obtained by removal of normal paraffins
Solvent-dewaxed heavy paraffinic distillate	64742-65-0	C20-C50	Paraffinic	≥ 19	-	Obtained by removal of normal paraffins
Solvent-dewaxed light naphthenic distillate	64742-64-9	C15-C30	Naphthenic	<19	-	Obtained by removal of normal paraffins
Solvent-dewaxed heavy naphthenic distillate	64742-63-8	C20-C50	Naphthenic	≥ 19	-	Obtained by removal of normal paraffins

Chem. Abstr. Name	CAS number[b]	Carbon number distribution	Crude oil type	Viscosity at 40 °C (mm^2/sec)	Boiling range (°C)	Remarks
Solvent-dewaxed residual oil	64742-62-7	>C25	-	-	>400	Obtained by removal of normal paraffins
Catalytic-dewaxed streams						
Catalytic-dewaxed light paraffinic distillate	64742-71-8	C15-C30	Paraffinic	<19	-	
Catalytic-dewaxed heavy paraffinic distillate	64742-70-7	C20-C50	Paraffinic	≥ 19	-	
Catalytic-dewaxed light naphthenic distillate	64742-69-4	C15-C30	Naphthenic	<19	-	Contains relatively few normal paraffins
Catalytic-dewaxed heavy naphthenic distillate	64742-68-3	C20-C50	Naphthenic	≥ 19	-	Contains relatively few normal paraffins

[a] From US Environmental Protection Agency (1978); TSCA, US Toxic Substances Control Act

[b] CAS number, Chemical Abstract Services Registry Number

1.2 Description

For the purposes of this monograph, the materials described in section 1.1 above and the products derived from them have been categorized into the following eight classes:

Class 1. Vacuum distillates
These may have undergone subsequent finishing steps, such as caustic neutralization, dewaxing, clay treatment and/or mild hydrotreatment. They have not been acid treated or solvent extracted.

Class 2. Acid-treated oils
These may have undergone subsequent finishing steps, such as caustic neutralization, dewaxing, clay treating and/or mild hydrotreatment. They have not been solvent extracted.

Class 3. Solvent-refined-oils (raffinates)
These may have undergone subsequent finishing steps, such as dewaxing, clay treating and/or mild hydrotreatment.

Class 4. Hydrotreated oils

Class 5. White oils and petrolatums suitable for food and/or medicinal use

Class 6. Aromatic oils
6.1 Solvent extracts
6.2 Catalytically cracked oils

Class 7. Miscellaneous materials
7.1 Formulated products
7.2 Used oils

Class 8. Petroleum-derived materials not otherwise classified (not sufficiently described to permit assignment to other classes)

This classification is based on increasing severity of processing or refinement; within each class a range of treatment severities is also possible. Mineral oils in class 7 comprise formulations of various base oils from the previous categories, together with chemical

additives, usually not identified with respect to exact composition. Mineral oils have been assigned to class 8 in cases where they were not sufficiently described for the Working Group to determine a more specific classification.

Throughout this monograph, when the names of lubricant base oils or derived products are used as headings for separate discussions, the class (representing the major processing step) to which the material belongs is given in brackets. In separate discussions of formulated products in which the base oils used to make the products are described, the appropriate classes of those base oils are given.

'Mineral oils' (lubricant base oils and products derived from them) should not be confused with oil distilled from coal and oil-bearing shale. The latter gave rise to the Scottish shale-oil industry from 1850 onwards; however, shale oil was increasingly unable to compete economically with liquid petroleum, although it survived on a small scale until as late as 1960. There was also a small production in Roumania which lasted from 1857 until 1939. Shale-oil production is now minimal, with a small activity in the People's Republic of China, the USA and the USSR.

The refining of petroleum crude oil produces two basic types of product: fuels and lubricating oils. The oils described in this monograph are used primarily as lubricating oils, which are substances intended to reduce friction between surfaces in relative motion. They may also serve other, secondary purposes, including heat transfer, metal processing, corrosion protection, medicinal and food uses, and others. Since the 1930s, nearly all the world's lubricating oils have been produced by refining distillate or residual fractions obtained directly from petroleum crude oils.

Processes used in the refining of lubricant base oils and subsequent product formulation have changed considerably over the years. The trend has been towards highly refined oils with substantially reduced levels of impurities, including polynuclear aromatic compounds. Today, over 74% of lubricant capacity in the USA and Canada is used to produce highly refined base oils.

The chemical composition of lubricant base oils depends both on the original crude substance and on the processes used during refining. With simple refining techniques, the composition of the finished oil used as the base oil in formulated products reflects that of the crude. After severe refining, variations due to crude are less apparent.

Finished base oils are predominantly hydrocarbons but also contain some organic sulphur, oxygen and nitrogen compounds and traces of a number of metal compounds. The hydrocarbons are normally a complex mixture of aromatics, naphthenes (cycloparaffins) and paraffins. The proportions of the different species are responsible for the different characteristics of the base oils. The higher the molecular weights, the more viscous are the oils.

Lubricant refinery streams

Lubricant base oils refined from petroleum crude oils are complex mixtures of straight- and branched-chain paraffinic, naphthenic (cycloparaffin) and aromatic hydrocarbons having carbon numbers of 15 or more and boiling-points in the range of about 300-600°C. Heavier lubricant base oils obtained from residual fractions may have components that boil at as high as 815 °C.

A lubricant refinery stream may be described as generally paraffinic or generally naphthenic, as determined by the source of the crude oil. Paraffinic crude oils are characterized by high wax content, high natural viscosity index (low rate of change in viscosity with temperature) and relatively low aromatic hydrocarbon content. Naphthenic crudes are normally low in wax and relatively high in cycloparaffins and aromatic hydrocarbons.

The various lubricant refinery streams have a wide range of properties. The inventory of chemicals adopted under the US Toxic Substances Control Act (TSCA) and the European Inventory of Existing Commercial Chemical Substances (EINECS) broadly describe the properties of each process stream according to its boiling range, carbon number distribution, crude oil source and viscosity. The properties of the lubricant refinery streams covered by this monograph are presented in Table 1. The viscosity is termed 'light' or 'heavy' on the basis of a maximum viscosity of 20.5 mm^2/sec. (centistokes) at 37.8°C for the 'light' viscosity oils. A stream is further classified according to the last process it has been through; however, such classification does not permit definition of process severity: therefore, it is possible for the same Chemical Abstract Service (CAS) Registry Number to be used for base oils treated to different degrees or by different previous processes (e.g., a hydrotreated distillate may have been either solvent-refined or acid-refined). Consequently, complete characterization of a stream should include its process history (i.e., all the processes it has been through).

White oils [class 5]

Medicinal: Medicinal white oils are highly refined, colourless oils free of all unsaturated compounds, aromatic compounds and other constituents that influence colour, odour, taste and acceptability as a pharmaceutical and food-grade material (World Health Organization, 1982). They can be made from paraffinic or naphthenic crudes with comparable yields; paraffinic medicinal oils generaly have lower specific gravity and volatility than naphthenic oils of the same viscosity (Lecomte *et al.*, 1977) and contain hydrocarbons predominantly with carbon numbers in the range 15-50 (US Environmental Protection Agency, 1978).

Technical-grade: Technical-grade white oils are less refined than medicinal oils; they are colourless oils and are made in several viscosity grades (Shell International Petroleum Company, Ltd, 1966). They can be made from naphthenic or paraffinic crudes (Lecomte *et al.*, 1977).

1.3 Chemical and physical properties

The materials covered by this monograph contain relatively high molecular-weight paraffinic, cycloparaffinic and aromatic hydrocarbons. Consequently, they can undergo a wide variety of characteristic chemical reactions (e.g., oxidation, hydrogenation, halogenation, sulphonation). However, the materials are used primarily for their physical properties, and this section concentrates on those characteristics.

Typical properties of representative lubricant base oils are given in Table 2.

Table 2. Physical properties of representative lubricant base oils

Type	Viscosity (mm^2/sec) at 40 °C	at 100 °C	Flashpoint[a] (°C)	Pourpoint (°C)	Density at 15 °C (kg/l)	Viscosity index[b]
White oils						
Paraffinic						
Medicinal						
Light	14.8	3.4	208	-12	0.844	99
Heavy	66.7	7.8	228	- 6	0.884	57
Technical						
Light	15.4	3.5	195	-15	0.843	100
Heavy	67.0	7.5	230	-14	0.890	68
Naphthenic						
Medicinal						
Light	14.2	3.1	--	-49	0.868	70
Heavy	68.7	7.8	--	-23	0.885	70
Base/Process oils						
Paraffinic						
Light	18.9	3.9	196	-12	0.820	
Heavy	650	34.8	307	- 9	0.846	
Naphthenic						
Light	7.9	2.2	150	-42	0.840	
Heavy	492	16.4	250	- 9	0.950	
High aromatic						
Light	65	6.0	212	3	1.016	
Heavy	1 080	25.1	247	26	1.001	

[a] Cleveland open cup method

[b] Viscosity index is a measure of the rate of change of viscosity over a given temperature range; the higher the index number, the less the viscosity varies as a result of temperature change

1.4 Technical products and impurities

The composition and properties of the lubricant base oils are described in sections 1.2 and 1.3, above. Additional information is presented here on the white oils and on the impurities found in lubricant base oils. The properties of the products derived from the lubricant base oils are presented in section 2.1 (*b*), *Use*.

(*a*) *Medicinal white oils* [class 5]

The majority of developed countries have established specifications and food regulations controlling the quality and usage of pharmaceutical-grade white oils. For example, the *US Pharmacopeia* (USP) has established specifications for medicinal white oils and light medicinal white oils. These require that medicinal white oils have a specific gravity of 0.845-0.905 and a viscosity of not less than 34.5 mm^2/sec (at 40°C). The corresponding requirements for light

medicinal white oils are: specific gravity, 0.818-0.880; viscosity, less than 33.5 mm^2/sec (at 40°C). Both types of medicinal white oil must be neutral to moistened litmus paper when boiled in alcohol, pass a test for readily carbonizable substances, have an ultraviolet absorbance in the range of 260-350 nm not greater than one-third that of a standard solution of naphthalene [a measure of the content of polynuclear aromatic compounds], and pass a test for the presence of solid paraffins, in which a chilled sample of medicinal oil retains its clarity. Medicinal white oils may contain a suitable stabilizer (US Pharmacopeial Convention, Inc., 1980).

The US Cosmetic, Toiletry and Fragrance Association has also established specifications for medicinal white oils, requiring that such oils be free of foreign materials, be odourless at room temperature and have no objectionable odour after heating, and meet buyer's specifications for taste and for viscosity at 38°C. These oils must meet *US Pharmacopeia* requirements for readily carbonizable substances, solid paraffins, and 'polynuclear compounds' [sic]. In addition, they must pass specific tests for the presence of water-soluble acids and alkalis, and sulphur and sulphides. Other requirements are: lead (as Pb), 20 mg/kg maximum; arsenic (as As), 3 mg/kg maximum; and ash, 0.005% maximum (Estrin, 1974).

Medicinal white oils may contain α-tocopherol (vitamin E) at levels of up to 10 mg/kg as an antioxidant (Marathon Morco Company, undated). The range of specifications for four grades of medicinal white oils that were formerly available from one US manufacturer are as follows (Exxon Corporation, 1980): specific gravity at 25°C, 0.864-0.871; viscosity (mm^2/sec at 40°C), 35.7-67.8; flash-point (°C), 185-221; and pour-point (°C), -23 to -18.

Polynuclear aromatic compounds have been detected in samples of mineral oil for medicinal and cosmetic uses. The results from three reports are summarized in Table 3. Another source (Concawe, 1983a) has reported the content of six polynuclear aromatic hydrocarbons (PAHs) in white oils (Table 4). However, Bingham *et al.* (1980) reported that no identifiable PAHs were detected at a level of 1 μg/kg in five samples of USP grade mineral oil.

Table 3. Polynuclear aromatic compounds (PACs) identified in mineral oils for medicinal and cosmetic uses

PAC	Concentration (mg/kg)		
	Medicinal oil[a]	Medicinal oil[b]	Suntan oil[c]
Phenanthrene	140.0	-	-
Triphenylene	1.5	-	-
Fluoranthene	-	18.4-25.9	116.3
Alkylfluoranthene	10.0	-	-
Perylene	-	1.1	2.0
Benzo[*k*]fluoranthene	1.0	0.4-1.1	1.3
Benzo[*b*]fluoranthene	-	2.0	-
Benzo[*a*]pyrene	-	3.1-8.6	1.5
Alkyl dibenzothiophenes	180.0	-	-

[a] From Popl *et al.* (1975)

[b] From Monarca *et al.* (1981)

[c] This suntan oil was a mineral oil-based commercial product used in Italy.

Table 4. Polynuclear aromatic hydrocarbon (PAH)[a] content of white oils[b]

White oil type	Manufacturing route	PAH content[c] (g/kg)
Viscosity grade, light		
Paraffinic	Conventional	0.4-1.6
	Hydrogenation	
	Type 1	0.07-1.6
	Type 2	0.06-1.0
Naphthenic	Conventional	0.1-0.9
Viscosity grade, heavy		
Paraffinic	Conventional	0.2-1.6
	Hydrogenation	
	Type 1	0.07-1.4
	Type 2	0.06-0.9
Naphthenic	Conventional	0.08-0.9
	Hydrogenation	
	Type 1	0.1-0.9
	Type 2	0.2-1.2

[a] The six PAHs are: fluoranthene, benzo[*b*]fluoranthene, benzo[*k*]fluoranthene, benzo[*a*]pyrene, benzo[*ghi*]perylene and indeno[1,2,3-*cd*]pyrene

[b] From Concawe (1983a)

[c] Range of results obtained by participating laboratories for sum of 6 PAHs

Japanese pharmaceutical specifications require that medicinal white oils contain no more than 0.4% aromatic compounds and a minimum of 99.6% saturated hydrocarbons. These oils must be free of colour, odour and taste, and exhibit no fluorescence.

(*b*) *Technical-grade white oils* [class 5]

In the USA, light technical-grade white oils made from paraffinic base stock for use as a component of nonfood articles intended for use in contact with food must meet specifications which require that the ultraviolet spectra of a dimethyl sulphoxide extract of the oil not exceed certain absorbance maxima at specific wavelengths (US Food & Drug Administration, 1980a).

The range of specifications for three grades of technical white oil available from one US manufacturer until recently was as follows (Exxon Corporation, 1979): specific gravity at 25°C, 0.833-0.855; viscosity (mm^2/sec at 40°C), 12.9-16.7; flash-point (°C), 171-185; and pour-point (°C), -20 to -7.

Some technical white oils contain α-tocopherol (vitamin E) at levels of up to 10 mg/kg as an antioxidant (Penreco, undated).

(*c*) *Impurities in lubricant base oils*

All crude oils contain some polynuclear aromatic compounds (PACs). Although the contents vary with crude source, the proportions and types of such compounds in finished base oils are determined mainly by the refining processes. Mild processing, such as acid/clay, reduces the total aromatic content slightly but does not significantly reduce the amount of PACs. Mild hydroprocessing, on the other hand, reduces the PAC content but has little effect on the total aromatic hydrocarbon content. Solvent extraction, or severe hydroprocessing reduces both the

PAC and the total aromatic content substantially. Sufficiently severe treatment with fuming sulphuric acid (oleum) can remove aromatics, including PACs, almost entirely, for example, to produce white oils of medicinal quality.

Trace amounts of water and insoluble particulates, e.g., sand, rust, etc., may be present in lubricant base oils. Other impurities include traces of solvent from solvent refining processes, e.g., phenol, furfural, etc., and traces of clays carried over from clay-treating processes.

A wide range of polynuclear aromatic compounds have been identified in unused engine lubricating oils [class 7.1]. As shown in Table 5, the levels of these compounds generally increase after the oil has been used [class 7.2] (Grimmer *et al.*, 1981a,b). Benzo[*a*]pyrene levels (ranging from 0-170 μg/l) in cutting oils [class 7.1] also increased with use [class 7.2] (0.6-250 μg/l) (Thony *et al.*, 1975).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

The processes used to produce lubricant base oils and, correspondingly, product formulation have changed considerably over the years. Until about 1940, processing consisted of acid refining with clay finishing and subsequent dewaxing by chilling. Solvent refining (and solvent dewaxing) was first introduced in the USA and in Europe in the 1930s. Hydrotreating, as a newer, more severe process than 'hydrofinishing' was introduced in the 1960s. The trend has been toward more highly refined oils with associated removal of unwanted impurities including polynuclear aromatic compounds.

In the USA and Canada, 74% of all finished lubricant capacity includes solvent refining as a processing step. Although figures are not readily available for other regions of the world, refining and product formulation practices are probably similar. This is particularly true for western Europe, Asia and Australia.

(*a*) *Production*

(i) *Lubricant base oils*

Lubricant refinery processes have as their objective the removal from the distillate of a variety of constituents that are undesirable from a product performance viewpoint. Some of these undesirable constituents are:

- bitumens, also known as 'asphalts' in the USA (these are thermally unstable, easily oxidized, usually too viscous and dark in colour);

- waxes (these interfere with desired flow properties in service);

Table 5. Ranges and most frequent concentrations of polynuclear aromatic compounds in various motor oils (fresh and used) (mg/kg)

Polynuclear aromatic compound	Fresh motor oil (22 samples)		Used motor oil from vehicles with Otto-engines (22 samples)		Used motor oil from diesel vehicles (10 samples)		Used motor oil from diesel lorries (10 samples)		Used motor oil[c] from diesel buses (12 samples)
	Range[a]	Most frequent[b]	Range[c]	Most frequent[b]	Range[c]	Most frequent[b]	Most frequent[b]	Range	Average
Fluoranthene	0.008-2.75	0.070	3.4-109.0	50.0	1.3-58.9	16.0	0.18-2.90	1.2	0.4-2.7 1.9
Pyrene	0.039-6.53	0.300	5.7-326.0	135.0	1.4-78.0	25.0	0.33-6.40	1.6	0.9-4.9 3.3
Benzo[*b*]naphtho[2,1-*d*]thiophene	0.097-9.43	0.700	ND[d]	ND[d]	0.7-4.3	2.5	0.78-6.20	1.5	1.6-4.8 3.3
Chrysene + triphenylene	0.182-11.9	0.700	8.7-74.0	40.0	5.1-42.8	10.0	1.60-6.10	2.0	1.9-8.0 3.2
Benzofluoranthenes [*b*+*j*+*k*]	0.013-0.234	0.080	5.7-44.3	30.0	1.8-16.8	6.0	0.26-1.30	0.5	0.37-1.2 0.57
Benzo[*e*]pyrene	0.030-0.402	0.200	6.4-48.9	35.0	1.3-10.7	3.0	0.23-1.10	0.3	0.29-1.04 0.57
Benzo[*a*]pyrene	0.008-0.266	0.060	5.2-35.1	23.0	0.7-11.9	5.0	0.13-0.60	0.2	0.07-0.55 0.22
Perylene	0.007-0.224	0.060	1.9-10.0	6.0	0.4-2.7	0.7	0.11-0.35	0.14	0.04-0.29 0.08
Indeno[1,2,3-*cd*]pyrene	0.001-0.020	0.001	2.1-12.5	9.0	0.8-9.0	2.0	0.06-0.28	0.12	0.07-0.25 0.15
Benzo[*ghi*]perylene	0.010-0.139	0.020	4.4-85.2	60.0	2.1-16.0	3.0	0.20-0.78	0.30	0.26-0.65 0.40
Anthanthrene	0.002-0.030	0.010	1.6-10.8	8.0	0.5-4.4	1.2	0.02-0.12	0.04	0.03-0.16 0.08
Coronene	0.001-0.016	0.020	2.8-29.4	20.0	0.1-6.4	1.0	0.10-0.13	0.02	0.00-0.08 0.05

[a] Grimmer *et al.* (1981a)

[b] Adapted from Grimmer *et al.* (1982a)

[c] Grimmer *et al.* (1981b)

[d] ND, not determined

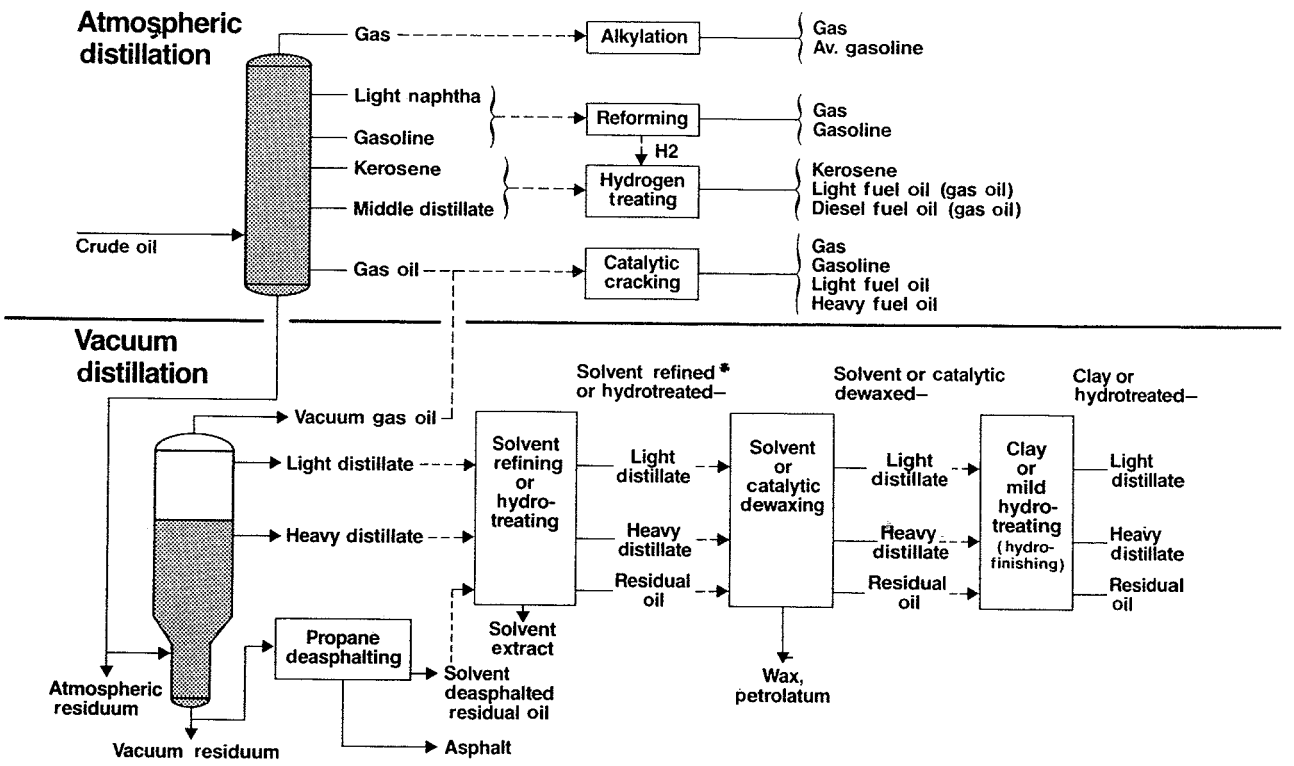
- unstable components (these are reactive under thermal oxidative conditions leading to discoloration, odour, thickening and shorter service life);

- dark-coloured materials (these are removed to improve colour and improve stability).

The processes used to produce lubricant base oils are described in the paragraphs that follow (certain processes discussed below also remove high-boiling polynuclear aromatic compounds, the carcinogenic potential of which has been the subject of intense studies).

Distillation: Figure 1 shows a typical processing plan for a petroleum refinery which includes both the fuels section and the lubricants section. Atmospheric distillation is undertaken to fractionate the petroleum crude oil into fuel components of various boiling ranges, i.e., gas, naphtha, gasoline, kerosene, middle distillate and gas oils, which are processed as shown to produce the normal boiling-range fuel products of specified boiling range.

Fig. 1. Simplified processing plan for a petroleum refinery



* Acid refining is also used but only on a small scale currently

The vacuum distillation unit is fed with the residuum from atmospheric distillation which is fractionated into distillates of progressively increasing viscosity, carbon number and boiling range. Normally, the vacuum gas oil is processed in the fuels section, except for a limited quantity that may be required to produce particularly low-viscosity spindle oils and transformer oils. The principal lubricant fractions, distillates and the vacuum residuum are processed further in modern lubricants refineries.

Propane deasphalting: Solvent deasphalting with liquid propane has become established in modern refineries as the most economic and efficient deasphalting process. The liquid propane solvent precipitates out the resins and the asphaltenes while dissolving the saturates and aromatic hydrocarbons, to produce a deasphalted residual oil that requires further solvent extraction to remove undesirable aromatic hydrocarbons.

Solvent extraction: Solvent extraction with furfural has become the predominant process for treating lubricants in modern refineries. Treatment with phenol solvent is practised to a more limited degree. More recently, some phenol and furfural units have been converted to use *N*-methyl-2-pyrrolidone, to take advantage of reported economies in processing.

The solvent-extraction process selectively removes undesirable components. Following solubilization of the aromatic compounds (including polynuclear aromatic compounds), the process proceeds selectively to remove olefins, naphthenes and then (least soluble) paraffins. The degree of solvent extraction is controlled to produce treated products of selected characteristics. 'Severe' solvent extraction produces highly refined oils with the oxidative and thermal stability required for use in automotive and industrial engines, hydraulic systems, turbines, etc. 'Mild' solvent extraction produces oils that may be more aromatic. These are used when better solvency characteristics are required.

Aromatic extracts (sometimes called 'aromatic oils') are obtained as by-products from the solvent extraction process. In general, extracts consist of liquid and resinous hydrocarbons, containing more than 40% aromatic compounds of widely varying complexity (American Petroleum Institute, 1969). The quantity and type of extracts recovered depends on the chemical composition of the base oil distillate, on the solvent used, and on the extraction ratio. Sulphur, nitrogen and acidic compounds tend to be concentrated in distillate extracts, which are also very rich in polynuclear aromatic compounds (PACs). Residual extracts are lower in PAC content.

Hydrotreating (hydrogen processing): Hydrotreating, in the presence of a suitable catalyst, is a general term embracing several different refinery processes, one of which, hydrofinishing, is described in Section 2.1 below. This catalytic hydrogenation processing of lubricant base oils is sometimes used in conjunction with solvent refining. Briefly, the lubricant base oil is made more paraffinic by the saturation of olefins. The severity of the hydrogenation dictates the degree of conversion of aromatic compounds (including polynuclear aromatic compounds) to naphthenes, and the opening of ring compounds by removal of chemically bound sulphur, nitrogen and oxygen.

Solvent dewaxing: In order to impart optimal low-temperature flow characteristics, waxes (high molecular-weight paraffins) must usually be removed from lubricant base oils following solvent extraction. The waxy lubricant oil fraction is diluted with a dewaxing solvent, e.g., a methyl ethyl ketone/toluene mixture or propane, and is then chilled, the wax crystals formed being separated from the solvent/oil mixture by filtration. The solvent is recovered by distillation.

In recent years, a new catalytic dewaxing process has been commercialized; long-chain paraffins are cracked and isomerized in the presence of a catalyst and hydrogen. The process includes mild hydrogenation as a final stabilization step, followed by removal of small amounts of light hydrocarbons by normal stripping methods.

Another dewaxing process involves mixing urea (three parts) with oil (one part) and heating to about 40°C. At this temperature, a wax-urea complex is formed which is insoluble in the

oil, and can be removed by filtration. The urea and wax are recovered by treating the complex with water at about 77°C (Kent, 1974).

Acid treating: For many years, mild acid refining has been used to improve the colour, odour and stability of lubricant base oils by removing unstable hydrocarbons, resins and asphalts as well as sulphur-, nitrogen- and oxygen-containing compounds. Sulphuric acid acts by both chemical and solvent action. The acid sludge which forms is separated by settling or centrifuging, and the remaining oil is freed from traces of acid by neutralization with caustic soda, water washing or absorption by clay, or a combination of these methods.

That process is being replaced by solvent refining and/or hydrotreating, except in the case of certain specialty oils with very particular specifications, such as transformer oils, cable oils and white oils. An example is the refining of medicinal white oils using fuming sulphuric acid (oleum), which removes virtually all aromatic compounds. As hydrotreating develops further it is expected that acid treating will be virtually eliminated or reduced to very limited specialty uses. Even medicinal white oils can now be produced solely by hydrotreatment.

Finishing: The principal utility of a finishing step is to remove trace impurities and to improve colour by clay treatment or mild hydrotreatment (hydrofinishing). Moderate removal of sulphur, oxygen and nitrogen compounds occurs during the mild hydrotreating process, with little other effect on bulk physical or chemical properties of the lubricant base oil.

(ii) *Derived products*

Lubricant refinery streams are the starting base oils from which formulated lubricating oils are manufactured. Depending upon the specific application, one or more additives may be incorporated into the chosen refinery stream(s) in amounts ranging from a few mg/kg to 20%, although, typically, individual additives are present at concentrations of less than 2%. Automotive crankcase lubricants are by far the largest market for additives, but they are also widely used in many industrial lubricants to impart or enhance the technical characteristics required for many special applications. Although the additives are categorized by the particular function they perform, it should be noted that some are multifunctional (e.g., certain viscosity index improvers also act as pour-point depressants or dispersants) (Wills, 1980; Booser, 1981).

Additives are usually proprietary materials and not necessarily well defined chemical substances; hence it is not possible to provide here complete details of their composition. The following are the main types of additives used (Concawe, 1983b).

Additives to modify physical characteristics include:

- viscosity index improvers, which modify the viscosity/temperature characteristics of the lubricant, i.e., they reduce the rate at which viscosity decreases as temperature increases; they are polymers or co-polymers based on methacrylates, olefins or styrenes;

- pour-point depressants, which improve fluidity at low temperatures, i.e., they decrease the temperature at which an oil ceases to flow; usually they are polymers related to those used as viscosity index improvers, but of higher molecular weight;

- tackiness agents, which are added when it is necessary that an oil adhere more firmly to surfaces; normally they are high molecular-weight polymers such as polybutenes;

- anti-foam additives, which are used when it is necessary to reduce foaming; normally they are methyl silicone polymers;

- emulsifiers, which impart water dispersibility characteristics and may be cationic, anionic or non-ionic materials; usually they are based on long-chain aliphatic acids, amines, alcohols, esters or ethers; and

- friction modifiers, which are used to adjust frictional properties; they include organic acids, amines or natural fats, oils and waxes, and their derivatives.

Additives to modify chemical characteristics include:

- antioxidants: a wide range of chemical types is used to reduce oil oxidation at elevated temperatures; they include amines (e.g., *N*-phenyl-1-naphthylamine), phenols (e.g., 2-naphthol and di-*tert*-butyl-*para*-cresol and related hindered phenols) and a variety of zinc, calcium, barium and magnesium salts, including dialkyl dithiophosphates, salicylates, phenates and sulphonates;

- antirust additives, which include derivatives of di-basic organic acids, salts of alkali and alkaline earth metals (e.g., organic sulphonates and phosphates), nitrites and aliphatic amine derivatives;

- metal deactivators, which control corrosion of metals, mainly those containing copper; frequently, they are substituted diamines or ring compounds containing nitrogen, e.g., triazoles or thiazoles;

- antiwear and extreme-pressure additives, which are used to improve lubrication properties under high-load and high-temperature conditions; a wide variety of compounds is used, including compounds containing oxygen (fatty acids, esters and ketones), compounds containing oxygen and/or sulphur (sulphurized fats), aliphatic chlorine compounds (chlorinated wax), organic sulphur compounds (sulphurized olefins), compounds containing both chlorine and sulphur, organic phosphorous compounds (tricresyl phosphate, thiophosphates and phosphites) and organic zinc and lead compounds (Booser, 1981);

- detergents/dispersants, which are widely used in engine oils; detergents are most frequently calcium and barium salts of organic sulphonates, salicylates and phenols, and may contain excess base; dispersants are often aliphatic amines, imides, ether derivatives or salts of various kinds; and

- biocides, which are materials used to control bacterial and fungal growth; they include boron compounds, phenol and chlorophenol derivatives, and compounds that slowly release formaldehyde under conditions of use, e.g., triazines.

The lubricant base oils described in the manufacturing sequences are used for a broad ranges of products. The principal base oils are produced predominantly from paraffinic crudes and used for lubrication of internal combustion engines and a wide variety of industrial, non-engine machinery e.g., gears, bearings and pumps. Refined naphthenic base oils are used to a lesser degree and for specific applications in which their low-temperature properties and other characteristics, such as their good solubility for additives, are required.

Since most of the concepts and technology utilized in formulating products are proprietary to each manufacturer, these matters can be discussed only in general terms. Table 6

(Concawe, 1983b) addresses the issue from the standpoint of the applications of lubricating oils in terms of their composition. (Table 6 also includes greases, which are lubricating oils thickened with metallic soaps or certain organophilic clays.) It gives a general indication of how the main types of lubricants for different applications fall into the different compositional groups. For each application, the compositional groups mainly used, other compositional groups used and compositional groups occasionally used are indicated. Also, lubricant oil refinery streams are divided into two broad groups: those that are *'highly refined'* and those that have undergone, at best, only *'limited refining'*. *'Highly refined'* oils are likely to have been severely hydrotreated and/or severely solvent refined (extracted) or oleum-treated. Those oils described as having undergone *'limited refining'* are those that have been subjected only to sulphuric acid/clay treatment, mild solvent refining (extraction) or mild hydrotreatment.

Table 6. Classification of lubricant use by compositional group[a,b]

Application	Compositional groups		
	Mainly used	Others used	Occasionally used
Crankcase engine oils	A_2	A_1, E	A_1
Other engine oils	A_2	-	-
2-Stroke engine oils	A_2, C	-	-
Automotive transmission gear oils	A_2	-	-
Industrial transmission gear oils	A_2	A_1	C, E, F
General circulating oils	A_2, A_1	B	-
Simple lubricating oils	-	A_1, A_2, B	-
Hydraulic oils	A_2	A_1	D, E
Turbine oils	A_2	-	-
Machine-tool oils	A_2	A_1	-
Compressor oils	A_2	A_1	E
Heat-transfer oils	A_1	-	A_2, B
Heat-treatment oils	A_1, B	-	A_2
Cutting oils	A_2, D	A_1	B, E, C
Rolling oils - ferrous	D	-	A_2
Rolling oils - non-ferrous	A_2, D	C	-
Other metal-forming oils	-	A_2, B, C, F	-
Electrical oils	A_1	B	A_2, E
Refrigerator oils	A_1	B	A_2, E
Food-machinery lubricants	A_1	F	-
Textile oils	A_2, D	-	A, C
Steam-cylinder oils	A_1, A_2	B	-
Automotive and industrial greases	F (A_1, A_2, B)[c]	-	F(E)
Protectives	C, F, A_2	B	D
Pneumatic-tool oils	A_2	-	-

[a] From Concawe (1983b)

[b] Compositional group classifications (which should be considered as only broadly indicative) are;

A_1 Lubricants without additives produced from highly refined mineral base oils [classes 3, 4, 5]

A_2 As A_1 but additionally containing additives, i.e., materials other than mineral oils, added in concentrations from a few mg/kg to about 20% [class 7.1, with base oils in classes 3, 4, 5]

B Lubricants with or without additives produced from base oils that have been refined to a limited degree by procedures which do not reduce aromatic hydrocarbon content to the levels achieved by normal solvent refining.

These now represent only a minority of production having been largely replaced by groups A_1 and A_2 [class 7.1, with base oils in classes 1, 2 or mildly treated 3, 4]

C Lubricants containing a significant proportion of light petroleum distillates (e.g., white spirit, kerosene) or other volatile solvents [class 7.1]

D Emulsifiable oils which readily form emulsions with water or are used as such [class 7.1]

E Lubricants containing a major (more than 50%) proportion of synthetic base oils with or without additives [class 7.1]

F Solid or semi-solid materials such as lubricating greases and compounds. (There is no precise definition of compounds but the term is normally applied to solid/semi-solid lubricants which do not fall within the definition of greases.) [class 7.1]

[c] Compositional groups listed in brackets indicate the fluid component types used.

Additional formulation concepts are described by product type below.

White oils [class 5]: Medicinal and technical-grade white oils are generally produced by severe refining of naphthenic or paraffinic distillates to remove unsaturated compounds and compounds that impart colour, odour or taste. The distillates are usually solvent-extracted and repeatedly treated with strong sulphuric acid (or oleum) and alkali (Shell International Petroleum Company Ltd, 1966). Neutralization and clay treatment yield the white-oil products. Technical grades are less rigidly purified than the medicinal grades, which receive more severe treatment. This severe treatment gives low yields (about 50%) and removes natural inhibitors; consequently, oxidation inhibitors such as α-tocopherol (vitamin E) may be added (Codd *et al.*, 1972).

An alternative method for medicinal white-oil production involves a two-stage hydrogenation process. The first stage reduces the content of most of the aromatic compounds and removes sulphur. The desulphurized product is then adjusted to the desired oil viscosity, flash-point and oil volatility before being hydrogenated in the second step to complete the saturation of aromatic compounds (Lecomte *et al.*, 1977).

Engine oils (for automotive gasoline and diesel, and industrial gas engines) [class 7.1]: These engine oils are made from highly refined base oils [classes 3, 4] and are formulated with a variety of additives, including viscosity index improvers, detergent/dispersants, antiwear additives, pour-point depressants and antioxidants.

Engine oils (for marine, railroad and industrial diesel engines) [class 7.1]: These engine oils are used in large diesel engines employed in power generation in marine, railroad and stationary service. Generally, highly refined, higher-viscosity base oils are required, and paraffinic base oils are preferred [classes 3, 4]. Additives for this type of engine oil are carefully selected to maintain engine cleanliness and to prevent wear under arduous conditions affecting oil degradation. They include non-metallic antioxidants, detergents, polymeric dispersants and extreme-pressure agents.

Automotive and industrial gear oils [class 7.1]: These oils are usually made from highly refined paraffinic base oils [classes 3, 4]. The higher-viscosity gear oils also contain some high-viscosity, solvent-refined residual oils [class 3], which are also known as 'bright stocks'. They are formulated primarily with extreme-pressure and antiwear additives to prevent wear and metal seizure during operation. Compounds containing phosphorus or sulphur are replacing, or have already replaced, lead soaps (e.g., lead naphthenates), which have been used as extreme-pressure additives.

Trichloroethylene was used widely as a non-inflammable diluent in open-gear lubricants to enable a highly viscous lubricant film to be applied easily to gear teeth surfaces. More recently, 1,1,1-trichloroethane has been used for this purpose.

Automotive transmission fluids (including fluids for power steering, manual transmissions, shock absorbers and universal tractor hydraulic/transmission fluids) [class 7.1]: These fluids are formulated using low-viscosity, highly refined base oils [classes 3, 4]. They generally contain a variety of additives, including antioxidants, corrosion inhibitors, defoamers, dispersant/detergents and pour-point depressants. Automatic transmission fluids may also contain coloured dye, to aid mechanics in finding leaks and to avoid mixing transmission fluids and motor oils (Bigda & Associates, 1980).

Hydraulic fluids [class 7.1]: These fluids are generally made from highly refined paraffinic oils [classes 3, 4] in a wide range of viscosity grades. They are carefully processed to have good water-separating ability and resistance to foaming. Rust and oxidation inhibitors and, sometimes, antiwear additives are used (Bigda & Associates, 1980; Wills, 1980).

Circulating, hydraulic and bearing oils, and general-purpose machine oils [class 7.1]: The base oils used for premium industrial grades are often more highly refined [classes 3, 4] than automotive grades, since the formulations are relatively low in additive content and must derive their inherent stability from the base oil and its refining process. The chemical additives employed include metallic and non-metallic antioxidants, antirust/corrosion inhibitors, pour-point depressants and antifoam agents.

Machine-tool (way) oils [class 7.1]: These oils are blends of medium-viscosity, highly refined, paraffinic base oils [classes 3, 4] for lubrication of the ways of complex machine tools. The additive chemistry is complex, requiring extreme-pressure agents, tackiness agents, corrosion inhibitors and antioxidants.

Compressor and refrigeration oils [class 7.1]: High-viscosity, highly refined, paraffinic base oils are a prerequisite for compressor oils [classes 3, 4], and these are prescribed in many industry/equipment specifications. No addition is made when they are used with special gases such as oxygen and nitrogen, and the additive level is generally low. Very specific compounds must be added for use with air and chemical gases such as ammonia.

In general, compressor oil additives are limited to mild extreme-pressure agents and rust/corrosion inhibitors. Refrigerator oils generally require the use of naphthenic base oils, which are free of wax. These may be either highly refined oils [classes 3, 4] or oils derived from limited refining [classes 1, 2].

Steam-engine oils [class 7.1]: These products utilize the highest-viscosity base oils available, i.e., solvent-refined residual oils (or bright stocks) [class 3]. They contain additives to maintain lubricant films under conditions involving high temperatures and wet surfaces, including mild extreme-pressure agents, rust/corrosion inhibitors, adhesive agents and emulsifying agents.

Textile oils [class 7.1]: These products cover a light- to intermediate-viscosity range and are used for lubrication of high-speed spindles. These textile oils may be derived from base oils that have undergone limited refining [classes 1, 2 or mildly treated 3, 4] or base oils that are highly refined [classes 3, 4]. The formulations are relatively low in additive content, containing antioxidants, mild extreme-pressure agents, rust inhibitors and self-scouring agents.

Air-tool oils [class 7.1]: Air-tool lubricants utilize medium- to heavy-viscosity base stocks. Generally solvent-refined paraffinic oils [class 3] with a high viscosity index are preferred. The additive content is low, including extreme-pressure agents and antirust additives. Oil emulsion type products [class 7.1] are also used in selected applications.

Metalworking oils [class 7.1]: Oils were first used in metalworking in the early 1900s to prolong the lifetime of metalworking equipment. In the 1950s, metalworking oils were formulated which contained fatty additives, sulphur, chlorine, and/or phosphorous compounds in varied amounts and combinations. Numerous formulations of metalworking oils from a variety of base stocks are now produced for different applications (Newhouse, 1982).

The major classes of metalworking oils are:

(1) *Cutting oils*

There are basically three types of cutting and grinding fluids in use today. The first are straight oils with additives, often referred to as 'neat' oils (no water phase); about 45% of the fluids employed today are of this type. Secondly, there are the emulsions, which are commonly called 'emulsifiable' oils or 'soluble' oils. These are fluids which contain a surface-active emulsifying agent so that, on dilution with water, a product containing an emulsified oil phase and water phase is produced. These soluble oils account for about 50% of all the metal-removing fluids. The remaining 4-5% are synthetic fluids, which are diluted with water and used for specialty application in place of soluble oils (Bigda & Associates, 1980). There are two types: semisynthetic fluids, which can contain relatively small amounts of oil, and water-based synthetic fluids, which contain no oil.

Highly refined oils [classes 3, 4] and oils derived from limited refining [classes 1, 2 or mildly treated 3, 4] can be used in varying amounts in all except the water-based synthetics, which are chemical solutions and contain no oil.

Chemical formulation technology for cutting oils is highly complex, since the cutting oil is expected to perform in a wide variety of functions, such as cutting, grinding, drilling, broaching and cooling. Other key properties of a cutting oil include antirust/anticorrosion properties, antibacterial properties and ease of disposal. Therefore, the chemical additives in cutting fluids must be multifunctional.

The following is a description of the formulation of the key products:

Straight cutting oils: Straight cutting oils are generally made from highly refined base oils [classes 3, 4] blended with appropriate additives, although oils derived from limited refining [classes 1, 2 or mildly treated 3, 4] may be used. Base oils are generally in the lower-viscosity range and can be either naphthenic or paraffinic types. Price and availability are important determinants in the consideration of which type of base oil to use (Bigda & Associates, 1980).

Non-corrosive[1] *straight cutting oils*: Additives include sulphurized non-active fats, polychlorinated paraffins, antirust agents and fatty esters.

Corrosive straight cutting oils: Additives include sulphurized base oils, sulphurized active fats, sulphurized/phosphorized hydrocarbons, fatty esters, polychlorinated paraffins and antirust agents.

Soluble cutting oils: These oils consist of base oils [classes 1, 2 and mildly or severely treated 3, 4] and emulsifiers and were developed to provide both the cooling properties of water and the lubricating properties of oils. Soluble cutting oils are made from higher viscosity

[1] Corrosive or active means: reacts with copper to form copper sulphide, i.e., contains active sulphur.

base stocks than straight cutting oils. Prior to use at the machine shop, these oils are mixed with 90-95% water to form the finished emulsified product (Bigda & Associates, 1980).

The general types and ranges of concentrations of the additives (in weight %) are: mineral oil, 60-90; emulsifiers (sodium and amine soaps; sodium naphthenates, rosinates and sulphonates), 5-30; coupling agents (alcohols, glycol ethers and glycols), 1-20; rust inhibitors (amines, fatty oils, sodium nitrite and sulphurized fatty oils, 1-10; water, 1-5; and biocides (chlorophenols, formaldehyde releasers, hexachlorophene and quaternary ammonium compounds), 0-1 (US Environmental Protection Agency, 1980).

N-Nitrosodiethanolamine (see IARC (1978a)) has been found at levels of 5-20 mg/kg in cutting oil emulsions. However, *N*-nitrosamines could not be found in straight cutting oils (Spiegelhalder, 1980). The combination of nitrite and amines which leads to the formation of these nitrosamines has already been eliminated in many products in many countries. In some applications, however, it has been found difficult to meet technical and cost requirements with alternative formulations.

Synthetic fluids: Additives include ethanolamines and their fatty acid salts, sodium nitrite, colourants, antirust additives and biocides. *N*-Nitrosamines have been identified in emulsifiable and water-based synthetic fluids, the latter showing the highest levels (Spiegelhalder, 1980). However, these water-based synthetic fluids do not contain lubricant base oils and are not, therefore, covered in this monograph.

(2) *Roll oils and can-forming oils*

These are a broad class of metal processing oils, in which the lubricant is in the neat form or applied as a water-containing emulsion. Paraffinic or naphthenic base oils that have been solvent extracted [class 3] are employed primarily.

Cold rolling oils: Various metals, e.g., aluminium, steel, copper, are rolled or processed under ambient temperature conditions. The lubricant is usually a light-viscosity (12-16 mm^2/s at 40°C), narrow-boiling-range base oil [classes 1, 2, 3, 4]. Rolling oils used in the aluminium industry are very low in viscosity, and may contain high molecular-weight alcohols for uniform spreading. For aluminium foil, kerosene or mineral oil/kerosene mixtures are sometimess used (Shell International Petroleum Company, Ltd, 1966). Restrictions are placed on the boiling range to control the annealing after rolling. Mild extreme-pressure additives are employed depending on the application.

Hot rolling oils - aluminium: A complex oil/emulsion technology is employed to meet the primary requirement for cooling during metal deformation while at the same time providing a combination of extreme-pressure/lubricity functions. The combination of additives required to achieve this performance includes fatty-amine soaps, mild extreme-pressure soaps, fatty esters and biocides.

The base oil employed is usually a light-viscosity, solvent-refined, paraffinic or naphthenic grade [classes 1, 2 and mildly or severely treated 3, 4] to minimize viscosity drag through the rolls.

Hot rolling oils - steel: Palm oil or palm oil substitutes have been the primary vehicle for the hot rolling of steel, although oil/emulsion/fatty soap technology has also been tried.

Can-forming oils - aluminium or steel: This application requires oil/emulsion/fatty soap [oil

classes 1, 2 and mildly or severely treated 3, 4] technology to supply both coolant and lubrication properties. The formulations are complex, and unique emulsifiers are required to ease removal of the oil from the can by washing.

(3) *Drawing oils*

Drawing-oil formulations include viscous base oils, base oils compounded with fats, and aqueous emulsions of fats with or without base oils (Shell International Petroleum Company Ltd, 1966). They may also contain sulphurized or chlorinated compounds for extreme-pressure performance.

Rust preventative oils [class 7.1]: Rust preventative oils contain base oils [classes 1, 2 or mildly or severely treated 3, 4] and chemical additives such as animal or vegetable fatty esters, sodium sulphonates and dewatering agents. The type of base oil is not critical, except that the oil should remain stable over time when used on equipment undergoing long-term storage. Easy removal of the rust preventative oil and replacement with conventional lubricant is another performance criterion.

Heat-treating oils [class 7.1]: Heat-treating oils are generally made from highly refined, paraffinic, high-flash, low-viscosity oils [classes 3, 4] for best performance. Less refined oils [classes 1, 2] are sometimes used as well. Surface-active agents are sometimes added to produce 'rapid quenching oils' (Shell International Petroleum Company Ltd, 1966). Although the first heat-treating oils were mineral oils with no additive, as higher temperatures were used oxidation inhibitors were added. Some of the earlier oils were naphthenic but, as temperatures rose, the better oxidation stability of the paraffinic oils was required (Bigda & Associates, 1980).

Transformer oils [class 7.1]: Transformer oils are made from naphthenic crudes, and have low viscosity (i.e., 12-16 mm^2/sec at 40°C). Oleum treatment was previously used to refine these products to meet equipment builders' requirements; however, acid treatment is being replaced by solvent extraction and/or hydrogenation processes [classes 3, 4]. Typically, there are no chemical additives in transformer oils, except when the builder specifies a small amount of phenolic oxidation inhibitor.

Greases [class 7.1]: Most grease products are physically homogeneous mixtures of complex thickeners and base oils. Base oils used for greases are usually blends of highly refined oils [classes 3, 4] or oils derived from limited refining [classes 1, 2 or mildly treated 3, 4]. Naphthenic and paraffinic base oils are used. The naphthenic content is adjusted to control the solubility/dispersibility of the soap in the oil phase. It is often important to utilize a solvent-refined base oil to achieve oxidation stability and resistance to degradation. The technology of greasemaking is highly complex, and is centred around the type of thickener to be homogenized into the oil phase. The consistency grade of the grease is adjusted by changing the ratio of thickener to oil. The most common thickeners used in industry are lithium hydroxystearate soaps, calcium fatty acid soap/ester complex, aluminium fatty acid soap/ester complex, polyurea, lead fatty acid soap/ester complex (the petroleum industry is phasing out the lead-soap greases in response to health and environmental concerns) and organophilic clay (alternative to soaps). Greases also contain other chemical additives to improve oxidation stability, antiwear, antirust and other properties.

Process oils [class 8]: Process oils are incorporated into products as part of the manufacturing process and are not used solely for their lubricating properties. Base oils ranging from highly refined oils [classes 3, 4] to oils that have undergone only limited refining [classes 1, 2 or mildly treated 3, 4] are used. In certain applications, notably rubber-tyre and printing-ink

manufacture, aromatic oils [class 6] are often used. The aromatic oils are usually the solvent extracts [class 6.1] from the solvent-refining process. Catalytically cracked oils [class 6.2] are sometimes used. Specifications for extender and process oils are met by redistillation, acid refining and clay treatment.

Process oils are grouped mainly according to their intrinsic chemical properties, although their physical characteristics are also important. The main functional applications are:

(1) *Product extenders*

The most important example of this application is in the manufacture and compounding of high molecular-weight elastomers (e.g., rubber tyres), in which the viscosity is reduced to aid mixing and the volume of the product is extended to increase value. Oil-extended rubber was first produced in the USA in 1951 and in Japan in 1965. Process oils are also used in reclaiming rubber.

(2) *Processing aids*

The oils are employed to reduce friction between the material and the processing machinery, or to provide internal lubrication, or both. Examples of such uses are found in the manufacturing of rubber, plastics and textiles.

(3) *Carriers and diluents*

In many applications, a process oil acts as a vehicle of adjuvant (as in printing inks) or as an inert diluent (for additives used in lubricating oils), to aid handling and permit satisfactory service use. Process oils are also used in the manufacture of bitumens (known as 'asphalts' in the USA) to adjust the final physical characteristics (viscosity, penetration and softening point). Another application in this category is use of low-viscosity oil as a carrier and spreading agent for insecticides.

(4) *Water repellents*

In this use, the inherent hydrophobic (water-repellent) nature of the oil is used to good effect in products such as polishes, pharmaceuticals and corrosion-preventatives.

(5) *Surface-active agents*

The surface-active properties of the oil are used to suppress dust (carpets), to provide anticaking properties (fertilizers) and to act as a binder (foundry sand).

(6) *Batching oils*

Low-viscosity oils are used to soften and lubricate natural fibres, e.g., jute and hemp, and to loosen hard adhering materials, e.g., bark.

(7) *Mould-release oils*

These are used to prevent materials from sticking to moulds, for example, concrete to shuttering, and to provide a good surface finish.

(8) *Wash oils*

Low-viscosity oils are used as alternatives to creosote fractions to remove benzene and naphthalene from raw coke-oven gas.

(*b*) *Use*

The production capacities and demands for lubricant base oils in various major regions are shown in Table 7 (Stewart & Helm, 1980).

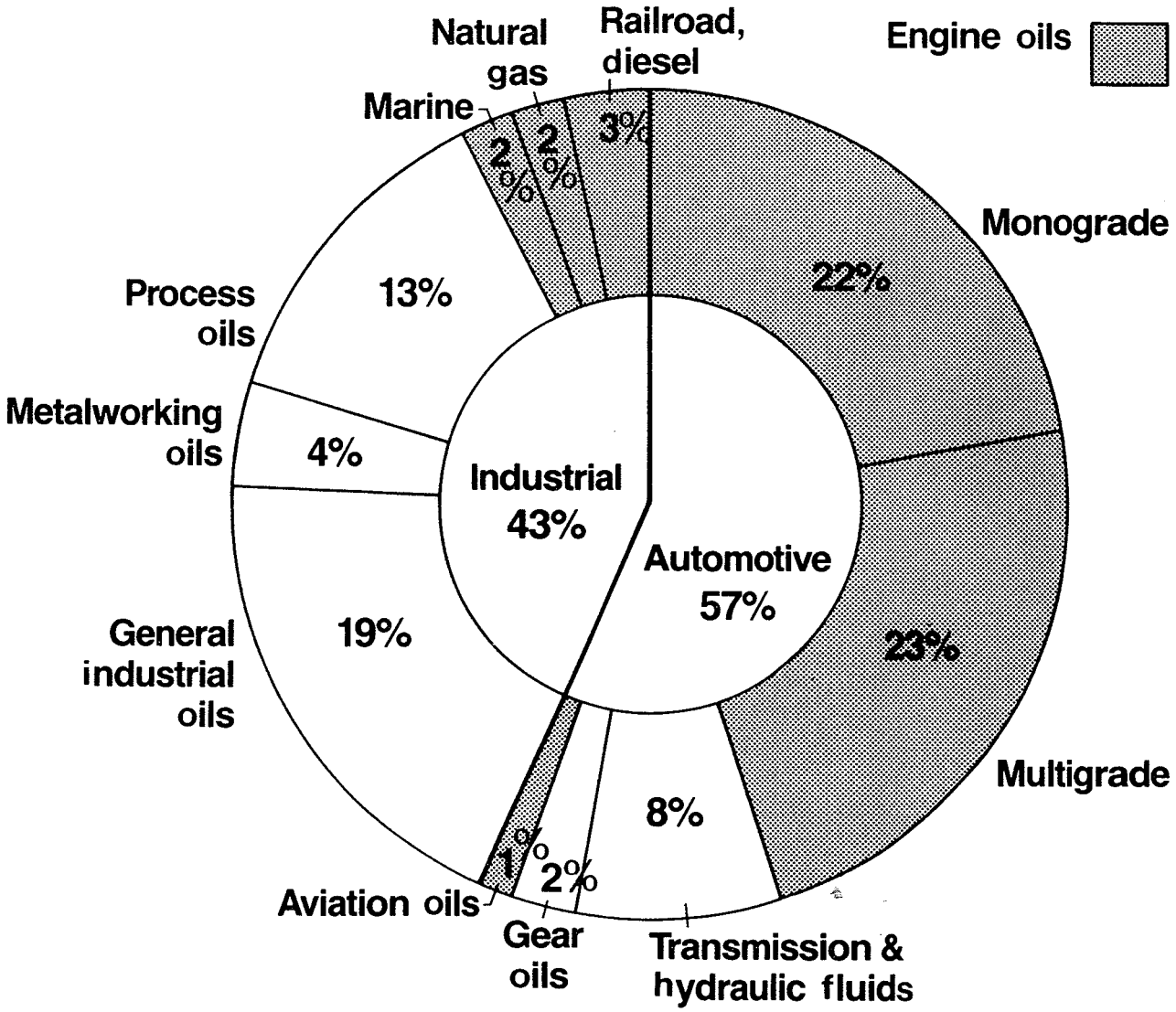
Table 7. World lubricant base oil capacity and demand in selected regions in 1980[a]

Region	Millions of tonnes	Percentage of total
Canada		
Effective capacity	1.4	5.4
Demand	1.4	6.0
USA		
Effective capacity	10.4	39.8
Demand	8.6	36.1
Caribbean and Central America		
Effective capacity	1.2	4.6
Demand	0.1	0.4
South America		
Effective capacity	1.2	4.6
Demand	1.3	5.5
Western Europe		
Effective capacity	6.5	24.9
Demand	6.	26.9
Middle East		
Effective capacity	0.7	2.7
Demand	1.1	4.6
Africa		
Effective capacity	0.4	1.5
Demand	1.0	4.2
Asia/Australia		
Effective capacity	4.7	18.0
Demand	3.9	16.4
Total effective capacity	26.1	
Total demand	23.8	

[a] From Stewart & Helm (1980)

Total US sales of products derived from lubricant oil refinery streams amounted to 8.65 million tonnes in 1981 and consisted of the following quantities of major products (in million tonnes): lubricating oils, 7.36; waxes, 0.70; aromatic oils, 0.37; and greases, 0.21. The distribution of the sales of the lubricating oils portion by major use categories is given in Figure 2; as illustrated by the shaded portion of the Figure, over 50% of the quantity of all lubricants sold went into automotive and engine oils. The following pattern has been reported for US lubricant usage in 1980: 78.5% in manufacturing, 5.0% in mining, 1.8% in construction and 14.7% in miscellaneous industries (Wills, 1980).

Fig. 2. Distribution of total US lubricating oil sales in 1981, by product (does not include aromatic oils, waxes or greases)[a]



[a] Total sales, 7.36 million tonnes; from National Petroleum Refiners Association (1981)

Table 8 provides a breakdown of US sales of automotive and industrial lubricating oils by major product category. Table 9 provides information on several types of products.

Table 8. US sales - 1981: Total reported basis[a]

Product	Sales (thousand tonnes)
Automotive oils	
SAE J-183a engine oils	
Monograded	1 626
Multigraded	1 687
Subtotal	3 313
NON SAE J-183a engine oils	
Aircraft	39
Gasoline-fueled two stroke	40
Subtotal	79
Transmission and hydraulic fluids	
Automatic transmission fluids	427
Universal tractor hydraulic/transmission fluids	136
Energy/shock absorber, power steering fluids	31
Other (manual transmission, etc.)	13
Subtotal	607
Gear oils	
GL-4 or less	25
GL-5 and 6	137
Subtotal	162
Total automotive oil sales	4 161
Industrial oils	
General industrial oils	
Hydraulic oils	724
Gear oils	132
Other, specified	
Turbine circ. oils	277
Refrigeration oils	32
Way oils	27
Compressor oils	24
Rock drill air tools	13
All others	147
Other, unspecified	11
Subtotal	1 387
Industrial engine oils	
Railroad diesel	199
Marine	174
Natural gas	144
Subtotal	517
Metalworking oils	
Specified	
Metal removing	179
Metal forming	60
Metal treating	23
Metal protecting	25
All other	10
Unspecified	7
Subtotal	304
Process oils (excluding aromatics)	
Electrical oils	252
White oils[b]	130
Rubber oils (excluding aromatics)	216
Other paraffinic	144
Other naphthenic	238
Subtotal	980
Total industrial oil sales	3188

[a] From National Petroleum Refiners Association (1981)

[b] Figures reported for white oils are incomplete.

Table 9. Data on the quantities used and the principal uses of different mineral oils

Type of oil	Quantity used (million l)			
	USA[a] (1978)	Japan (1981)	Typical areas of use	References[b]
Medicinal white oils	--	23	Pharmaceutical preparations (processing aids, intestinal lubricants); cosmetics (cold creams, hair preparations); food applications (release agents, binders, flotation sealants, defoamants, protective coatings); food packaging and processing; chemical and plastics industry (processing medium, extenders, plasticizers); and animal feed products	Shell International Petroleum Company, Ltd (1966); Exxon Corp. (1980)
Technical-grade white oils	157 (for use as process oils only)	--	Cosmetics (hair oils, creams); textile-machine lubricants; horticultural sprays; wrapping paper; corrosion protection in meat-packing industry; and lubricants for watches, bicycles and spindles	Shell International Petroleum Company, Ltd (1966); Exxon Corp. (1979); Wills (1980)
Extender oils	304 (for rubber use only)	85 (principally for SBR rubber)	Rubber processing; and solvents for insecticides and herbicides	Shell International Petroleum Company, Ltd (1966); Wills (1980); Cochrane & Stewart (1981)
Turbine oils	317	150	Coolants and gear lubricants for steam, gas and dual-cycle turbines	Larsen & Shmunes (1982); Wills (1980)
Hydraulic oils (including automatic transmission fluids)	1700	225	Automatic transmission fluids; tractor transmission fluids; energy, shock absorber and power steering fluids; and industrial hydraulic oils (for draw benches, elevators, jacks, coal-mining, die-casting, plastic-moulding and welding machines)	Wills (1980)
Transformer oils	370 (including cable coating oils)	62	Heat transfer oil in electrical transformers and cable coating	Bigda & Associates (1980)
Automotive motor oils	4249	697	Automobiles, light trucks and aircraft	Wills (1980)
Gear oils	191	114	Automotive gear oils and industrial gear oils	Wills (1980)
Metalworking oils (including rolling oils, drawing oils and heat-treating oils)	418	126	Metal-removing, metal-forming, metal-protecting and metal-treating	Wills (1980)

[a] From Wills (1980)

[b] Only for section on uses

2.2 Examples of legislation concerning lubricant base oils and derived products

Occupational exposure limits for mineral-oil mist have been established by regulation or by recommended guidelines in the following countries: Australia, Belgium, the German Democratic Republic, Italy, Japan, the Netherlands, Switzerland, the USA and the USSR. The generally accepted limit is 5 mg/m^3 on an eight-hour time-weighted average (TWA), except for Japan

where it is 3 mg/m^3 (International Labour Office, 1980). The American Conference of Governmental Industrial Hygienists (1982) also recommends a short-term exposure limit (STEL) of 10 mg/m^3, and the German Democratic Republic (International Labour Office, 1980), one of 15 mg/m^3. In Finland and Sweden, the TWA is 3 mg/m^3 (National Board of Labour Protection, Finland, 1981; National Board of Occupational Safety & Health, Sweden, 1981).

The US Food and Drug Administration (FDA) has approved the use of white mineral oil [class 5] as a direct additive to food for human consumption, with various limitations for the following uses: releasing agent, binder, lubricant, defoamer, protective coating or float- and dust-control agent. Mineral oil [class 5] has also been approved, with various restrictions, as a component of the following materials used in contact with food products: adhesives and various coatings for articles used in packaging, transporting and holding food; paper or paperboard used in contact with aqueous and fatty foods; cellophane used in articles intended for single or repeated use; resin-bonded filters; rubber articles or textiles and textile fibres intended for repeated use in processing, packing and holding food; and lubricants with incidental food contact from machinery used in processing, packing and holding food. The FDA has also approved the use of mineral oil [class 5], with some limitations, for use as an animal feed additive for polymeric materials subjected to irradiation incidental to the radiation treatment and processing of prepackaged foods (US Food & Drug Administration, 1982a-h).

The FDA has recommended, but not required, warning labels for drugs containing mineral oil [class 5] that are taken internally, in order to prevent possible interferences by mineral oil with the absorption of various vitamins from the digestive tract (US Food & Drug Administration, 1982i). In addition, the FDA proposed a rule that would allow the following over-the-counter drug products containing mineral oil to be classified as generally recognized as safe and not misbranded: ophthalmic drugs, anorectal drugs, hair growth and hair-loss prevention drugs, and external analgesic drugs for diaper rash and fever blisters (US Food & Drug Administration, 1980b-d; 1982j,k).

The FDA has announced that no US standard will be established for raisins based on the recommended international standard (Codex standard, CAC/RS 67-1974) developed by the Codex Alimentarius Commission, which limits mineral oil [class 5] as an additive to a level not to exceed 5 g/kg (US Food & Drug Administration, 1981).

The US Environmental Protection Agency (EPA) has established tolerances for total residues of mineral oil [class 5] of 0.2 g/kg in or on shelled corn and grain sorghum from post-harvest applications. Mineral oil is exempted from the requirement of a tolerance when used as an inert ingredient in pesticide formulations applied to growing crops or to raw agricultural commodities after harvest (US Environmental Protection Agency, 1982a). In addition, the EPA has designated mineral oil [class 5] as inert when used as an ingredient in antimicrobial pesticides (US Environmental Protection Agency, 1982b).

The US Bureau of Alcohol, Tobacco and Firearms has listed mineral oil [class 5] as an approved surface antioxidant for wine during storage, provided that no mineral oil is present in the finished product (US Department of the Treasury, 1982).

In Europe, lubricating oils placed on the market as pure substances without additives, which are either substances included in the European Core Inventory (ECOIN) or are new substances undergoing the notification procedure, are to be regarded as dangerous substances and, therefore, to be classified and labelled as required by Council Directive 79/831/EEC on the sixth modification of Council Directive 67/548/EEC concerning the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling

of dangerous substances. Annex VI of the Directive, Part I, gives the general principles of the classification of dangerous substances, and Part IID is a guidance for the adequate choice of risk and safety advice phrases which should appear on the label. Lubricating oils with additives are not to be considered in the framework of the sixth amendment on dangerous substances; they will be covered in the Directive on 'preparations', currently under consideration (Commission of the European Communities, 1979).

In the United Kingdom, the Mineral Hydrocarbons in Food Regulations 1966 (Minister of Agriculture, Fisheries and Food, and Minister of Health, 1966) prohibit the use of any mineral hydrocarbon in the composition or preparation of any food. Additionally, the selling, consignment, delivery or importation of food containing mineral oil is forbidden. Permitted exceptions to the above are listed together with maximum permitted concentrations of mineral hydrocarbons. Quality requirements for mineral oils deemed suitable for use in the permitted applications are detailed in the Regulations.

Relevant legislation in the Federal Republic of Germany includes: 'Statutory regulation on the trade of food additives and foodstuffs used as additives - Food additives trading regulation'. This regulation limits benzo[*a*]pyrene content to a maximum of 0.1 mg/kg and fluorescence at 254 nm to zero in mineral oils for permitted applications (Federal German Authority of Health, 1976).

2.3 Used oils [class 7.2]

There is strong evidence that the polynuclear aromatic hydrocarbon (PAH) content of petroleum-derived lubricants may increase during use (Grimmer, 1983). The extent of the increase appears to depend on the type of application -- up to 10-fold for cutting oils and diesel-engine oils, but perhaps 100-fold or more for gasoline-engine oils and heat-treating oils. Much of the increase in PAH in engine oil appears to arise from gasoline combustion products. Non-engine industrial lubricants, such as hydraulic and gear oils, would not be expected to undergo any significant increase in PAH content during use because of the limited increases in temperature to which they are subjected (Concawe, 1983b).

Used gasoline-engine oils can contain up to 1% of lead, which originates mainly from lead additives in gasoline (Concawe, 1983b). It has been reported that *N*-nitrosodiethanolamine [level unknown] has been identified in used cutting oil emulsions (Speigelhalder, 1980). Used transformer oils can contain various levels of polychlorinated biphenyls, owing to previous use of these compounds in transformers (see IARC, 1978b).

2.4 Occurrence

(*a*) *Natural occurrence*

The typical major hydrocarbon constituents of lubricant base oils and derived products, i.e., straight- and branched-chain paraffins and naphthenic hydrocarbons with carbon numbers in the approximate range of 15-50, occur naturally in crude petroleum.

(*b*) *Occupational exposure*

In the studies cited below, the descriptions of the exposures were generally inadequate to allow assignment of classes to oils. In most cases, however, exposure was probably to used and unused formulated products [classes 7.1 and 7.2].

On the basis of the 1974 National Occupational Hazard Survey in the USA, the National Institute for Occupational Safety and Health (1980, 1981) projected that approximately six million US workers in non-agricultural industries were exposed to mineral oils, two million to lubricating oils, one million to cutting oils and one million to motor oils.

Table 10 summarizes reported exposure to mineral-oil mist in several industries where mineral oils are used, e.g., as coolants, cutting oils and lubricants. Average exposure levels were probably less than 15.0 mg/m^3 (Hendricks *et al.*, 1962). Surveys of the occurrence of mineral oils in the occupational environment of several US plants, performed for the National Institute of Occupational Safety and Health, are summarized in Table 11.

Table 10. Exposures to oil mist in selected US industries[a]

Industry	No. of observations	Concentration range (mg/m^3)
Automobile manufacture	37	1.0-56.5
Brass and aluminium production	5	1.4-20.7
Copper mining	7	5.4-22.0
Manufacture of steel products	33	0.8-50.0
Newspaper (pressroom)	8	2.0-16.6
Screw manufacture	6	1.0-14.2

[a] From Hendricks *et al.* (1962)

Table 11. Occupational exposure to mineral oils in US plants

Type of oil	Operation	Type of exposure		Reference
		Direct contact	Oil mist concentration (mg/m^3)	
Cutting oil	Polishing of aircraft engine blades	-	0.37-0.55	Larsen & Shmunes (1972)
	Machining of rough iron castings into auto parts	+	0.4-6.0	Hervin & Lucas (1973)
	Metallizing *via* flame spraying	+	-	Kramkowski & Shmunes (1973)
	Manufacture of oil pipeline couplings and electric pipe conduits	+	-	Lucas & Rosensteel (1975)
	Production of perforated metal goods	+	-	Straub & Emmett (1976)
	Manufacture of aircraft components	-	1.1-20	Gunter (1976)
	Manufacture of parts for automotive industry with automatic screw machines	+	0.3-1.3 (mean, 0.6)	Kronoveter & Elesh (1978)
	Fabrication of precision metal parts	-	< 0.03-0.8	Gilles (1978)
	Milling and machining		< 0.035-3.1	Gunter (1979)
Transformer oil	Manufacture of very large power transformers; overhaul of old transformers	+	0.1-1.4	Hervin *et al.* (1977)
	Coal mining	+[a]	-	Hewett (1981)

[a] One exposure during clean-up of leakage from a broken separator electromagnet

Gromiec *et al.* (1981) reviewed occupational exposure to oil mist resulting from the use of cutting fluids (concentrations varying from 0.07-148 mg/m^3) as well as analytical methods used to determine oil mist in the air: the fluorescence method was regarded as the best for determining occupational exposures to low concentrations.

The use of die lubricants resulted in the presence of oil droplets in the air of a US factory where a hot forging operation was used in the manufacture of large artillery shells; the concentration of total airborne particulates was in the range of 3.5-7.2 mg/m^3 (Goldsmith *et al.*, 1976).

Oil mist resulting from the use of metalworking fluids with machine tools at three US plants, along with the control technologies being used to limit mist levels, were studied by the National Institute for Occupational Safety and Health. Average concentrations of oil mist in the vicinity of several different machines using straight cutting oils (generally containing antimisting additives) or soluble cutting oils, ranged from 0.2-2.9 mg/m^3 (O'Brien & Frede, 1978).

Ely *et al.* (1970) described oil-mist exposures detected in machine shops at three US plants at levels ranging from 0.07-110 mg/m^3 (with means of 3.7 and 5.2 mg/m^3 on two occasions). Measurements were made using high-volume air flow filters. The machines, which included lathes, mills, grinders and shapers, were lubricated by flow-on, brush and mist applicator techniques.

Printing-ink mist levels in the pressroom of a New York City newspaper were determined by Lippmann and Goldstein (1970). The ink was a suspension of carbon black in mineral oil. Around the press itself, mist was detected at levels of 0.12-0.73 mg/m^3 (average, 0.31 mg/m^3) before the press run, at 2.59-3.43 mg/m^3 (average, 2.88 mg/m^3) with the presses running and the exhaust control on, and at 2.08-6.75 mg/m^3 (average, 4.26 mg/m^3) with the presses running and the exhaust control off. Table 12 summarizes employee exposure to the ink mist. The respirable fraction of ink mist in the vicinity of Goss (offset) presses ranged from 7-26% (average, 15%); respirable mist levels for pressmen working with these presses averaged 1.8 mg/m^3 (maximum, 6 mg/m^3; time-weighted average, 1.4 mg/m^3).

Table 12. Oil-mist exposures in a New York newspaper pressroom[a]

Exposed groups	Average oil-mist concentration in various work phases (mg/m^3)			
	Production	Press makeup and breakdown	Rest break	Time-weighted average
Goss press, pressmen and helpers	12.20	0.63	1.30	8.63
Goss press, reelroom[b] crew	3.40	0.63	1.30	2.58
Wood press, pressmen and helpers	9.80	0.66	1.30	6.98
Wood press, reelroom crew	1.20	0.66	1.30	1.07

[a] From Lippmann & Goldstein (1970)

[b] Area in which paper is loaded onto a reel which feeds it to the printing unit

Goldstein *et al.* (1970) reported that the New York State Department of Labor detected oil mist in a New York newspaper pressroom at levels of 5-21 mg/m^3.

In the pressroom of an English newspaper, total dust concentration ranged from 250-1060 μg/m^3 in 1981 (actual ink mist present in total dust was 216-510 μg/m^3). A review from 1967-1981 of total dust concentrations in various English newspaper pressrooms showed concentrations of 620-2160 μg/m^3 for particles of <60 μm, of 62-987 μg/m^3 for particles of <20 μm, and of 10-900 μg/m^3 for particles of <7 μm. In particles of <60 μm, the concentration of benzo[*a*]pyrene was 5.2-18.0 μg/m^3 (Casey *et al.*, 1983).

(*c*) *Water and sediments*

A stream in New Jersey, USA, which received runoff from a road oiled with waste crankcase oils for dust control, was examined for the presence of these oils. Two oil patches were noted in shallow pools on the banks of the stream. The oil in the patches was similar in composition to that extracted from the road material; it was believed that the oils were deposited during a period of high stream flow (Freestone, 1979).

Hydraulic oil was detected in samples of industrial cooling water during 1971, 1973 and 1974 in the United Kingdom. Analysis by infrared spectroscopy showed levels of soluble and total oil of 20-46 mg/l and 37-56 mg/l, respectively. Solvent extraction-gravimetric analysis showed levels of 37-56 mg/l and 46-65 mg/l, respectively. The infrared method reportedly detected only non-degraded hydraulic oil (Nicholson & Taylor, 1975).

(*d*) *Soil and plants*

A number of studies have reported on the occurrence of used lubricating oils in the environment. In one recent study, about 2 × 10^9 litres of used lubricating oil were reported to be released annually into the environment in the USA, including approximately 750 million litres used as road oil or incorporated into asphalt (Maugh, 1976). Armstrong and MacDonald (1979) reported that about 900 million kg of used lubricating oils (including hydraulic oils and industrial cutting oils) are sold in Canada each year and that 42% was potentially recoverable. However, only about 27 million kg are re-refined annually, approximately 100 million kg of which are used for road oiling and about 250 million kg used or disposed of in one of several ways, including use as a fuel, incineration and dumping in sewers or on the ground.

As part of a study on thermal treatment of hazardous wastes, the North Atlantic Treaty Organization (1981) surveyed disposal methods in member nations for mineral oil wastes. The USA reported that about 1.5 × 10^9 litres (equal to approximately 30% of the total) of the used lubricating oil generated annually is disposed of in landfill; the United Kingdom and the Federal Republic of Germany also reported that some mineral oil wastes are disposed of in this way, but no amounts were specified.

Golwer (1982) reviewed the seepage and spreading of mineral oils and chemicals in subsoil. According to the porosity of the subsoil, 5-40 l oil/m^3 soil can remain. The saturation concentration of oil varies from 5 to 300 mg/l ground water, depending on the mineral oil.

Two rural roads in New Jersey known to have been oiled with waste crankcase oil for dust control over an indeterminate number of years were analysed for the presence of oil residue. Roughly 1% of the total oil estimated to have been applied remained in the top 3 cm of the road surface. The application rate was believed to have been about 2 l/m^2. The levels of hydrocarbons remaining in the top 3 cm of the road surface were in the range of 0.13-13.4 g/kg; oil penetration below the top 3 cm was minimal (Freestone, 1979).

(*e*) *Other*

Mineral oil was found at levels of < 1-9.4 μg/ml in several batches of technical ethanol in the USSR (Ulanova & Vyrodova, 1980).

2.5 Analysis

A review of methods for sampling and analysing oil mist has been published (Sanderson & Eyres, 1980), in which comparisons are made of methods and their efficiency for various types of mineral oil. Methods for sampling and analysis of lubricating oils are listed in Table 13.

Table 13. Methods for the analysis of lubricating oils in various matrices

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Air	Collect on membrane filter; extract (chloroform)	Fluorescence spectrophotometry	0.05 mg/m^3	National Institute for Occupational Safety & Health (1977)
	Collect on membrane filter; extract (carbon tetrachloride)	IR (2940 cm^{-1})	0.3 mg/m^3	National Institute for Occupational Safety & Health (1978)
	Collect on four-stage impactor	Microscopic counting of droplets to obtain size distribution of aerosol	--	Goldsmith *et al.* (1976)
Road surfaces and soil	Extract (carbon tetrachloride)	IR	--	Freestone (1979)
Water	Extract (carbon tetrachloride)	IR	2 mg/kg	Ambruso *et al.* (1972)
	Pyrolysis of water/oil mixture	FID	1 mg/kg	Ambruso *et al.* (1972)
	Emulsify	TOC	--	Hearst (1979)
	Mix sample; add sodium chloride and hydrochloric acid; shake; add 1,1,2-trichlorofluoroethane; collect and dry lower layer	IR	--	Nicholson & Taylor (1975)

[a] Abbreviations: IR, infrared spectrometry; FID, flame-ionization detection; TOC, total organic carbon analysis

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

As outlined in section 1.2, p. 90, the Working Group found it convenient to divide the petroleum-derived materials into eight classes, generally based on increasing severity of processing or refinement. Within each class, a range of severities of treatment may also exist. The categories 'formulated products' [class 7.1] and 'used oils' [class 7.2] represent formulations of various base oils from the previous categories with chemical additives, usually not identified with respect to exact composition.

Catalytically cracked oils [class 6.2] are used primarily as components of heavy fuel oils (marine, engines, stationary power plants). They have also been and may in some cases still be used in rubber processing and extender oils. The catalytically cracked oils discussed here are not identical with oils used commercially; however, they correspond in a general way to such oils, and the carcinogenicity data are thought to be representative.

In some instances, the material was not sufficiently well described and so was assigned to class 8 - 'petroleum-derived materials not otherwise classified'.

In reporting on the individual studies, the Working Group used the authors' own description but followed it with a number which related the material to the appropriate class. This determination represented the best judgement of the experts in the Working Group.

3.1 Carcinogenicity studies in animals[1]

(a) *Oral administration*

Rat: A group of 30 rats of strains BD I, BD III and W [sex unspecified] received 2% liquid paraffin [class 5] in the diet (total dose, 136 ml/animal in 500 days); no significant tumour induction was reported (Schmähl & Reiter, 1953).

Three samples of petrolatum [class 5] (snow-white US Pharmacopeia XVI grade, white US Pharmacopeia XVI grade and yellow National Formulary XI grade) were fed at a concentration of 5% in the diet to groups of 50 male and 50 female weanling rats (FDRL strain) for two years. None of the tests yielded a treatment-related tumour increase (Oser *et al.*, 1965).

(b) *Skin application*

Mouse: Early studies reported the induction of skin tumours (10 benign and 11 malignant) in a group of 100 mice [strain and sex unspecified] given twice-weekly skin applications of a heavy fraction (distilled between 300 and 360°C under 12 mm pressure) of a paraffinic oil

[1] The Working Group was aware of several studies in progress of skin painting of mice with various distillates, lubricant base oils and motor oils (IARC, 1982). The Working Group considered three recently published papers on the carcinogenicity of petroleum lubricating oil vacuum distillates (Doak *et al.*, 1983; Halder *et al.*, 1984; Kane *et al.*, 1984), which summarized three series of mouse skin-painting studies carried out over an extended period of time. The Group noted that in one of these reports (Kane *et al.*, 1984), the authors were not the original investigators.

[class 1] which was used in cotton spinning; a lighter fraction (240-300°C) of this oil induced one benign and no malignant tumour in 100 mice. The tumour yield in similar groups of 100 mice was six benign and four malignant tumours for the heavy fraction (distilled at 385-420°C under atmospheric pressure) from a paraffinic oil [class 1] blended with 10% sperm oil before distillation; the lighter fraction (distilled at 355-385°C at atmospheric pressure) produced no tumour (Twort & Ing, 1928).

Of 30 male C3H mice receiving skin applications of 50 µl two to three times a week of a paraffinic distillate [class 1] (benzo[*a*]pyrene content, less than 0.1 mg/kg), four developed papillomas and two developed carcinomas of the skin, with an average latent period of 64 weeks (Bingham & Barkley, 1979). While none of 24 untreated stock male control mice developed a malignant skin tumour, six of 24 mice [p = 0.01] developed such tumours after treatment with an undiluted mineral oil (benzo[*a*]pyrene content, less than 1 mg/kg) used in the spinning of jute (jute batching oil) [probably a distillate (class 1)]. In the same study, 2/24 mice treated with 7,12-dimethylbenz[*a*]anthracene alone developed a malignant skin tumour, as compared with 11/24 in a group treated with this PAH plus the mineral oil [p = 0.004] (Roe *et al.*, 1967).

The heavy distilled fraction (300-360°C, 12 mm pressure) from a paraffinic oil was extracted with sulphuric acid [class 2]; when tested in 100 mice [strain and sex unspecified] by twice-weekly skin applications, it yielded no skin tumour (Twort & Ing, 1928).

Twelve fractions obtained by vacuum distillation and derived from a Borneo crude oil were treated with sulphuric acid and further refined by treatment with clay [class 2]. Each refined fraction was tested on 100 mice [strain and sex unspecified] by skin application, five times weekly for 45 weeks. At that time, the reported malignant tumour yield was: for the crude oil (viscosity, 1351.0 mm^2/sec) [temperature not given], 35 malignant tumours; for fractions 1-5 (viscosity range, 3.7-34.7 mm^2/sec), no tumour; and for fractions 6 (62.7 mm^2/sec), 7 (167.8 mm^2/sec) and 8 (303.8 mm^2/sec), respectively, 23, 50 and 67 malignant tumours. The tumour yield was lower with fractions 9-12 (viscosity ranges, 726.7-4033.0 mm^2/sec) (Twort & Lyth, 1939).

Groups of 15 or 30 male C3H/HeJ mice received twice-weekly skin applications of 50 mg of undiluted oils refined by treatment with a relatively small amount of 93% sulphuric acid and by contact with clay [class 2]. This refined paraffinic distillate (viscosity, × 20.5 mm^2/sec at 37.8°C) resulted in a 70% skin tumour incidence. Five similarly refined naphthenic distillates of different viscosities gave the results reported in Table 14 (Bingham *et al.*, 1965; Bingham & Horton, 1966).

Table 14. Mouse-skin bioassays of naphthenic distillates [class 2] refined by acid and clay treatments[a]

Viscosity (mm^2/sec at 37.8 °C)	Effective no. of mice	No. of mice with skin tumours	
		Malignant	Benign
20.5	10	9	0
31.9	11	10	0
64.6	7	3	2
162	14	9	3
162	11	2	1

[a] From Bingham *et al.* (1965)

Table 15. Mouse-skin bioassays of materials of different classes[a]

Material tested	Class	Dose (mg)	Doses per week	Strain (males)	Effective no. of mice	Duration of treatment	No. of mice with tumours		
							Benign (papillomas)	Advanced (carcinomas)	
								No.	%
Heavy paraffinic distillate	1	100	3	C3H	17	80 weeks[b]	7	6	35.3
Light paraffinic distillate	1	50	2	C3H/HeJ	23	"	0	1	4.3
"	1	50	2	"	23	"	2	5	21.7
Heavy naphthenic distillate	1	100	3	C3H	14	"	5	5	35.7
"	1	100	3	"	16	"	13	2	12.5
"	1	100	3	"	17	"	14	1	5.9
"	1	50	3	"	18	"	7	6	33.3
Light naphthenic distillate	1	50	2	C3H/HeJ	18	"	2	2	11.1
"	1	50	2	"	45	"	6	21	46.7
Solvent-refined light naphthenic distillate	3	50	2	"	32	lifetime[c]	1	1	3.1
Solvent-refined heavy naphthenic distillate	3	50	2	"	32	"	0	1	3.1
"	3	100	3	C3H	19	80 weeks[b]	0	0	
"	3	50	2	C3H/HeJ	42	"	0	0	
Solvent-refined dewaxed light paraffinic distillate	3	50	2	C3H	38	lifetime	1	0	
Solvent-refined dewaxed heavy paraffinic distillate	3	50	2	"	40	lifetime	1	0	
"	3	50	2	"	37	"	0	0	
"	3	50	2	"	37	"	0	0	
"	3	50	2	"	41	"	0	0	
"	3	50	2	C3H/HeJ	19	80 weeks[b]	0	0	
"	3	50	2	"	5	"	0	0	
Solvent-refined dewaxed residual oil	3	50	2	"	14	"	0	0	
"	3	50	2	"	23	"	0	0	
Solvent extract, combined from several refinery streams	6.1	50	2	"	49	104 weeks[t]	4	35	71.4
Solvent extract from heavy paraffinic distillate	6.1	25	2	"	40	80 weeks[b]	20	19	47.5
"	6.1	25	2	"	20	"	4	16	80.0
Solvent extract from residual oil	6.1	25	2	"	26	"	0	3	11.5
"	6.1	25	2	"	23	"	0	1	4.3
Acid-treated solvent-dewaxed hydrofinished light paraffinic distillate	4	50	2	"	24	104 weeks[b]	4	7	29.2
Clay-treated solvent-refined dewaxed light paraffinic distillate	3	50	2	"	12	lifetime[d]	0	0	

Material tested	Class	Dose (mg)	Doses per week	Strain (males)	Effective no. of mice	Duration of treatment	No. of mice with tumours		
							Benign (papillomas)	Advanced (carcinomas)	
								No.	%
"	3	50	2	"	10	"	0	0	
Clay-treated dewaxed light paraffinic distillate	1	50	2	"	19	"	4	11	57.9
"	1	50	2	"	22	"	4	8	36.4
Clay-treated dewaxed heavy paraffinic distillate	1	50	2	"	27	"	7	14	51.9
Hydrofinished light naphthenic distillate (non-solvent-refined)	4	50	2	"	32	104 weeks[b]	4	18	56.3
Chemically neutralized hydrofinished light naphthenic distillate (non-solvent-refined)	4	50	2	"	17	80 weeks[b]	1	1	5.9
"	4	50	2	"	7	"	0	1	14.3
Chemically neutralized hydrofinished heavy naphthenic distillate (non-solvent-refined)	4	50	2	"	42	"	2	34	81.0
"	4	50	2	"	30	"	8	13	43.3
"	4	50	2	"	29	"	3	9	31.0
Hydrofinished solvent-refined light naphthenic distillate	3	50	2	"	14	"	0	0	
Hydrofinished solvent-refined heavy naphthenic distillate	3	50	2	"	42	"	0	0	
Composite unused gasoline-engine oil	7.1	50	2	"	36	lifetime[c]	0	1	2.8
Unused diesel-engine oil	7.1	0.2 ml	2	Carworth Farms female	35	78 weeks	1	0	
Unused gasoline-engine oil	7.1	0.2 ml	2	"	34	"	0	0	
"	7.1	0.2 ml	2	"	33	"	0	0	

[a] From Kane *et al.* (1984)

[b] Or until a papilloma is formed

[c] Or until an advanced tumour is formed

[d] Or until a papilloma 1 mm^3 was seen

Groups of 30 C3H/HeJ male mice given twice-weekly skin applications of 50 mg of undiluted paraffinic solvent-refined oil [class 3] for up to 80 weeks, developed no tumour with any of three samples with viscosities, respectively, of 20.5, 41 and 540 mm^2/sec at 37.8°C. In a similar test, a sample of undiluted naphthenic solvent-refined oil [class 3] (viscosity, 31.9 mm^2/sec at 37.8°C) also yielded no skin tumour (Bingham *et al.*, 1965).

A group of 30 Swiss female mice received skin applications of 0.05 ml of a dewaxed paraffinic distillate [class 1] (viscosity, 24 mm^2/sec at 37.8°C) three times weekly for one month and twice weekly for the next 11 months; animals were observed for an additional six months; a total of 13 mice developed skin tumours, and in five of the mice the tumours were malignant. After solvent treatment of the same distillate, the aromatic extract [class 6.1] produced skin tumours in 25/30 mice, and in 15 mice the tumours were malignant; in contrast, two samples of raffinate [class 3] gave no tumour in two groups of 30 mice (Gradiski *et al.*, 1983).

Male C3H or C3H/HeJ (in a few cases, from Carworth Farms) mice received skin applications of undiluted test materials two or three times each week. In some studies, skin applications were continued for a predetermined period, usually for at least 80 weeks or until a tumour was grossly diagnosed (if the papilloma regressed, applications were resumed). 'Advanced tumours' were usually examined histologically and diagnosed as carcinomas. In other studies, skin applications were continued for the lifetime of the animals or until an advanced tumour was grossly diagnosed. The results (Table 15) show that distillates [class 1] not subjected to further treatment were generally active in the skin carcinogenesis assay; solvent refining produces raffinates [class 3] that are usually not active; however, extracts [class 6.1] from the process are positive and in general show high activity in this assay; and clay-treated distillates [class 1] showed carcinogenic activity that was not present in corresponding solvent-refined materials (Kane *et al.*, 1984).

Male C3H or C3H/HeJ mice received twice-weekly skin applications of 50 µl (for C3H mice) or 50 (or 75) mg (for C3H/HeJ mice) of a series of lubricant base oils for 98-134 weeks or 80 weeks, respectively. The results, reported in Table 16, were largely confirmatory of the work of Kane *et al.* (1984). Although the nature of the solvent used did not appear to influence carcinogenic activity, the severity of solvent extraction did (Halder *et al.*, 1984).

Table 16. Mouse-skin bioassays of materials of different classes[a]

Material tested[b]	Class	Dose (2 per week)	Strain	Effective no. of mice	No. of mice with skin tumours	
					Papillomas	"Advanced"
1. *Dewaxed distillates*	1					
Heavy paraffinic LV		50 µl	C3H	42	0	27
" " LV		50 mg	C3H/HeJ	28	4	20
" " LV		50 mg	C3H/HeJ	23	5	14
" " HV		50 mg	C3H/HeJ	27	10	9
" " HV		50 µl	C3H	44	2	0
Light paraffinic LV		50 µl	C3H	40	2	15
" " LV		50 mg	C3H/HeJ	39	6	26
" " LV		50 mg	C3H/HeJ	23	6	16
" " LV		50 mg	C3H/HeJ	26	2	22
" " LV		50 mg	C3H/HeJ	24	1	22
2. *Solvent-dewaxed, refined distillates*[c]	3					
Heavy paraffinic (phenol) LV		50 µl	C3H	45	1	0
" " (NMP) LV		50 µl	C3H	46	0	0
" " (NMP) HV		50 µl	C3H	45	0	0

Material tested[b]	Class	Dose (2 per week)	Strain	Effective no. of mice	No. of mice with skin tumours	
					Papillomas	"Advanced"
Light paraffinic (furfural) LV		50 µl	C3H	45	0	0
" " (lightly extracted) LV		50 mg	C3H/HeJ	25	1	5
" " (lightly extracted) LV		50 mg	C3H/HeJ	17	4	12
3. *Dewaxed, hydroprocessed distillates*	4					
Heavy paraffinic LV		50 mg	C3H/HeJ	25	5	7
" " LV		50 mg	C3H/HeJ	10	2	4
" " HV		50 mg	C3H/HeJ	16	3	2
Light paraffinic LV		50 mg	C3H/HeJ	33	9	7
" " LV		50 mg	C3H/HeJ	24	4	3
" " LV		75 mg	C3H/HeJ	352	0	0
" " LV		75 mg	C3H/HeJ	27	0	0
4. *Solvent-refined, hydroprocessed dewaxed distillates*	3					
Heavy paraffinic (phenol or NMP) HV		50 µl	C3H	86	0	0
Light paraffinic LV		50 mg	C3H/HeJ	24	0	0
" " LV		50 mg	C3H/HeJ	17	0	0
5. *Blends of dewaxed, solvent-refined distillates and hydroprocessed, dewaxed distillates*[d]	3,4					
Heavy paraffinic LV		50 mg	C3H/HeJ	87	2	5
" " HV		50 mg	C3H/HeJ	71	2	5
Light paraffinic LV		50 mg	C3H/HeJ	54	0	0

[a] Modified from Halder *et al.* (1984)

[b] LV, low viscosity; HV, high viscosity

[c] Solvents used included phenol, furfural and *N*-methylpyrrolidone (NMP)

[d] 50-90% solvent-refined dewaxed distillate, remainder hydroprocessed and dewaxed distillate

[The data in Tables 15 and 16 indicate that variable results are obtained in the mouse carcinogenesis assay according to the severity and conditions of hydrogen treatment of distillates. Hydrofinishing, which is a relatively mild treatment, may reduce but does not eliminate the activity of untreated distillates; Hydrofinishing and solvent refining together can eliminate this activity. Tests on samples from hydroprocessing, a more severe hydrogen treatment, are discussed below.]

Groups of 27 or 50 female CF1 mice were given skin applications of one of 12 undiluted lubricant base oils once or twice weekly or once every two weeks from six weeks of age for 78 weeks. A volume of 0.25 ml was applied for the first 22 weeks; thereafter the volume was reduced to 0.2 ml. The results are summarized in Table 17. Two or three treatment regimens were used with each oil; the table gives the results of the most intensive treatment; less severe treatments produced less severe effects. Malignant skin tumours were found in 4/27 (14.8%) animals painted with acid-treated naphthenic distillate [class 2]. One malignant tumour was found in each of the groups painted with a hydrofinished naphthenic oil [class 4] and a hydrofinished solvent-extracted paraffinic oil [class 3] (Doak *et al.*,1983). [The Working Group noted that in this study the overall skin tumour response rate was lower than in the Kane *et al.* (1984) and Halder *et al.* (1984) studies. This may reflect differences in sensitivity between the strains used with respect to skin tumorigenesis.]

Table 17. Tumours at site of application in mouse-skin bioassays of materials of different classes[a]

Material tested	Class	Number of doses			Maximum cumulative volume in 78 weeks per mouse	No. of animals	No. of animals with tumours		
		Per week (weeks 0-22)	Per week (weeks 23-78)	Per 2 weeks (weeks 23-78)			Benign	Malig-nant	%
Acid-treated									
Naphthenic (+ clay treatment)	2	2	0	-	11.0	27	2	4	14.8
Solvent-refined									
Naphthenic (+ clay treatment)	3	2	2	-	33.4	50	0	0	
Naphthenic (+ clay treatment)	3	1	1	-	16.7	50	0	0	
Naphthenic (+ clay treatment)	3	1	1	-	16.7	50	1	0[b]	
Solvent-refined/ dewaxed									
Paraffinic	3	2	2	-	33.4	50	0	0[c]	
Paraffinic	3	2	2	-	33.4	50	0	0[d]	
Hydrotreated									
Naphthenic	4	1	-	1	11.1	50	2	1	2
Paraffinic (+ solvent extraction)	3	2	-	-	11.0	27	0	1	2
Paraffinic (+ solvent extraction)	3	2	2	-	33.4	50	1	0	
White oil									
Solvent-extracted, oleum- and clay-treated	5	1	1	-	16.7	50	0	0	
Naphthenic, solvent-extracted, hydrotreated	5	1	-	1	11.1	50	0	0	
Naphthenic, solvent-extracted, oleum- and clay-treated	5	2	2	-	33.4	50	0	0	

[a] From Doak *et al.* (1983)

[b] Squamous-cell carcinoma in eye

[c] Squamous-cell carcinoma on neck and dermal fibrosarcoma

[d] Basal-cell carcinoma on ventral abdomen

A sample of National Formulary grade amber petrolatum [a highly solvent-refined waxy semisolid (class 5)] (15% in iso-octane) was tested by twice-weekly skin applications of 60 µl in 40 male and 30 female Swiss mice. Five papillomas and no carcinoma were reported in the treated mice, with two papillomas in 100 iso-octane controls (no significant difference). Chromatographic removal of remaining aromatic material resulted in a fraction that also gave negative results in groups of 31 male and 30 female mice. The adsorbed aromatic fraction, concentrated 50 times compared to the original material, produced 29 skin tumours (9 carcinomas) in 17 (29%) of the 59 mice. This fraction was partitioned between nitromethane and cyclohexane; both of these subfractions induced benign and malignant skin tumours (Lijinsky *et al.*, 1966, 1967).

The high-boiling fractions of 10 catalytically cracked oils [class 6.2], characterized by varying percentages distilling above 370°C, were tested for skin tumorigenicity. Groups of 30 male albino stock mice received skin applications of these materials three times per week, starting at eight weeks of age and continuing until death. Each application by brush delivered about 15 mg of material to a skin area of 1 cm^2. The skin tumour-inducing activity of these oils ranged from none detectable when the volume distilling above 370°C was less than 1% to activity producing a 57-87% incidence (including a 33-67% incidence of skin carcinoma) when 45-78% by volume distilled above 370°C (Smith *et al.*, 1951).

A high-boiling fraction of a catalytically cracked oil (MH 191) [class 6.2] was further separated into a series of narrow distillation cuts. Each of these was tested for skin tumour induction in mice (Table 18). Carcinogenic activity appeared to increase with boiling range from 370°C up to 500-520°C and then showed a decrease. Further tests showed that the carcinogenic activity was concentrated in the aromatic fractions (Smith *et al.*, 1951).

Table 18. Mouse-skin bioassays of fractions of a catalytically cracked oil, MH 101 [class 6.2][a]

Fraction (boiling range in °C)	% By volume from MH 191	No. of mice with skin papillomas and carcinomas	Mice with skin carcinomas (%)
MH 101		62	25
MH 191[b]	100.0	32	16
0-370	48.0	3	3
316-343	24.1	0	0
343-370	29.1	0	0
370-399	21.4	30	0
399-427	11.1	29	0
427-482	1.9	36	14
482-499	2.1	50	17
499-510	2.1	43	22
510-518	2.1	64	28
518-527	2.1	60	10
527-543	1.5	46	19
>543	2.5	15	4

[a] From Smith *et al.* (1951); see text for details

[b] Filtered MH 101

Some of the fractions shown in Table 18 were further tested by twice-weekly skin applications in groups of 20 Swiss mice. The samples were applied undiluted for 10 weeks and subsequently diluted to 50% with acetone and applied for an additional 15 weeks. Each sample was applied to a group of previously untreated mice and to a group of mice initiated with a single skin application of 7,12-dimethylbenz[*a*]anthracene (DMBA) one week before. The results (Table 19) show that the fractions tested with boiling ranges above 316°C had significant promoting activity (Shubik & Saffiotti, 1955; Saffiotti & Shubik, 1963).

Table 19. Skin bioassays for carcinogenicity and for tumour promotion in mice and rabbits of fractions from a catalytically cracked oil [class 6.2][a]

Boiling range (°C)	Carcinogenicity in mice			Tumour promotion in mice after DMBA[b] initiation			Carcinogenicity in rabbits		Tumour promotion in rabbits after DMBA[b] initiation	
	No. of skin tumour-bearing mice	Total no. of papillomas	Total no. of carcinomas	No. of skin tumour-bearing mice	Total no. of papillomas	Total no. of carcinomas	No. of tumour-bearing skin areas	Total no. of papillomas	No. of tumour-bearing skin areas	Total no. of papillomas
0-370	-	-	-	-	-	-	1/6	8	4/4	43
316-343	0/20	0	0	9/30	32	9	3/6	12	NT[c]	NT
343-370	0/20	0	0	9/10	60	2	5/6	22	NT	NT
370-400	5/20	12	0	13/20	187	4	4/6	29	NT	NT
400-427	7/20	24	21	14/20	126	25	5/6	39	NT	NT

[a] Modified from Shubik & Saffiotti (1955); Saffiotti & Shubik (1963)

[b] DMBA, 7,12-dimethylbenz[*a*]anthracene

[c] NT, not tested

A different catalytically cracked residuum [class 6.2] [containing 0.4% benzo[*a*]pyrene (Tye *et al.*, 1966)], was applied two or three times weekly to the skin of 30 C3H male mice; all 30 mice developed skin carcinomas (average latent period, 8 $\pm$ 1 weeks), while no papilloma was found (Bingham & Barkley, 1979).

Samples of cutting oils [class 7.1] were tested by skin application three times weekly in groups of mice (about equally divided by sex), and results were reported after 310 days' exposure. The first sample tested was a soluble cutting fluid in the form of a stable oil-in-water emulsion containing various additives, about 45% sulphurized mineral oil base derived from a straight-run distillate and 40% water, when marketed (the material was usually diluted with eight or more parts of water before use). This cutting oil, when tested undiluted in 20 C3H mice, induced skin tumours in 61% (22% with carcinomas); the same sample, tested in 40 C57BL mice, induced skin tumours in 19% (3% with carcinomas). A separate sample of the cutting oil obtained 12 months later was tested undiluted: of 30 C3H mice, 58% developed skin tumours (19% with carcinomas); of 30 C57B1 mice, 27% developed skin tumours (3% with carcinomas); and of 30 Rockland Farm mice, 33% developed skin tumours (7% with carcinomas). No tumour was seen in control mice (Gilman & Vesselinovitch, 1955).

Small groups of female NMR1 mice received skin applications, three times weekly for 31 weeks, of 50 mg of three different cutting oils formulated from either a naphthenic distillate [class 1] or a solvent-refined paraffinic distillate [class 3]. Both unused [class 7.1] and used [class 7.2] materials were tested. The results (Table 20) show papilloma induction in most groups of mice (Jepsen *et al.*, 1977). [The Working Group noted the small number of animals used in each group.]

Table 20. Mouse-skin bioassays of three cutting oils[a]

Test material	Class	No. of mice treated	No. of mice with papilloma	No. of mice with carcinoma *in situ*[b]
Paraffinic distillate, solvent-refined, containing additives[c]	7.1	11	5	1
Same, used	7.2	9	0	0
Same, supernatant after centrifugation	7.2	10	7	1
Naphthenic distillate (with animal fat oil)	7.1	10	4	0
Same, used	7.2	9	9	4
Naphthenic distillate, emulsifiable with water, containing additives[c]	7.1	10	8	0
Same, diluted in water	7.1	8	0	0

[a] From Jepsen *et al.* (1977)

[b] No invasive carcinoma was reported in this study.

[c] Groups of mice treated with individual additives had no significant induction of skin tumours.

A sample of unused gasoline-engine oil [class 7.1] was applied undiluted twice weekly for 66 weeks to the skin of two groups of Swiss female mice: one group of 18 mice was otherwise untreated, and one group of 14 mice had received a single skin application of 7,12-dimethylbenz[*a*]anthracene (1% in mineral oil) one week prior to the start of the treatment with the test material. No skin tumour was observed in either group (Saffiotti & Shubik, 1963).

A group of 20 male and 20 female stock albino mice, aged six to eight weeks, received skin applications twice weekly for 45 weeks and, after a five-week rest period, once weekly until termination of the test at 456 days of 0.3 ml of an oil additive used in the production of engine lubricating oils [class 7.1]. The additive was composed of a base oil and an additive concentrate, one component of which was lead naphthenate. The total dose was 32 ml per mouse (Baldwin *et al.*, 1964). Of 35 animals alive when the first tumour occurred, six developed skin papillomas and 18 developed skin carcinomas (Baldwin *et al.*, 1961). Components of the additive were tested in young male mice (Schofield strain), which received skin applications once or twice weekly for up to 12 months and were observed until termination at 18 months. With the base oil component [probably an unrefined distillate (class 1)], 19/29 mice at risk developed papillomas and five developed skin carcinomas; each animal received a total of 21 ml of oil. Only 1/32 animals at risk developed a skin papilloma when painted with the additive concentrate (additive minus base oil; total dose, 6 ml, equivalent to 60 ml of whole additive). Papillomas developed with the lead naphthenate component (total dose, 6 ml) in 2/59 mice at risk. These results suggest that the carcinogenic activity of the additive lay principally, if not entirely, in the base oil component (Baldwin *et al.*, 1964). [The Working Group noted the absence of controls in these tests.]

Groups of 65 CFLP random-bred female mice received twice-weekly skin applications of 0.1 ml 'used' gasoline engine oil [class 7.2] dissolved in a 3:1 mixture of acetone and cyclohexane, for a total of 104 weeks; the test material was an engine oil artificially aged in a gasoline-driven car, and the individual test doses were 0.625, 1.875 and 5.625 mg. The dose-related increase [$p < 0.01$] in the incidence of tumours is shown in Table 21. No comparison was made with unused oil (Grimmer *et al.*, 1982b). [The Working Group took special note of this study in view of the large number of animals used and the strong dose-response relationship.]

Table 21. Mouse-skin bioassays of a 'used' gasoline-engine oil [class 7.2][a]

Dose (mg)	Tumour incidence		
	Papillomas	Carcinomas	% Tumour-bearing mice
Solvent controls	0	1	1.5
0.625	3	0	4.6
1.875	8	9	26.6
5.625	14	29	69.4

[a] From Grimmer *et al.* (1982b)

Rabbit: A group of six adult female New Zealand white rabbits was treated twice weekly on each of six areas of skin, about 9 cm^2 each (two on the ears and four on the sides), with undiluted fractions from a high-boiling catalytically cracked oil [class 6.2]. The results (Table 21) confirm the tumorigenic and promoting activity of these materials (Shubik & Saffiotti, 1955; Saffiotti & Shubik, 1963).

A group of 21 rabbits [sex, strain and age unspecified] received thrice-weekly skin applications to the inner surface of the ears of 0.5 g of the high-boiling fraction of a catalytically cracked oil [class 6.2] for two years; all rabbits developed papillomas (1-18 each), and three developed carcinomas (Smith *et al.*, 1951).

Monkey: Rhesus monkeys (three male and three female) were painted on the skin with a high-boiling fraction of catalytically cracked oil [class 6.2]; all developed skin papillomas, and two developed skin carcinomas within four years (Smith *et al.*, 1951).

(c) *Inhalation*

Mouse: A group of 130 male CAF_1/JAX mice was exposed daily in an exposure chamber to an aerosol (mean particle diameter, 1.3 μm) generated from a light white naphthenic oil [class 5] at a concentration of 100 mg/m^3 for 7-13 months and were killed at monthly intervals. No overall significant difference in tumour incidence between exposed mice and the 130 control animals was reported (Wagner *et al.*, 1964). [The Working Group noted the short duration of exposure.]

A total of 132 strain A mice (11 groups of 12 mice each), approximately equally divided by sex, were exposed continuously in a chamber to a diesel lubricating oil [class 7.1] at a concentration of 63 mg/m^3. One group was killed each month up to 11 months. Groups of 10-12 unexposed controls were killed concurrently. The reported incidence of lung tumours did not appear to be significantly different in treated and control mice (Lushbaugh *et al.*, 1950).

Other species: Male rats (two groups of 80), hamsters (one group of 106 and one of 112), rabbits (two groups of 23) and dogs (two groups of 9) were exposed daily in an exposure chamber to an aerosol (mean particle diameter, 1.3 μm) generated from a light white naphthenic oil [class 5] for periods of 6-26 months, at concentrations of 5 and 100 mg/m^3. No tumours was reported (Wagner *et al.*, 1964). [The Working Group noted inadequacies in experimental design, including short exposure periods, and incomplete reporting.]

(*d*) *Subcutaneous and/or intramuscular administration*

Mouse: Three samples of petrolatum [class 5] (snow-white US Pharmacopeia XVI grade, white US Pharmacopeia XVI grade and yellow National Formulary XI grade) were tested by single s.c. injection of 100 mg in groups of 50 male and 50 female Swiss-Webster mice, which were observed for tumour development for 18 months. None of the tests yielded any treatment-related tumour increase (Oser *et al.*, 1965).

Rat: Groups of 30 rats of strains BD I, BD III and W [sex unspecified] were given single s.c. injections of 2.5 ml of liquid paraffin [class 5], and groups of 26 rats were given similarly 1 ml of yellow petrolatum (Deutsches Arzneibuch-6) [class 5] and were observed until death. No local tumour was reported in those given paraffin; but an osteosarcoma arose near the site of injection of yellow petrolatum (Schmähl & Reiter, 1953).

(*e*) *Intraperitoneal administration*

Mouse: Two highly refined mineral oils were tested extensively in i.p. studies in mice. One oil, a US Pharmacopeia grade [class 5], had a viscosity range of 37-71 mm^2/sec at 37.8°C, and the other, a technical-grade white mineral oil [class 5], had a viscosity range of 14-18 mm^2/sec at 37.8°C, depending on specific designation. Three groups of two-month-old female BALB/c mice (40, 32 and 32 animals each) received, respectively, a single i.p. injection of 0.4 ml, a single i.p. injection of 0.5 ml, or three i.p. injections of 0.5 ml, at two-month intervals of the lower-viscosity oil (Bayol F); 8, 2 and 22 intraperitoneal plasma-cell neoplasms arose in each of the three groups, respectively, from 5 to 14 months after the initial treatment. No such tumour was found in control mice given a single i.p. injection of corn oil or saline (Potter & Boyce, 1962). The same morphology was observed in these tumours and in those induced by injections of a mixture of incomplete Freund's adjuvant (which contains an oil of a similar viscosity and mannide monooleate) and heat-killed *Staphylococcus* cultures (Potter & Robertson, 1960). Plasma-cell neoplasms were also induced in 13/56 BALB/c mice given i.p. injections of the high-viscosity oil (Primol D) (Potter & Boyce, 1962). The histogenesis of plasma-cell neoplasms was described by Potter and MacCardle (1964), who noted that the tumours appeared to arise from induced mesenteric oil granulomas.

The high-viscosity oil, Primol D [class 5], was also given as three i.p. injections of 0.5 ml each to 36 DBA/2 and 12 CBA female mice, at the age of 10, 15 and 21 weeks. Peritoneal reticulum-cell sarcomas [type A of Dunn (see Dunn, 1954)] developed in 15 (42%) of the DBA/2 mice and plasma-cell leukaemia in three, myeloid leukaemia in three and lymphocytic leukaemia in two. In the 12 CBA mice, only one reticulum-cell sarcoma (probably type B of Dunn) was found plus one lymphocytic leukaemia (Rask-Nielsen & Ebbesen, 1965). Other strains of mice, e.g., strains IC and C3H, injected with the low-viscosity oil (Bayol F) developed oil granulomas but not plasma-cell tumours, while BALB/c mice developed both (Hermann, 1966). Marked enhancement of the incidence of plasma-cell tumours induced by three i.p. injections of the high-viscosity oil, Primol D, was observed in female BALB/c mice that also received i.p. injections of nanogram doses of bacterial endotoxins (Bober *et al.*, 1976).

Rat: Groups of 30 BD I, BD III and W strain rats of both sexes received i.p. injections of liquid paraffin [class 5] to give a total dose of 9 ml over a 40-week period. Four male rats developed sarcomas in the abdominal cavity, two of which appeared to be of testicular origin. Yellow petrolatum [class 5] (3 ml) was similarly injected into eight rats, but no tumour developed (Schmähl & Reiter, 1953).

3.2 Other relevant biological data

(*a*) *Experimental systems*

Reviews on the toxic effects of mineral oils in animals are available (Bingham *et al.*, 1980; Chircova, 1982; World Health Organization, 1982).

Toxic effects

Acute 14-day oral toxicity studies have been performed in the Sprague-Dawley rat with paraffinic base stock [class 8] (13.1-194 mm^2/sec at 37.8°C) and naphthenic base stock [class 8] (15.7-432 mm^2/sec at 37.8°C) administered by gavage; no mortality occurred at the highest dose tested, 5 g/kg bw. The same oils did not induce primary eye irritation in rabbits, acute or subacute dermal toxicity in rabbits, or dermal sensitization in guinea-pigs (Beck *et al.*, 1982).

No alteration in respiratory function was observed in guinea-pigs exposed to medicinal-grade mineral oil [class 5], laboratory-grade paraffin oil [class 5], light lubricating oil S-75 [class 7.1] or multigrade motor oil (SAE 10 W-30) [class 7.1] at concentrations of 10 or 40 mg/m^3 for one hour. At concentrations above 200 mg/m^3, the light lubricating oil significantly reduced lung compliance; the reduction persisted for one hour after cessation of exposure (Costa & Amdur, 1979).

Aspiration of 0.2 ml mineral oil [class 5] or a multigrade motor oil [class 7.1] by groups of five adult male Wistar rats caused no mortality after 24 hours; however, a second multigrade motor oil (SAE 10W-20W-30) caused mortality in one of five animals. These oils did not produce the severe acute pulmonary oedema or haemorrhage characteristic of kerosene and of similar low-viscosity hydrocarbon mixtures (Gerarde, 1963).

An extensive study of the dermatological effects of mineral oils, their fractions and aliphatic hydrocarbons has been reported (Hoekstra & Phillips, 1963). A number of light mineral oils [class 2] applied to the skin of male albino guinea-pigs produced marked epidermal hypertrophy, hyperplasia, hyperkeratosis and subsequent depilation. Application of individual aliphatic hydrocarbons produced skin-damaging effects that appeared to be related to the molecular size of the compound, hydrocarbons with carbon numbers in the range 14-19 being the most active.

A group of 13 albino mice exposed to an aerosol of US Pharmacopeia grade liquid petrolatum [class 5] at a concentration of 4500 mg/m^3 intermittently for a total of 80-84 hours over a four-week period showed a survival rate of 77% [sex of survivors unspecified], whereas in another group, 6/7 mice survived 92 hours' exposure to SAE No. 10 motor oil [class 7.1] [particle sizes, 2.2 (US Pharmacopeia) - 2.7 (SAE) μm mass median diameter] at a concentration of 4330 mg/m^3. Oil was found evenly dispersed throughout the lung after 96 hours. Both oils produced localized foreign-body reactions of moderate severity in the lung as well as infrequently occurring patches of lipid pneumonia (Shoshkes *et al.*, 1950).

Treatment of male Sherman rats thrice weekly by gavage with mineral oil [class 5] at a dose of 2 ml/kg bw for three months did not produce toxic effects (Kimbrough *et al.*, 1980).

Inhalation of automobile lubricating oil, SAE No. 10 [class 7.1] at a concentration of 132 mg/m^3 (for 30 min per hour, 24 hours per day) by 80 CF1 mice for 100 days or of diesel lubricating oil, S.G.E. No. 1 [class 7.1] at 63 mg/m^3 by 250 strain A mice, 80 albino rats and four rabbits for up to one year caused no increased incidence of lipid pneumonia compared

to controls. Exposure of six monkeys (*Macaca mulatta*) to the automobile lubricating oil for 100 days caused the death of two animals, while similar exposure of seven monkeys to the diesel lubricating oil at a concentration of 63 mg/m^3 for 100 days caused death in six animals. All monkeys died with possible infectious pneumonitis, had evidence of pulmonary lipophages and exhibited severe hyperplastic gastritis probably because of the swallowing of inhaled oil (Lushbaugh *et al.*, 1950).

Groups of dogs, rats, mice and gerbils were exposed by inhalation to an aerosol of a complex oil mixture (supplemented with esters, waxes and resins) at a concentration of 5 or 100 mg/m^3, together with acetone vapour (possibly impure) at 788 mg/m^3. The base oil of the complex oil mixture was a paraffinic white oil [class 5]. Exposures were for six hours per day, five days per week for up to two years. Oil was detected within lung macrophages of all species at both dose levels. At 100 mg/m^3, oil microgranulomas were detected in dogs and rats, but not in mice or gerbils (Stula & Kwon, 1978). These results correspond essentially to those obtained in dogs, rabbits, hamsters, rats and mice exposed by inhalation to a pure paraffinic white oil mist [class 5] at a concentration of 5 or 100 mg/m^3 for periods of one year to 26 months (Wagner *et al.*, 1964).

A suppressive effect on immune response in albino rats and guinea-pigs exposed to concentrations of 10-125 mg/m^3 spindle oil [class 8] and machinery oils [class 8] has been reported (Bruskin, 1965; Lutov, 1973).

Effects on reproduction and prenatal toxicity

Marked embryolethal and teratogenic effects were observed when used crankcase oil [class 7.2] was applied at concentrations of 1-15 μl to the egg shell of Mallard ducks (*Anas platyrhynchos*) and quails (*Colinus virginianus*). These effects were not due to physical factors, such as clogging of shell pores and anoxia, since application of larger volumes of mixed aliphatic hydrocarbons present in the oils did not cause the same effects. Unused crankcase oil [class 7.1] was less embryolethal than used crankcase oil and was not teratogenic, perhaps because of the much higher lead content in used crankcase oil (4600 mg/kg) than in unused crankcase oil (2 mg/kg) and the higher concentration of aromatic hydrocarbons (Hoffmann *et al.*, 1982).

Absorption, distribution, excretion and metabolism

When large amounts of liquid petrolatum [class 5] were fed to rabbits, rats and guinea-pigs, small quantities were deposited in the mesenteric lymph nodes and, in several cases, in the intestinal mucosa, liver and spleen (Stryker, 1941).

Paraffinic oil [class 5], injected intravenously into rabbits is taken up by the liver, bone marrow, lung and the endothelial cells of the spleen. Liver granulomas were also observed (Gonet *et al.*, 1960; Buhrer & Widgren, 1963).

After exposure to diesel-engine lubricating oil [class 7.1] at a concentration of 63 mg/m^3, oil was found in alveolar macrophages, in mediastinal lymph nodes and in the lymphatic channels of the lungs and pleura of mice, rats and rabbits (Lushbaugh *et al.*, 1950).

The metabolic fate and distribution of mineral-oil adjuvant emulsions [class 7.1] formulated with white oil [class 5] and spiked with [^{14}C]-*n*-hexadecane, a major constituent, was examined in female albino rats and female squirrel monkeys injected subcutaneously and intramuscularly with 0.1 ml and 0.3 ml, respectively. One week after treatment, less than 2% of the

radioactivity was recovered in expired carbon dioxide and less than 0.01% in the urine and faeces, while 85-99% remained at the site of injection in both species; after 10 months, approximately 25-30% remained at the site of i.m. injection in both species. Some of the mineral oil tracer which left the site of injection was incorporated into lipids (Bollinger, 1970).

Tritiated mineral oil (US Pharmacopeia grade liquid petrolatum) [class 5] was administered orally or by i.p. injection to Sprague-Dawley and Holtzman rats. Five hours after oral administration of 0.66 ml/kg bw, 1.5% of the dose had been absorbed unchanged, and an additional 1.5% was found in the carcasses as non-mineral oil substances. Liver, fat, kidney, brain and spleen contained mineral oil. Within two days, only 0.3% remained in the animals. After i.p. administration, the mineral oil was retained to a greater extent, and only 11% had been excreted in the faeces eight days after treatment (Ebert *et al.*, 1966).

Mutagenicity and other short-term tests

Vacuum distillates [class 1]

Samples of two distillates obtained by vacuum distillation [class 1] (distillation ranges, 380-500°C and 300-430°C; content of 'polynuclear aromatic hydrocarbons'[1], 78 g/l and 54 g/l, respectively) and solvent-refined samples from the corresponding distillates [class 3] (polynuclear aromatic hydrocarbon content[1], 20 g/l and 9.7 g/l) were dispersed in Tween 80 or extracted in dimethyl sulphoxide (DMSO) and tested for mutagenicity in *Salmonella typhimurium* strain TA98. Both distillates and refined samples were mutagenic in the presence of an Aroclor-induced rat-liver metabolic system (S9); the mutagenic activity of the refined sample was significantly less than that of the unrefined sample (Hermann *et al.*, 1980a,b).

Hydrotreated oil [class 4]

A hydrotreated petroleum residue [class 4] (distillation range, 400 to 550°C; 'polynuclear aromatic hydrocarbon'[1] content of 2.5 g/l), dispersed in Tween 80 or extracted in DMSO, was mutagenic to *S. typhimurium* strain TA98 in the presence of S9 (Hermann *et al.*, 1980a,b).

White oils [class 5]

A white oil of 'medicinal quality' [class 5] ('polynuclear aromatic hydrocarbon content'[1], 0.64 g/l), dispersed in Tween 80 or prepared as an organic solvent extract (redissolved in DMSO), was tested for mutagenicity in *S. typhimurium* strain TA98 in the presence of S9. No mutagenic activity was observed with amounts up to the equivalent of 20 µl oil/plate (Hermann *et al.*, 1980a,b).

Steel-hardening oils [classes 7.1 and 7.2]

A highly-refined steel-hardening oil [class 7.1] ('polynuclear aromatic hydrocarbon'[1] content, 2.6 g/l) and the corresponding oil 'used under an inert atmosphere' [class 7.2] ('polynuclear aromatic hydrocarbon'[1] content, 8.3 g/l), dispersed in Tween 80 or prepared as an organic solvent extract (redissolved in DMSO), were tested for mutagenicity in *S. typhimurium* strain TA98 in the presence of S9. The unused oil was not mutagenic when tested at amounts up

[1] Oil, dissolved in cyclohexane, was extracted with DMSO. The DMSO extract was diluted in 4% sodium chloride solution, extracted with cyclohexane and then washed and desiccated. The residue obtained after vacuum distillation of the solvent was used for mutagenicity assays and determinations of polynuclear aromatic hydrocarbon content.

to the equivalent of 20 µl of oil/plate, while the used oil was mutagenic both in the presence and absence of the metabolic system (Hermann *et al.*, 1980a,b).

Crankcase oils [classes 7.1 and 7.2]

DMSO extracts of a pooled sample of 15 commercially available 10W-40 gasoline-engine oils [class 7.1] and of a pooled sample of used oil [class 7.2] (produced by operating gasoline engines with each of the same 15 component oils for 5000 miles and then blending equally) were tested for mutagenicity in *S. typhimurium*. The extract from the used sample only was mutagenic in strains TA1537, TA1538, TA98 and TA100 in the presence and absence of S9; the extract of unused oil showed no mutagenic activity (Schreiner & Mackerer, 1982).

Similar results were obtained in three other studies. Wang *et al.* (1978) reported that an unused oil was not mutagenic but that used oil (obtained from four different cars) was mutagenic to *S. typhimurium* in the absence of metabolic activation [details not given]. In a second study, DMSO extracts of each of five commercially available crankcase oils [class 7.1] and one used sample [class 7.2] (obtained locally) were tested for mutagenicity in *S. typhimurium* strain TA98. The used sample was mutagenic in the presence of an [presumably] uninduced rat-liver metabolic system; the extract of unused oil showed no mutagenic activity (Payne *et al.*, 1978). In the third study, a 'highly refined' crankcase oil [class 7.1] and the corresponding used oil [class 7.2] obtained in a special wearing test (Petter engine), dispersed in Tween 80 or prepared as an organic solvent extract[1] (redissolved in DMSO), were tested for mutagenicity in *S. typhimurium* strain TA98 in the presence of S9. The unused oil was not mutagenic when tested at amounts up to the equivalent of 20 µl of oil/plate, while the used oil was mutagenic both in the presence and absence of the metabolic system (Hermann *et al.*, 1980a,b).

In contrast, Peake and Parker (1980) reported that both unused [class 7.1] and used [class 7.2] samples of oil were mutagenic. Two samples of used oil were obtained from the oil sumps of two automobiles with four-stroke gasoline engines after five to six months' use, and a third sample was from a pooled sample of used oil obtained from a service station. DMSO extracts were prepared. The used oil samples were reported to be mutagenic to *S. typhimurium* strains TA1535, TA1537, TA1538, TA98 and TA100, when tested in the presence of S9, and to be active in one or more strains in the absence of the metabolic system. Seven unused oils (including re-refined used oils) were also examined. The authors reported that most of the unused motor oils showed some mutagenic activity in the absence of S9, and little or no activity in its presence (Peake & Parker, 1980). [The Working Group noted the incomplete reporting of the data.] In a later study, in which one of the unused samples was re-tested, no mutagenic activity was observed (Schreiner & Mackerer, 1982).

(*b*) *Humans*

Toxic effects

The terms 'lung paraffinoma', 'lipogranuloma' and 'lipid granuloma' have all been used in the reports cited below. As these terms describe similar lesions, only the term 'lipid granuloma' is used throughout this monograph to describe them.

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[1] Oil, dissolved in cyclohexane, was extracted with DMSO. The DMSO extract was diluted in 4% sodium chloride solution, extracted with cyclohexane and then washed and desiccated. The residue obtained after vacuum distillation of the solvent was used for mutagenicity assays and determinations of polynuclear aromatic hydrocarbon content.

Reviews on the toxic effects of petroleum-derived oils in humans are available (Jampolis *et al.*, 1953; Key *et al.*, 1966; Kipling, 1967; Hodgson, 1970).

The major sites in humans affected by the toxicity of petroleum-derived oils are the lungs and the skin. Inhalation, aspiration or ingestion of these materials produces lipid pneumonia and lipid granuloma of the lung (Jampolis *et al.*, 1953); effects generally observed on the skin are eczematous dermatitis, contact dermatitis, folliculitis, oil acne, lipid granuloma and melanosis (Hodgson, 1970).

Up to 1978, more than 400 cases of lipid pneumonia were reported in the literature to be related to oral administration of mineral oil (paraffin oil) [class 5], to oil-based nose drops [class 5] or to intralaryngeal injection of medicinal oil [class 5] (Facquet & Langeard, 1947; Meyers & Griffith, 1955; Miller *et al.*, 1962; Zurrow & Sergay, 1966; Salm & Hughes, 1970; Scully *et al.*, 1977; Heckers *et al.*, 1978). Mineral oil may enter the trachea and bronchi after oral or nasal administration to individuals (especially in the supine position) with a reduced or absent gag reflex (Schneider, 1949), or through its ability to inhibit the normal cough reflex (Cannon, 1940): mineral oil inhibits the action of respiratory cilia (Proetz, 1934), allowing passage to the alveoli. Mineral oils do not produce pulmonary necrosis and are taken up by macrophages (called lipophages), which remain within the alveolar spaces (Cannon, 1940; Schneider, 1949).

Lipid granulomas of the lung are localized lipid pneumonias, usually found in adults as a result of habitual use of large amounts of mineral oil (liquid petrolatum) [class 5] by nasal, oral or pharyngeal administration for prolonged periods of time (Ikeda, 1937; Buechner & Strug, 1956). Numerous cases of lipid granuloma have been reported in the literature (Pinkerton & Moragues, 1940; Singer & Tragerman, 1941; Berg & Burford, 1950; Jampolis *et al.*, 1953; Nelson, 1954; Buechner & Strug, 1956; Siddons, 1958; Eyal *et al.*, 1961; Genevrier *et al.*, 1972; Borrie & Gwynne, 1973; Meyer, 1976).

Peritoneal lipid granuloma was observed in an individual who received mineral oil [class 5] in the chest for a permanent collapse of the lung (oleothorax); it was noted that the substance had been introduced inadvertently into the abdominal cavity (Tuschka, 1961). Wilson (1965) reported two patients who retained mineral oil [class 5] in the pleural cavity for periods of up to 32 years with no ill effect.

Eight cases of lipid granuloma, usually accompanied by calcification, have been documented after intra-abdominal instillations of mineral oil [class 5] were carried out following abdominal surgery (Bennett & Collins, 1952; Campbell *et al.*, 1964; Pear & Boyden, 1967).

A 30-year-old woman received 160 injections of mineral oil [class 5] and two injections of olive oil in the medial and lateral muscles of both calves, resulting in sclerosing lipid granuloma of the calves with lymph node and pulmonary involvement (Urbach *et al.*, 1971). Another case of lipid granuloma has been reported in a man 20 years after he received several injections of mineral oil [class 5] in the pectoral muscles (Dumont-Fruytier *et al.*, 1980).

Nineteen men occupationally exposed (about two hours per shift, equivalent to 600 hours per year) to an oil mist (estimated concentration, 9 mg/m^3) in a tandem steel-rolling mill were examined after 9-18 years' employment. At the time of sampling, the oil mist (diameter of 70% of the droplets, 0.8-1 μm) was derived from a rolling oil [class 7.2] containing a naphthenic spindle oil, petroleum sulphonates, rosin soaps and cresylic acid. No evidence of lipid or other pneumonia, bronchitis, gastric disorders, dermatological conditions or diseases of the ears, nose or throat was observed. The only possibly significant finding was an increase in linear striations of the lung in 12 men (Jones, 1961).

In a Swedish pilot study of six male lathe operators exposed for 4-29 years to non-synthetic cutting mineral oil [class 7.2], nasal mucosa biopsies were compared with samples from various men, matched for age and smoking, without oil-mist exposure. Exposed men more frequently showed: lack of cilia, basal-cell hyperplasia, squamous metaplasia and subepithelial hyalinization (Irander *et al.*, 1980). [The Working Group noted that the criteria used for selecting exposed workers for biopsy were not explained; although five of the six exposed workers had nasal symptoms, their relative frequency among all exposed workers is not stated.]

Klauder and Brill (1947) investigated the irritant action of mineral seal oil No. 1 [class 2] and its fractions, using patch tests to identify dermatitis and eczematous noxae. An inverse correlation between the boiling-point range of the mineral oil and its irritant action was found. A similar study, carried out using different oils (lubricating, cutting) [various classes] on normal and eczematous individuals, showed that the latter were more sensitive to the irritant actions of the oils (Hodgson, 1960).

A study was conducted among 200 men occupationally exposed to cutting fluid in a machine-tool factory in order to identify specific occupations at risk. The capstan-lathe operators and automatic-lathe operators (exposed only to insoluble oils) had more severe degrees of oil folliculitis, probably owing to their exposure to cutting oils [class 7.2] (Finnie, 1960). Cruickshank and Squire (1950) reported that 80% of workers in a UK machine-tool factory exposed to cutting oils [class 7.2] had evidence of oil folliculitis.

In a field survey of 3023 jute workers and 667 flax workers, Kinnear *et al.* (1955) observed that the incidence of oil acne in the former, as a group, was 15.4%, compared to 10% in flax workers. Of 95 jute 'batchers' surveyed, 33.7% exhibited oil acne, while only 1/18 (5.6%) of their counterparts in flax manufacturing exhibited this effect [exposures to oil classes 1 and 8, respectively]. [The Working Group noted the possible presence of chlorophenol additives in the jute-batching oil].

Absorption, distribution, excretion and metabolism

In general, mineral oil [class 5] is absorbed to only a limited extent from the gastrointestinal tract (Anon., 1967; Goodman & Gilman, 1975). However, it was found in the liver, spleen, mesenteric and portal-hepatic lymph nodes and lungs of a man known to have ingested large amounts of liquid paraffin [class 5] over many years (Nochomovitz *et al.*, 1975). Mineral oil has been observed by differential staining and gas-chromatographic procedures in the lung tissue of many individuals who routinely use mineral oil by oral or nasal administration (Singer & Tragerman, 1941; Wagner *et al.*, 1955, Salm & Hughes, 1970; Heckers *et al.*, 1978).

Mutagenicity and chromosomal effects

The urine of 17 men exposed occupationally to both mineral oils [class 8] and iron oxide particles and of 16 men exposed only to mineral oils was tested for mutagenicity in *Salmonella typhimurium* strains TA98 and TA100. Both groups of workers exhibited mutagenic activity in their urine in the presence of an Aroclor-induced rat-liver metabolic system and β-glucuronidase (Laires *et al.*, 1982). [The Working Group noted the lack of suitable controls.]

3.3 Case reports and epidemiological studies of carcinogenicity in humans

In the studies cited below, the descriptions of the exposures were generally inadequate to allow assignment of classes to oils. In most cases, however, exposure was probably to used and unused formulated products [classes 7.1 and 7.2].

(a) *Case reports and case series*

(i) *Occupational exposures*

A number of case reports and case series of cancer in association with occupational exposure to mineral oils have been published from different countries. These are summarized in Table 22.

(ii) *Non-occupational exposures*

Five cases of bronchogenic carcinoma (including one adenocarcinoma and one epidermoid carcinoma) have been reported in association with lipid pneumonia and lipid granuloma, which are non-malignant pathological lung conditions that may follow aspiration of mineral oil and other kinds of oily products (Wood, 1943; Sante, 1949; Bryan & Boitnott, 1969; Keshishian *et al.*, 1969). Volk (1964), in a general review of lipid pneumonia, stated that in a series of over 100 cases, most of whom were under his care for up to 25 years, there had not been a single instance of bronchogenic carcinoma. A review of 114 consecutive cases of adenocarcinoma of the lung from autopsy and surgical pathology files of the Johns Hopkins Hospital revealed no lesion suggestive of mineral oil pneumonia (Bryan & Boitnott, 1969).

(b) *Epidemiological studies*

(i) *Metalworkers*

Ely *et al.* (1970) conducted a proportional mortality study of male workers at three plants of a company in Rochester, New York, USA. The study group comprised 343 deaths occurring between 1942 and 1961 among men with five or more years' experience in machine shop areas where exposure to oil mist occurred; a comparison group was available of 3122 deaths among men at the same plants who had had no employment in oil-mist work areas. All subjects within the study group were persons who died while (1) actively employed, (2) covered by disability insurance or (3) in retirement. [No age-adjustment was carried out, although the average ages at death for the two groups did not differ excessively (62.9 years for the exposed groups, 63.9 years for the comparison group).] Of 69 deaths in the exposed group from cancers at all sites, 10 were from cancer of the respiratory system, accounting for 2.9% of all deaths against 3.2% in the comparison group. The only other cancer sites specified were Hodgkin's disease and leukaemia, from which there was no death in the exposed group. The equipment in the machine shops studied included lathes, mills, shapers, automatic screw machines, grinders and gear hobbers, and the principal oils used were of mineral origin. During the period 1955-1970, concentrations of oil mist ranged from 0.07-110 mg/m^3, with a median of 1.5 mg/m^3 and a mean of 3.7 mg/m^3. [The authors do not state how causes of death were classified and coded and do not give results for other specific cancer sites of interest, such as those within the gastrointestinal tract.]

Decouflé (1976) studied the mortality experience of a cohort of 5189 white males employed at any time between 1938 and 1967 at a heavy industrial plant in the USA and who had spent at least one year in metal-machining jobs. Subjects were followed until 1967, by which time 901 deaths had occurred. The cause-specific mortality experience of the study group was compared to death rates in the general US white male population by computing age- and calendar year-adjusted expected numbers of deaths and standardized mortality ratios (SMRs). The report subdivided all cancer deaths into three categories: respiratory system, digestive system, and all other sites combined. Overall, there were 46 deaths from cancer of the

Table 22. Case reports and case series of cancer in association with occupational exposure to mineral oils

Reference	Country (of exposure)	Numbers of cases and jobs[a]									Reported exposure	Comments
		Mulespinners			Machinists			Other jobs				
		Scrotum	Other skin	Other	Scrotum	Other skin	Other	Scrotum	Other skin	Other		
Green (1910)	USA/UK	2	-	-	-	-	-	-	-	-		
Southam & Wilson (1922)	UK	69	-	-	-	-	-	72	-	-	Mineral oil	
Hoffman (1928)	USA/Canada/UK	3	-	-	-	-	-	3*	-	-	-	Deaths. *Textile workers
Bridge & Henry (1928)	UK	268	93	-	-	-	-	35	22	-	Mineral oil	Notifications of epitheliomatous skin ulceration from 1920-1927
Heller (1930)	USA/UK	6	2*	3	-	-	-	-	-	-	Mineral oil (sulphuric acid-refined)	*Deaths. US mule-spinning same as in UK
Henry & Irvine (1936)	UK	105	-	-	-	-	-	27	-	-	-	Deaths and hospital cases of scrotal cancer: Blackburn (1837-1929)
Henry (1937)	UK	345	-	-	-	-	-	1142	-	-	-	Deaths from scrotal cancer England and Wales (1911-1935)
Graves & Flo (1940)	USA	3	-	-	1	-	-	10	-	-	9 Exposed to mineral oils	
Henry (1947)	UK	857*	545* +14***	-	28**	21**	-	16	15	-	Mineral oil	*Male cotton workers. **Metal workers. **Female cotton workers. Included in 'Other jobs' are 6 cases among wool workers, 2 of which were scrotal cancers. Figures refer to *sites not persons*.
Dean (1948)	USA	-	-	-	3	-	-	24	-	-	9* Exposed to mineral oil	*One questionable
Huguenin *et al.* (1950)	France	-	-	-	-	-	23*	-		- 9**	Oil mist	* Metal workers, lung cancer **Lung cancer

Reference	Country (of exposure)	Numbers of cases and jobs[a]									Reported exposure	Comments
		Mulespinners			Machinists			Other jobs				
		Scrotum	Other skin	Other	Scrotum	Other skin	Other	Scrotum	Other skin	Other		
Cruickshank & Squire (1950)	UK	1*	-	-	9	-	-	2	-	-	Mineral oil	*Cotton worker
Cruickshank & Gourevitch (1952)	UK	-	-	-	-	7	-	-	11	-	Mineral oil	
Kinnear *et al.* (1954)	UK (Scotland)	-	-	-	-	-	-	-	66*	-	Two types of mineral oil	*Includes premalignant skin lesions. Jute workers
Kinnear *et al.* (1955)	UK (Scotland)	1	5	-	-	-	-	1	3	-	Mineral oil	Jute workers
Mastromatteo (1955)	Canada	-	-	-	1	5	-	-	-	-	Cutting oils	
Taylor & Dickes (1955)	USA	-	-	-	-	2	-	-	-	-	Cutting oils	
Fife (1962)	UK	-	-	-	2*	-	-	50**	29**	-	Mineral oil	*Exposed to cutting oils **Industries other than cotton
Despierres *et al.* (1964, 1965)	France	-	-	-	-	-	1*	-	-	-	Mineral oil	*One case of lung cancer in a non-smoker exposed to inhalation of mineral oil fumes
Tourenc (1964)	France	-	-	-	21	-	-	-	-	-	Mineral oils	
Bremner (1964)	S. Africa	-	-	-	-	-	-	1	-	-	Oils.& grease	Bicycle repair work
Spink *et al.* (1964)	UK	-	-	-	-	-	-	2	1	-	Mineral oils	'Stanford jointing' of earthenware pipes
Lee & McCann (1967)	UK	-	2	-	-	-	-	-	-	-	Mineral oil	Wool industry reportedly entails less exposure than cotton
Avellán *et al.* (1967)	Sweden	-	-	-	8	-	-	-	-	-	Mineral oil	Automatic lathe operators
Kickham & Dufresne (1967)	USA	12	-	-	10	-	-	6	-	-	Mineral oil	Of these, 12 had already been included in Graves & Flo (1940)
Milne (1970)	Australia	-	-	-	2	-	-	3	-	-	3 Exposed to mineral oils	Cases collected from Control Cancer Registry, Victoria

Reference	Country (of exposure)	Numbers of cases and jobs[a]									Reported exposure	Comments
		Mulespinners			Machinists			Other jobs				
		Scrotum	Other skin	Other	Scrotum	Other skin	Other	Scrotum	Other skin	Other		
Wahlberg (1972, 1974)	Sweden	-	-	-	7	-	-	27	-	-	13 Exposed to mineral oils	Cases from Swedish Cancer Registry
Thony *et al.* (1975)	France	-	-	-	84	49	-	-	-	-	Cutting oils	Oils contained benzo[*a*]pyrene at concentrations of 0.6-170 mg/kg
Hundeiker & Glossmann (1975)	Federal Republic of Germany	-	-	-	1	-	-	-	-	-	Mineral oil	

[a] For an explanation of the asterisks, in each case see the 'Comments' column

respiratory system compared to 46.3 expected, for which analyses by duration of exposure and interval from onset of exposure showed no pattern indicative of an association with employment. There were 58 deaths from cancer of the digestive system compared to 60.3 expected, and a breakdown of the deaths by duration of exposure and time since onset of exposure did not suggest a definite relationship with the work environment. Mortality from cancers at 'all other sites combined' in the total cohort was not excessive (46 observed deaths, 51.5 expected).

Decouflé (1978) expanded his earlier report (Decouflé, 1976) by examining mortality from cancer at more specific sites among 2485 white males with five or more years' employment in a variety of jobs involving exposure to oil mist at the same plant. A subgroup of 1137 men, who had accumulated five or more years' employment in metal-machining jobs, was included. Exposures to oil mist in metal-machining jobs were classified on a qualitative scale as being 'heavy', while all other jobs in adjacent areas were denoted as being either 'moderate' or 'minimal' exposures. No additional follow-up was made, and almost 99% of subjects were traced successfully. Comparisons were made with the general US white male population, as before. Among 15 different cancer-site categories analysed, the only indication of unusual mortality was for cancers of the stomach and large intestine combined, and this was confined to workers accumulating five or more years of employment prior to 1938, the opening year of the study. Among 835 men whose pre-1938 employment included five or more years in any job involving exposure to oil mist, there were 15 deaths from cancers of the stomach and large intestine occurring 20 years or more after 1 January 1938, compared to 7.6 expected ($p < 0.05$). Among 384 men who had had five or more years' employment in the heavily exposed metal-machining jobs prior to 1938, there were seven deaths observed compared to 3.6 expected (not statistically significant) after 20 years' follow-up beginning 1 January 1938. Results for cancer of the respiratory system in these same subgroups did not indicate any pattern of increased mortality. [The reasons for combining data on stomach and large intestine are not given.]

Roush *et al.* (1980) conducted a case-control study of sinonasal cancer in Connecticut, USA. Cases included 216 men aged 35 years or more who were registered in the Connecticut Tumor Registry and who had died between 1935 and 1975 while resident in the state. Approximately three times as many controls were selected at random from the population of all males dying in Connecticut at age 35 years and over during the period 1935-1975. Persons dying of lung or laryngeal cancer were excluded from the control group. No matching of any kind was employed; however, cases and controls were found to be comparable with respect to year of death, age at death and proportion born abroad. Occupational information for cases and controls was obtained from statements on death certificates, supplemented by entries in city directories published annually for towns and other small areas in Connecticut. The city directories consulted were those published one, 10, 20, 25, 30, 40 and 50 years prior to death or when the subject was less than 20 years of age. Job titles and industries indicative of airborne exposure to cutting oils were defined as those associated with an increase in skin cancer risk, based on a review of the literature, which consisted mainly of Canadian and UK studies. They included: toolmaker, toolsetter, set-up man, tool hardener, hardener, turner, polisher and fitter (steamfitter). Relative risk estimates adjusted for age, year and date of birth were computed using occupational information from death certificates only, from city directories only, and from both sources combined. For these three definitions of potential exposure to cutting oils, relative risks for sinonasal cancer were 2.3, 2.3 and 2.8, respectively (for the latter, the 95% confidence interval was 1.4-5.7 and $p = 0.002$). The predominant occupations among cases were toolsetter, set-up man and toolmaker. The authors specifically excluded from their list of 'exposed' occupations the titles 'machinist' and 'machine operator', since the literature seemed to link only certain kinds of metalworking machines (bar automatic,

capstan lathe, broaching) with skin and lung cancer. [Inclusion of the above two general job titles appeared to lower relative risk estimates, based on the numbers of cases and controls cited in the paper that were so employed.]

Roush *et al.* (1982) carried out a case-control study of scrotal carcinoma in Connecticut. Cases were identified from the Connecticut Tumor Registry and included 45 men diagnosed in the state between 1935 and 1973. Three controls were selected from state death registers for each of the 34 deceased cases and matched for age at death (within eight years), year of death (within three years) and number of jobs identified from two sources (one to three *versus* four to eight). Men who died of lung or laryngeal cancer were excluded from the control group. Three living controls for each of the 11 cases still alive were selected from the files of the State Department of Motor Vehicles and matched for age (within one year), year of birth (within one year), number of jobs and town of residence. In addition, a separate unmatched group of 460 controls for the 34 deceased cases was selected from the population of all males who died in Connecticut in the years 1935-1975 at the age of 35 years and over. Occupational information was obtained from death certificates and city directories in the manner described by Roush *et al.* (1980). For living subjects, the only source of job data was the city directories. Each subject was required to have had at least one job in one industry. Occupations used as indicators of exposure to cutting oils included those previously used by Roush *et al.* (1980), as well as 'machinist' and 'machine operator'. In the matched analysis, the odds ratio for squamous-cell carcinoma of the scrotum for all jobs involving exposure to cutting oils, except machinist and machine operator, was 4.9 (95% confidence interval, 1.8-15.9; $p = 0.002$). Four of the cases were tool or machine setters and four were automatic screw machine operators. When the job titles 'machinist' and 'machine operator' were included, the odds ratio increased to 10.5 (95% confidence interval, 4.0-36.9; $p < 0.001$). Among deceased cases and controls in the unmatched analysis, elevated risks were seen in both native-born and foreign-born men (odds ratios, 9.5 and 7.2, respectively).

Järvholm *et al.* (1981) investigated the pattern of cancer morbidity among men exposed to oil mist (for at least five years) in a metalworking plant in Sweden. The cohort comprised 792 men, only 22 of whom were lost to follow-up. The expected cancer morbidity was calculated by using age-specific incidence rates for cancer obtained from the Swedish Cancer Registry. The total numbers of cancer observed were below the expectations (43 observed, 52.9 expected). The overall mortality of the group in the period 1958-1976 was also significantly ($p < 0.05$) below expectation (126 deaths, 154.1 expected). Four cases of scrotal cancer were found, all in men who were turners, against an expectation of virtually zero, and among grinders there were seven stomach cancers against 3.7 expected (none in turners), though the excess was not statistically significant. There were 16 tumours of the digestive tract compared with 11.2 expected; four of the prostate (10.1 expected); and the remainder were all single tumours, except for three of the bladder. Three cases of lung cancer were found in men exposed to oil mist for five years or more, compared to 5.4 expected.

Järvholm and Lavenius (1981) undertook a cohort study of cancer in Sweden among 98 workers (78 women, 20 men) exposed to an anti-rust oil, acid refined, who had worked at any time between 1954 and 1957. They were led to make the study because of the finding of three cases of cancer in a packing department, consisting mainly of women. The expected cancer rates were calculated from national sex- and age-specific rates. In the whole of this department, 12 of the 78 women had developed a cancer between 1964 and 1973 (three cases of cancer of the cervix uteri, two of the ovary, one of the bladder; the other six cases consisted of cancers at single unrelated sites) against 3.9 expected ($p < 0.005$), and none of the 20 men. In another packing department, smaller in size and with slightly different exposure, there were four cases of cancer compared to two expected - not a significant excess. The authors

suggested that the most probable causative agent was *N*-phenyl-1-naphthylamine, to which workers were exposed, or its *N*-nitroso derivative. They also discussed its possible contamination by 2-naphthylamine, especially as there were two cases of bladder cancer (one case also included in the first packing department group) in another small group of workers, also exposed to mineral oils, some of whom had become sensitized to *N*-phenyl-1-naphthylamine. However, no chemical analysis of *N*-phenyl-1-naphthylamine for its impurities (such as 2-naphthylamine) or for its potential to form *N*-nitroso compounds was reported.

Case-control studies conducted in different parts of the world (the USA, the UK, Canada, Finland and Italy) suggest that the jobs of machinist, enginnering fitter and engineer are associated with elevated risks for bladder cancer (Vineis, 1983). Reported age-adjusted relative risks for males were 4.0 (4 observed, 1 expected) (Dunham *et al.*, 1968), 4.8 (14 cancer cases, 3 surgical controls, exposed for 20 or more years) (Anthony & Thomas, 1970), 2.7 (95% confidence limits, 1.1-7.6; the risk was not changed after controlling for smoking) (Howe *et al.*, 1980), 5.0 (based on 5 cases and 1 control in discordant pairs) (Tola *et al.*, 1980), 1.5 (95% confidence limits, 1.2-1.8; the predominant category was represented by turners, lathe operators and tool setters) (Cartwright, 1982) and 2.7 (11 cases and 4 controls in discordant pairs had worked as turners before 1945, out of 225 case-control age-matched pairs) (Vineis, 1982). Other available case-control studies cannot be evaluated since occupational categories do not permit the identification of machinists or engineers (Cole *et al.*, 1972; Wynder & Goldsmith, 1977). [The Working Group noted that these data could be relevant to the problem of health effects of additives in mineral oils, particularly aromatic amines. Only one study took smoking habits into account in the analysis of data.]

Results of a case-control study of cancer in relation to occupation in which metalworkers were considered (Decouflé *et al.*, 1977), are reported in the following section.

(ii) *Printing pressmen*

Printing pressmen are exposed to oil mist ('ink mist') consisting of mineral oils that may contain carbon blacks (5-25%), pitch, other pigments and additives (see monograph on carbon blacks, p. 35).

Goldstein *et al.* (1970) studied a large newspaper plant in New York City, USA, in which oil-mist concentrations in the pressroom ranged from 5-21 mg/m^3. Analysis of particle size of the mineral-oil mist showed a mass median diameter of 'about 15 μm' with about 15% of the material in droplets, generally considered to be 'respirable'. The particles of carbon black in the ink used were about 0.1-0.2 μm in size. Mortality rates among actively employed and retired pressroom workers (about 460 individuals) during the years 1947-1962 were examined using life-table techniques and compared to those of compositors (about 700 men) not exposed to oil mist. Among pressmen, there were three deaths from pulmonary carcinoma out of 2797 person-years at risk (crude rate = 1.07 per 1000) and six among compositors with 5127 person-years at risk (crude rate = 1.17 per 1000). No death from neoplasms of the nasopharynx or paranasal sinuses occurred in either group and no other cancer site was mentioned. [No data were given on the age distribution of the subjects. Furthermore, the authors did not state the degree of completeness of death ascertainment and did not describe how causes of death were determined and classified.]

Pasternack and Ehrlich (1972) updated and expanded the study of Goldstein *et al.* (1970) with a cross-sectional analysis of mortality rates during the period 1958-1969 confined to actively employed and pensioned workers. Subjects consisted of 778 newspaper pressmen and a comparison group of 1207 compositors. The average age of pressmen at entry to the

study was 39.7 years compared to 46.5 years for compositors, with 5841 person-years at risk among pressmen and 9189 among compositors. No cause-specific death rates were shown in the report. The authors present numbers of deaths by selected site for cancers among pressmen and compositors but report no obvious trend (six deaths from cancer of the mouth and respiratory system in pressmen, eight in compositors); no mortality pattern was discernible; however, the numbers of deaths involved were small. [Follow-up after exposure may be too short for a definitive assessment of cancer risk.]

Moss *et al.* (1972) and Moss (1973) undertook a proportional mortality survey of newspaper workers in London and Manchester, UK, for the period 1952-1966 (3485 deaths). Significant ($p < 0.01$) excesses of deaths from lung cancer were found for all manual printing trade workers (365 observed, 273 expected lung cancer deaths): a 30% excess in London and a 40% excess in Manchester. In Manchester, there was also an excess of lung cancer of the same order of significance among machine-room men (relative risk = 2.0) (38 observed, 18.7 expected) ($p < 0.01$). In London, 71 deaths from lung cancer were detected among machine-room men as against 57.3 expected (relative risk = 1.2). There was no significant difference between expected and observed figures for non-manual workers. [The study included all manual workers in the newspaper printing industry (compositors, machine-room men, publishing-room men, etc.) and did not specifically mention printing pressmen.]

Greenberg (1972) conducted a proportional mortality study based on 670 death certificates of male newspaper printing workers in London who died in the years 1954-1966. These certificates had been submitted by next of kin in support of an application for a grant. Prediction of numbers of deaths was made using Greater London figures in the Registrar General's Statistical Review of England and Wales for the years 1954-1966. He found a significant excess of deaths from all malignancies (195 observed, 163.1 expected cancer deaths) ($p < 0.02$) and from lung cancer (93 observed, 70 expected) ($p < 0.01$); stomach cancers (29 observed, 20.5 expected) were also in excess (but did not attain statistical significance: $p < 0.10$). [This study addressed partly the same newspaper worker population as the one reported by Moss *et al.*, 1972.]

Menck and Henderson (1976) conducted a cross-sectional study of lung cancer rates by occupation in Los Angeles County, California, USA. The data covered all 2161 deaths among white males aged 20-64 years during the period 1968-1970, for which mention of lung cancer was made on the death certificate, and were pooled with those from the 1777 incident cases of lung cancer occurring in the same demographic subgroup that were reported to the Los Angeles County Cancer Surveillance Program during the years 1972-1973. Occupational titles and industries of employment were extracted from death certificates for the deceased and from hospital records for living cases. No occupation was reported for almost 20% of the deaths, and no industry was stated on 29% of the death certificates. Among living subjects, the extent of incompleteness was 15% for occupation and 34% for industry. The population at risk, by age, occupation and industry, was estimated from 1970 census data for Los Angeles County. Lung cancer rates among men in a variety of occupations and industries were compared with those of all male employees, using the indirect method of age adjustment to produce expected numbers and standardized mortality ratios (SMRs). Among men classified as 'pressmen', the SMR was 276 ($p < 0.01$), based on 10 deaths and 10 incident cases. Among industries classified as printing, newspaper, the SMR was 98, based on 30 deaths and 16 incident cases. [It is possible that men included in the pressmen category could have worked in settings other than newspaper pressrooms.]

Lloyd *et al.* (1977) conducted a proportional mortality study of 2604 white male members of a labour union representing printing pressmen in the USA. The study group consisted of

members for whom a death benefit was paid between 1966 and 1968; subjects were classified as being newspaper or commercial pressmen according to the local union to which they had last been affiliated. Age-adjusted expected numbers of deaths by cause were computed using the mortality experience of US white males in 1967. Among 676 newspaper pressmen deaths, there was an excess from cancer of the buccal cavity and pharynx (9 observed, 3.8 expected; $p < 0.05$), confined mainly to men aged 20-54 years (7 observed, 0.7 expected; $p < 0.01$). Mortality from each of nine other cancer sites analysed among newspaper printing pressmen was not statistically different from expectation. Lung cancer deaths numbered 41 compared to 36.4 expected; there were 11 deaths from stomach cancer, 7.1 expected; 7 from rectal cancer, 4.5 expected; and 2 from nasal cancer, 0.2 expected. Among 1840 deaths among commercial pressmen, there was no statistically significant difference between observed and expected deaths from cancer at any of the ten sites specified, including lung and stomach cancer. Nevertheless, this group too showed a suggested excess of rectal cancers (19 observed cases, 12.2 expected). [There were no data showing how risks varied by duration of employment, and the extent of exposure to oil mists among commercial pressmen was not characterized in any way.]

In a case-control study of cancer in relation to occupation conducted at the Roswell Park Memorial Institute, USA, elevated and statistically significant age-adjusted relative risks (RRs) were reported for men in the following jobs (entailing exposure to mineral oils or cutting oils): machinists (leukaemia, RR = 2.85, $p = 0.02$), mechanics and repairmen (prostate, RR = 2.09, $p = 0.02$), print workers [not specified] (buccal cavity and pharynx, RR = 2.58, $p = 0.04$). Smoking-adjusted RRs were also computed for some cancer sites; for buccal cavity and pharynx a RR of 2.33 ($p = 0.04$) was found among print workers (Decouflé *et al.*, 1977).

Greene *et al.* (1979) conducted a proportional cancer mortality study of 347 male former US Government Printing Office (GPO) employees in Washington DC. The study group consisted of men whose last federal service had been at the GPO, who had died from cancer (all sites) in the years 1948-1977, and who had left a death annuity to a beneficiary who was still living. Subjects were further classified by the job held longest at the GPO. Site-specific expected numbers of cancer deaths were computed using the ratio of each site to all cancer deaths in the male population of the Washington DC area during the period 1950-1969 for comparison; adjustment was made for race, age and year of death. Only three cancer sites were shown for subjects classified specifically as 'printing pressmen': multiple myeloma, leukaemia and colon. No death from multiple myeloma was observed; there was a 79% increase in the relative frequency of leukaemia based on four observed deaths and a 58% increase in the frequency of colon cancer based on ten observed deaths; neither of these increases was statistically significant. In the whole study population (pressmen included) there were 11 cancers of the mouth and throat, whereas 13.9 were expected. The authors pointed out that ascertainment of cancer deaths among GPO employees was incomplete for a number of reasons, but felt this should not have biased the site distribution of cancer deaths studied. [The authors did not characterize the extent of exposure to oil mists in this particular printing facility.]

Paganini-Hill *et al.* (1980) conducted a cohort mortality study of 1361 newspaper pressmen who had been members of the Los Angeles Pressmen's Union for at least one year between 1949 and 1965; 65% of the cohort had worked in the trade for 20 years or more and most subjects began their employment as pressmen before the age of 35. Follow-up was conducted until 31 December 1978, at which time 91% of the cohort had been traced successfully. Of 354 deceased subjects identified, death certificates were located for 344. Cause-specific mortality rates among pressmen were compared to those in the general US white male population, with adjustment for age and calendar year. Expected numbers of deaths and standardized mortality ratios were computed. Results were presented for 12 specific cancer

sites; statistically significant differences between observed and expected deaths were seen for kidney cancer (5 observed, 1.6 expected; $p < 0.05$) and leukaemia (7 observed, 2.8 expected; $p < 0.05$). There were 22 deaths from lung cancer compared to 14.8 expected, while for stomach cancer there were three observed deaths compared to 4.3 expected; neither difference was statistically significant. Two cancers of the buccal cavity and pharynx were detected, whereas 2.2 were expected. Eight cancers of colon-rectum were seen, whereas 8.9 were expected. No mention of nasal cancer was made in the report. [The authors did not present any result relating to duration of employment].

(iii) *Jute workers*

Kinnear *et al.* (1955) reported that in a field survey of 3023 workers in seven jute establishments in Dundee, Scotland (in which jute fibres were treated with an emulsion of oil and water to soften and lubricate them before they were spun), premalignant skin changes (keratoses) were seen in 219 (7.2%). Prevalence was highest in spinners (15.9%), but lesions were noted among workers in all departments except office and canteen workers and electricians.

(iv) *Other workers*

Hendricks *et al.* (1959) reported that out of 82 workers employed for ten or more years as pressmen in a wax manufacturing department of an oil refinery in the USA and observed from 1937-1956, 19 developed cancer, 11 of which were of the scrotum. The authors report that this corresponds to a rate of 806 per 100 000 for men aged 45-64, in contrast to a rate of 0.15 for US white males of the same age group, calculated from data obtained from the American Cancer Society.

(v) *Studies of second primary cancers among scrotal cancer patients*

An excess risk of second primary cancers among British cases of scrotal cancer has been reported. Following a report by Holmes *et al.* (1970), Waterhouse (1972) and Waldron (1975) successively reported extension of the same initial series of cases, with the following results: 187, 228 and 288 scrotal cancer cases were found with 22/8.3, 32/11.6 and 42/17.1 observed second primary/expected second primary in the three studies, respectively. Excess numbers of second primaries were found in the skin, the respiratory system and the upper alimentary tract. When the last group (Waldron, 1975) was subdivided by occupational exposure, the excess of second primary cancers was confined to the 162 cases with known exposure to oil, except that there was also an excess of second primary skin cancers among workers exposed to pitch and tar. [Three hypotheses to explain these findings have been published: multiple sites of carcinogenicity following skin contact with mineral oil; oil-mist carcinogenicity; and different individual susceptiblity. It is impossible to choose among these or other explanations on the basis of the available studies.]

(vi) *Childhood malignancies*

The Working Group considered a number of studies investigating the possible association between parental occupation and malignancies in children (Fabia & Thuy, 1974; Hakulinen *et al.*, 1976; Kantor *et al.*, 1979; Kwa & Fine, 1980; Zack *et al.*, 1980; Hemminki *et al.*, 1981; Peters *et al.*, 1981; Sanders *et al.*, 1981; Gold *et al.*, 1982). None of these studies has explicitly addressed the issue of exposure to mineral oil. Instead, occupations related to exposure to

hydrocarbons have been examined, the occupational categories usually being defined on a rather broad basis (for instance: 'machinist', 'motor-vehicle mechanic', 'railroad worker'). The results of such investigations are inconsistent.

(c) *Mortality statistics by occupation*

Lung cancer excesses have been consistently reported in some jobs entailing exposure to mineral oils or cutting oils. In a report from Washington, USA, on occupational mortality in 1950-1971, such jobs were: mechanics and repairmen, tool and die makers and setters, oilers and greasers, and pressmen and plate printers (Milham, 1976). Also, in the 1970-1972 occupational mortality report of the UK Office of Population Censuses and Surveys, standardized (SMR) and proportional mortality ratios for lung cancer were elevated (attaining statistical significance) for the following jobs: machine-tool setters and setter-operators, motor mechanics and auto engineers, fitters and machine erectors. An excess of skin cancer deaths was reported for mechanical engineers. Six and two scrotal cancer deaths were reported for machine-tool operators (SMR, 2655) and machine tool setters (SMR, 1013), respectively (Office of Population Censuses and Surveys, 1978).

[Such sources of data are usually used only for hypothesis generation, because (1) there are limitations to information on occupational titles reported only on death certificates; (2) multiple comparisons are made leading to excesses that are statistically significant by chance alone; and (3) confounding factors cannot be taken into account, particularly smoking in relation to lung cancer. However, it is worth noting that the listed jobs were chosen *a priori* by the Working Group as entailing exposure to mineral oils or cutting oils; and that the excesses observed for lung and skin cancer deaths are biologically plausible. Despite the inherent limitations of the sources, these data cannot be disregarded entirely.]

4. Summary of Data Reported and Evaluation

4.1 Experimental data

Experiments involving repeated applications of petroleum-derived base oils and formulated products to the skin of mice have been used to evaluate potential skin carcinogenicity. Certain compounds have also been tested in a feeding study, and by subcutaneous and intraperitoneal injection.

Vacuum distillate fractions [class 1][1], either naphthenic or paraffinic in nature, produced a significant skin tumour response. Dewaxing of these distillates did not appreciably alter their activity.

[1] See scheme by which mineral oils were classified, p. 90.

Acid-treated oils [class 2] of either naphthenic or paraffinic origin produced a significant skin tumour response, unless severe acid treatment had been applied.

Solvent-refined oils (raffinates) [class 3], either naphthenic or paraffinic in nature, generally did not produce skin tumours, unless the solvent treatment had been only mild; in that case, samples retained some of the skin tumour-inducing activity of the original distillate.

Hydrotreated oils [class 4], principally paraffinic in nature, induced a moderate incidence of skin tumours when treatment of the distillates was mild, while no tumour was induced by severely hydrotreated oils. The combination of mild hydrotreating and solvent extraction appears to reduce or eliminate skin tumorigenicity.

White oils and petrolatums [class 5], which are produced from oils that have undergone the most severe acid and/or hydrogen treatment, showed no activity in the skin tumour assay. Subcutaneous injection of three different grades of medicinal petrolatum [class 5] into mice induced no tumour. Intraperitoneal injection of two food-grade mineral oils [class 5] into certain strains of mice induced plasma-cell neoplasms and reticulum-cell sarcomas. A study in rats involving subcutaneous or intraperitoneal injection of liquid paraffin and yellow petroleum [class 5] could not be evaluated. In two feeding studies in which three different samples of medicinal-grade petrolatum and liquid paraffin [class 5] were fed to rats for two years, no significant increase occurred in tumour incidence.

Solvent extracts (sometimes called aromatic oils), which are by-products of solvent refining [class 6.1], induced a significant incidence of skin tumours. The same response was produced with highly concentrated aromatic extracts of medicinal-grade petrolatums. High-boiling fractions from catalytically cracked oils (also classified as aromatic oils) [class 6.2] produced increasing numbers of skin tumours in mice with increasing boiling-ranges above 370°C; further fractionation established that the activity is maximal in those boiling at 500-520°C and is concentrated in the aromatic portion of the oils. Promoting activity was also detected in some portions. High-boiling, catalytically cracked oils also produced skin tumours in rabbits and monkeys.

Three formulated products [class 7.1], consisting of blends of base oils and chemical additives, were tested. One of the products, an unused gasoline-engine oil, gave some indication of skin tumorigenic activity (one squamous-cell carcinoma in 36 treated animals); three further samples of unused gasoline-engine oil gave negative results. One sample of unused diesel-engine oil also failed to induce a significant increase in tumour incidence. Used gasoline-engine oils [class 7.2] have tended to have a greater skin tumour activity than unused products. Four samples of cutting oil [class 7.1] tested in the mouse-skin tumour assay had significant activity (the degree of refining of the base oil is not known). Two samples of used cutting oil [class 7.2] were also tested; one was more active than a comparable unused oil, and the other was inactive.

Mineral oils have been found to be embryotoxic and teratogenic to birds; no study on teratogenicity of mineral oils in mammals was available to the Working Group.

Samples of a white oil [class 5], of a refined steel-hardening oil [class 7.1] and of unused crankcase oils [class 7.1] were not mutagenic to *Salmonella typhimurium* strain TA98 in the presence or absence of an exogenous metabolic system. Samples of vacuum distillates [class 1] of solvent-refined oils [class 3], of hydrotreated oils [class 4], of a used hardening oil [class 7.2] and of used crankcase oils [class 7.2] were mutagenic to *S. typhimurium* in the presence and absence (class 7.2 only) of an exogenous metabolic system.

Overall assessment of data from short-term tests on mineral oils[a]

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes		+[b] ?[c]		
Fungi/green plants				
Insects				
Mammalian cells (*in vitro*)				
Mammals (*in vivo*)				
Humans (*in vivo*)				
Degree of evidence in short-term tests for genetic activity : *Inadequate.*				Cell transformation : No data

[a] The groups into which the table is divided and '+', '−' and '?' are defined on pp. 16-17 of the preamble; the degrees of evidence are defined on p. 17.

[b] Vacuum distillates [class 1], solvent-refined oil (distillate) [class 3], hydrotreated oil [class 4], used hardening oil [class 7.2], used crankcase oil [class 7.2]

[c] White oil [class 5], unused refined steel-hardening oil [class 7.1], unused crankcase oil [class 7.1]

4.2 Human data

Mineral oils (lubricant base oils and derived products) are produced in large quantities and are contained in a wide variety of products which are used primarily for lubricating purposes. The composition of these oils varies depending on the crude oil source, the refining process and the additives present. The degree of human exposure to these products also varies widely: in the case of cutting oils, appreciable skin contact and inhalation can occur, unless adequate care is taken, whereas limited exposure occurs to oils (such as hydraulic, circulating, turbine and engine oils) used in closed systems, with which only incidental contact is likely. There are thus various opportunities for occupational, consumer and environmental exposure to these products from their production, use and disposal.

Inhalation, aspiration or ingestion leading to aspiration of white oils and petrolatums suitable for food and medicinal use [class 5] can lead to lipid pneumonia and lipid granuloma.

Exposure to the mineral oils that have been used in a variety of occupations, including mulespinning, metal machining and jute processing, has been associated strongly and consistently with the occurrence of squamous-cell cancers of the skin, and especially of the scrotum.

The epidemiological studies of metal workers that were available to the Working Group comprised one proportional mortality study, three case-control studies and three cohort studies. No excess of respiratory cancer was reported from any of the studies. Excess gastrointestinal malignancies were seen in each of the three cohort studies (stomach in one study, the sum of stomach plus large intestine in one study, and digestive tract in one study). Four cases of scrotal cancer were detected in one relatively small cohort study of metal industry workers. In a case-control study, a relative risk of 4.9 was reported for the association of scrotal cancer with potential exposure of metal workers to mineral oils. Neither the actual levels of exposure nor the classification of the nature of the mineral oil to which the machine

workers were potentially exposed were available in the reports of the epidemiological studies. In another case-control study, an excess of sinonasal cancers was seen in toolsetters, set-up men and toolmakers.

An examination of the incidence of second primary cancer among men with scrotal cancer demonstrated excesses of respiratory, upper alimentary tract and skin cancers; when the occupations were grouped, the excess was largely confined to those with oil exposure.

Excesses of bladder cancer have been reported in case-control studies in several countries among machinists and engineers, who were possibly exposed to cutting oils containing aromatic amines as additives.

With regard to printing pressmen, the Working Group considered the results of three cohort mortality studies (one of these was an extension of another) and two proportional mortality studies. There were three additional proportional mortality studies on manual workers in the newspaper printing industry; one of these included two separately exposed groups at different geographical locations. One of the two cohort studies addressing lung cancer showed an excess (not tested for statistical significance). One of the two proportional mortality studies showed a small, statistically non-significant excess of lung cancer among the newspaper pressmen but no excess among non-newspaper pressmen; the other study did not address lung cancer. One of the three proportional mortality studies on manual workers in the printing industry, not specifically addressing printing pressmen, did not show an increased lung cancer risk, whereas the other two studies (not on independent populations) found a statistically significant excess. One of the two proportional mortality studies of printing pressmen indicated a statistically significant excess of rectal cancers, and the other showed a statistically non-significant increase of colon cancers; the cohort study considering colorectal cancers did not show an increased occurrence. One proportional mortality study among newspaper and other commercial printing pressmen showed a statistically significant excess of cancers of the buccal cavity and pharynx, whereas no such excess was observed in a cohort study. One proportional mortality study among employees in the printing industry (pressmen were not singled out) showed a slight deficit of cancers of the mouth and throat. One case-control study indicated a statistically significant excess of cancers of the buccal cavity and pharynx. The findings regarding other malignancies were inconsistent; scrotal cancers were not mentioned. The type and amount of exposure were usually not described; exposure to both mineral oils and carbon blacks would probably have been involved.

In mortality statistics from the United Kingdom and from Washington State, USA, lung and skin cancer excesses have been registered for jobs entailing exposure to mineral oils; despite limitations of this kind of source as to a causal interpretation, the consistency of such suggestions is worth noting.

4.3 Evaluation[1]

There is *sufficient evidence*[2] for the carcinogenicity in experimental animals of untreated vacuum distillates, acid-treated oils, and aromatic oils, including extracts from solvent treatment of distillates and the high-boiling fraction of catalytically cracked oils [classes 1, 2 and 6].

There is *sufficient evidence*[2] that mildly solvent-refined oils [class 3] are carcinogenic to

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[1] See the preamble, pp. 15 and 19 for definitions of italicized terms.

[2] In the absence of adequate data in humans on individual classes of mineral oils, it is reasonable, for practical purposes, to regard fractions for which there is *sufficient evidence* of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans.

experimental animals. There is *no evidence* that severely solvent-refined oils [class 3] are carcinogenic to experimental animals.

There is *sufficient evidence*[2] that mildly hydrotreated oils [class 4] are carcinogenic to experimental animals; the available data on severely hydrotreated oils [class 4] are *inadequate* to permit an evaluation of their carcinogenicity to experimental animals.

There is *no evidence* for the carcinogenicity to experimental animals of white oils [class 5] when administered by routes other than intraperitoneal injection; when white oils were given by intraperitoneal injection to mice, plasma-cell tumours were produced in repeated experiments. The significance of the latter findings is difficult to interpret.

The data are *inadequate* to evaluate the carcinogenicity to experimental animals of formulated products [class 7.1] as a class, since the possible carcinogenic activity of individual products is dependent upon the severity of processing of the base oils and the nature and concentration of additives.

The data are *inadequate* to evaluate the carcinogenicity to experimental animals of used formulated products [class 7.2] as a class, since the possible carcinogenic activity of individual products is dependent upon the quality of the base oils used, the nature and concentration of additives and contaminants, and the conditions of use.

There is *sufficient evidence*[2] for the carcinogenicity of one sample of used gasoline-engine oil [class 7.2] and *limited evidence* for the carcinogenicity of some cutting oils [classes 7.1 and 7.2] to experimental animals.

There is *sufficient evidence* from studies in humans that mineral oils (containing various additives and impurities) that have been used in occupations such as mulespinning, metal machining and jute processing are carcinogenic to humans.

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NITROARENES

1,8-DINITROPYRENE

1. Chemical and Physical Data

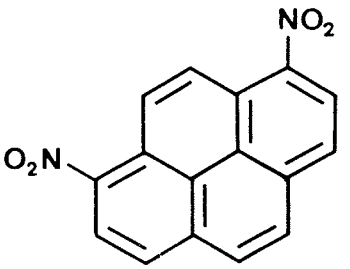
1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 42397-65-9

Chem. Abstr. Name: Pyrene, 1,8-dinitro-

IUPAC Systematic Name: 1,8-Dinitropyrene

1.2 Structural and molecular formulae and molecular weight



$C_{16}H_8N_2O_4$ Mol. wt: 292.3

1.3 Chemical and physical properties of the pure substance

Spectroscopy data: Nuclear magnetic resonance spectra have been reported (Kaplan, 1981).

1.4 Technical products and impurities

No information was available to the Working Group.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

1,8-Dinitropyrene was first synthesized by Vollmann in 1937 by heating pyrene in nitric acid/glacial acetic acid at 90-100°C; a mixture of 1,6-dinitropyrene and 1,8-dinitropyrene was obtained (Boit, 1965).

No evidence was found that 1,8-dinitropyrene has been produced in commercial quantities.

(*b*) *Use*

1,8-Dinitropyrene has been reported to be a photosensitizer, increasing the spectral sensitivity of bis-azide compounds in the long wavelength region (Tsunoda *et al.*, 1973). However, no evidence was found that 1,8-dinitropyrene has been used commercially for this or other applications.

2.2 Occurrence

(*a*) *Air*

A summary of the quantitative data on 1,8-dinitropyrene levels in particulates of exhaust emissions and in the extracts from these particulates is given in Table 1.

Table 1. 1,8-Dinitropyrene levels in diesel exhaust particulates

Sample	1,8-Dinitropyrene concentration		Reference
	(mg/kg extract)	(mg/kg particulate)	
Passenger car	0.5-0.7	--	Salmeen *et al.* (1983)
	0.4	--	Nishioka *et al.* (1982)
Bus	5.7	[2.4][a]	Nakagawa *et al.* (1983)

[a] Calculated by the Working Group for comparison purposes from data in the reference

(*b*) *Carbon blacks*

Toners for use in photocopy machines have been produced in quantity since the late 1950s and are currently in widespread use. The mutagenicity of one photocopy toner was shown to be due to trace amounts of nitropyrenes which accompanied the carbon black used in the toner. This particular 'long-flow' furnace black was first used in photocopy toners in 1967. Its manufacture involved an oxidation whereby some nitration also occurred; however, changes

in the production technique reduced the total extractable nitropyrene content from an uncontrolled level of 5-100 mg/kg to below 0.3 mg/kg (Rosenkranz *et al.*, 1980; Sanders, 1981; Butler *et al.*, 1983). Toners produced from the carbon black in question after 1980 have not been found to contain detectable levels of mutagenicity and, hence, nitropyrenes (Rosenkranz *et al.*, 1980; Butler *et al.*, 1983).

1,8-Dinitropyrene was found in an extract of carbon black (a pre-1979 sample of furnace black that had been after-treated by an oxidation-nitration process) at a level of 23.4 mg/kg (Sanders, 1981). One lot of this grade made in 1980 was found to contain 0.16 mg/kg (Giammarise *et al.*, 1982).

In a more recent study, an undetermined level of 1,8-dinitropyrene was detected in an extract of a formerly commercial furnace black (produced before 1980) (Ramdahl & Urdal, 1982).

2.3 Analysis

Typical methods for the analysis of 1,8-dinitropyrene are summarized in Table 2.

Table 2. Methods for the analysis of 1,8-dinitropyrene

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Carbon black	Soxhlet extract (toluene)	Capillary GC/MS (NCI)	1 pg	Ramdahl & Urdal (1982)
	Soxhlet extract (toluene or acetone)	HPLC/UV	ND	Rosenkranz *et al.* (1980)
	Soxhlet extract (chlorobenzene)	HPLC/UV	1 ng	Giammarise *et al.* (1981)

[a] Abbreviations: GC/MS (NCI), gas chromatography/mass spectroscopy (negative chemical ionization); HPLC/UV, high-performance liquid chromatography/ultraviolet detection

ND, not determined

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

Nitroarenes are generally synthesized or formed in the environment as mixtures of isomers by nitration of the parent hydrocarbons. They may thus be contaminated by isomers, different nitrocompounds or higher nitrated derivatives. Since such by-products often have much higher biological activities, certain experimental results may reflect the presence of trace impurities for which no analysis was performed.

3.1 Carcinogenicity studies in animals

No data were available to the Working Group.

3.2 Other relevant biological data

(*a*) *Experimental systems*

No data were available to the Working Group on toxic effects, on effects on reproduction and prenatal toxicity, or on absorption, distribution, excretion and metabolism.

Mutagenicity and other short-term tests

Reviews of the genetic effects of nitroarenes, including 1,8-dinitropyrene, are available (Rosenkranz & Mermelstein, 1983; Rosenkranz *et al.*, 1983).

1,8-Dinitropyrene did not bind covalently to DNA or intercalate with calf thymus or plasmid DNA following incubation [details not given] (Rosenkranz *et al.*, 1980; Mermelstein *et al.*, 1981; Rosenkranz & Mermelstein, 1983).

1,8-Dinitropyrene was mutagenic to *Salmonella typhimurium* strains TA1537, TA1538, TA98 and TA100 in the absence of an exogenous metabolic system (Rosenkranz *et al.*, 1980; Löfroth, 1981; Mermelstein *et al.*, 1981; Tokiwa *et al.*, 1981; McCoy & Rosenkranz, 1982). Mutagenic activity in strains TA98 and TA100 was significantly reduced in the presence of an Aroclor-induced rat-liver supernatant (e.g., Tokiwa *et al.*, 1981). 1,8-Dinitropyrene was not mutagenic to *S. typhimurium* strain TA1535 (Rosenkranz *et al*; 1980; Mermelstein *et al.*, 1981), or to *Escherichia coli* WP2 *uvr* A (Mermelstein *et al.*, 1981). This compound induced forward mutations to 5-methyltryptophan resistance in *S. typhimurium* (Mermelstein *et al.*, 1982).

1,8-Dinitropyrene induced dose-related mitotic gene conversion at the *trp* 5 and *his* 4 loci in stationary phase cultures of the yeast *Saccharomyces cerevisiae* JD1 (Wilcox & Parry, 1981). However, McCoy *et al.* (1983) observed no such effect in *S. cerevisiae* strain D4 when testing at concentrations of up to 1 mg/plate. [The Working Group considered that these differences may be attributable to the physiological state (anaerobiosis) of the cultures.]

A dose-related increase in mutations to diphtheria-toxin resistance was demonstrated in Chinese hamster lung fibroblasts treated with 1,8-dinitropyrene at concentrations of 0.03-8 μg/ml (Nakayasu *et al.*, 1982). Resistance to four selective media (methotrexate, 1-β-D-arabinofuranosyl cytosine, 6-thioguanine and ouabain) was induced in mouse lymphoma L5178Y cells by 1,8-dinitropyrene at concentrations of 0.025-2.5 μg/ml. A dose-related resistance was observed in all cases only after 48 hours' exposure. No toxicity was observed at the highest concentration (Cole *et al.* 1982). [The Working Group noted the unusually long exposure time required to demonstrate activity.]

1,8-Dinitropyrene (0.2-2.0 μg/ml) induced a dose-related increase in mutations at the HGPRT gene locus in Chinese hamster ovary cells. Addition of Aroclor induced rat-liver supernatant resulted in a decrease in mutagenic activity (Li & Dutcher, 1983). 1,8-Dinitropyrene (0.01-0.1 μg/ml) induced a dose-related mutagenic response to ouabain resistance in Chinese hamster V79 cells. Addition of irradiated Syrian hamster embryo feeder cells slightly increased this response (Takayama *et al.*, 1983). In an abstract, Sanders *et al.* (1983) reported that 1,8-dinitropyrene induced mutations to both ouabain and 6-thioguanine resistance in human diploid lymphoblasts.

Exposure of normal or xeroderma pigmentosum human skin cells 1,8-dinitropyrene at a concentration of 2.5 mg/ml for up to 96 hours resulted in no detectable induction of mutations

to 6-thioguanine resistance. No preferential toxicity was observed in this cell line when compared to normal human fibroblasts (Arlett *et al.*, 1983).

In a rat-liver epithelial cell line (RL4), 1,8-dinitropyrene induced chromosomal aberrations, primarily of the chromatid type (Danford *et al.*, 1982). The numbers of aberrant metaphases were dose related up to a concentration of 1.25 μg/ml when cells were exposed for either 24 or 48 hours. Only marginal clastogenic activity was observed, however, when a fibroblast cell line of human origin (HSBP) was exposed to 1,8-dinitropyrene at concentrations of up to 5.0 μg/ml (Wilcox *et al.*, 1983).

Following exposure of Chinese hamster ovary cells to 1,8-dinitropyrene for 24 hours, there was a dose-dependent induction of sister chromatid exchanges at concentrations of 1-6 nmol/ml. The response was increased in the presence of an Aroclor-induced rat-liver supernatant (Nachtman & Wolff, 1982).

In an abstract, Tu *et al.* (1983) reported no transformation activity when 1,8-dinitropyrene was tested at concentrations of up to 250 μg/ml in BALB/c 3T3 cells. When tested in a clonal morphological transformation assay using Syrian hamster embryo cells, 1,8-dinitropyrene induced a dose-dependent transformation over the concentration range of 1.7-17 nmol/ml (DiPaolo *et al.*, 1983).

(*b*) *Humans*

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

No study of the carcinogenicity of 1,8-dinitropyrene to experimental animals was available to the Working Group.

1,8-Dinitropyrene was mutagenic to *Salmonella typhimurium* in the absence of an exogenous metabolic system under reduced oxygen tension. In one study, it induced mitotic gene conversion in *Saccharomyces cerevisiae* under reduced oxygen tension. It induced sister chromatid exchange and was mutagenic and clastogenic to mammalian cells in culture in the absence of an exogenous metabolic system. The compound induced morphological transformation in Syrian hamster embryo cells.

Overall assessment of data from short-term tests on 1,8-dinitropyrene[a]

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes		+		
Fungi/green plants		+		
Insects				
Mammalian cells (*in vitro*)		+	+	+
Mammals (*in vivo*)				
Humans (*in vivo*)				
Degree of evidence in short-term tests for genetic activity : *Sufficient*				Cell transformation : Positive

[a] The groups into which the table is divided and '+', '−' and '?' are defined on pp. 16-17 of the preamble; the degrees of evidence are defined on p. 17.

4.2 Human data

Environmental exposure to 1,8-dinitropyrene occurs, since it is a constituent of particulate matter in diesel engine exhaust. It has also been found as a trace contaminant of some furnace blacks. It is not produced commercially.

No case report or epidemiological study was available to the Working Group.

4.3 Evaluation

No data were available to evaluate the carcinogenicity of 1,8-dinitropyrene to humans or to experimental animals.

No evaluation of the carcinogenicity of 1,8-dinitropyrene to humans could be made.

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9-NITROANTHRACENE

1. Chemical and Physical Data

1.1 Synonyms and trade names

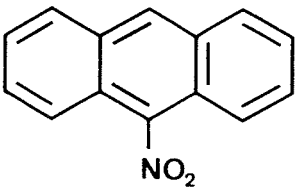
Chem. Abstr. Services Reg. No.: 602-60-8

Chem. Abstr. Name: Anthracene, 9-nitro-

IUPAC Systematic Name: 9-Nitroanthracene

Synonym: 5-Nitroanthracene

1.2 Structural and molecular formulae and molecular weight



$C_{14}H_9NO_2$ Mol. wt: 223.2

1.3 Chemical and physical properties of the pure substance

From Buckingham and Donaghy (1982), unless otherwise specified •

(*a*) *Description*: Yellow needles (recrystallized from ethanol) (Prager & Jacobson, 1922) or bright orange-yellow prisms

(*b*) *Melting-point*: 145-146°C

(*c*) *Spectroscopy data*: Ultraviolet (in ethanol) (Trotter, 1959), visible (Luckenbach, 1980), infrared (Pouchert, 1981), nuclear magnetic resonance (Pouchert & Campbell, 1974) and mass spectral data (NIH/EPA Chemical Information System, 1980) have been reported.

(*d*) *Solubility*: Slightly soluble in glacial acetic acid and acetic anhydride (Prager & Jacobson, 1922); insoluble in aqueous alkali; sparingly soluble in ethanol; and very soluble in benzene and carbon disulphide

(*e*) *Stability*: Stable in ethanolic solution in the dark, but decomposes to anthraquinone, acetaldehyde and nitric acid when exposed to sunlight (Richter, 1943)

(*f*) *Reactivity*: Forms 9-aminoanthracene by reduction of the nitro group (Rappoport, 1967). Forms anthraquinone by oxidation with chromic acid in acetic acid, and can be chlorinated and brominated at the 9,10-positions. Forms anthranol (9-hydroxyanthracene) by reaction with tin in boiling acetic acid (Prager & Jacobson, 1922)

1.4 Technical products and impurities

9-Nitroanthracene is available for research purposes in the USA as a 97% pure grade (Aldrich Chemical Company, 1982).

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

9-Nitroanthracene was first synthesized by Liebermann and Lindemann in 1880 by treating 9,10-dinitroanthracene dihydride with sodium hydroxide (Prager & Jacobson, 1922). It can also be synthesized by treating anthracene with nitric acid in glacial acetic acid, followed by treatment with hydrochloric acid in glacial acetic acid to form 9-nitro-10-chloro-9,10-dihydroanthracene, which is converted to 9-nitroanthracene by treatment with 10% aqueous sodium hydroxide (Rabjohn, 1963; Boit, 1965).

9-Nitroanthracene is offered for sale in research quantities by two US companies (Aldrich Chemical Company, 1982; Pfaltz & Bauer, Inc., undated). However, no evidence was found that it has been produced in commercial quantities.

(*b*) *Use*

9-Nitroanthracene has been reported to be a photosensitizer, increasing the spectral sensitivity of bis-azide compounds in the long wavelength region (Tsunoda *et al.*, 1973). However, no evidence was found that 9-nitroanthracene has been used commercially for this or other applications.

2.2 Occurrence

(a) *Air*

9-Nitroanthracene has been detected in extracts of diesel-exhaust particulates at a level of 58 mg/kg (Pitts *et al.*, 1982). In another study, 9-nitroanthracene was 'tentatively identified' in extracts of diesel-exhaust particulates (Xu *et al.*, 1982).

9-Nitroanthracene has been found in airborne particulates. In one study, particulate samples were collected in February-April 1982 in a rural area 30 km west of Copenhagen, Denmark; 9-nitroanthracene was detected at a level of 30 $\pm$ 10 pg/m^3 (Nielsen *et al.*, 1983). It was also identified in urban-air particulates from St Louis, MO (Ramdahl *et al.*, 1982a).

(b) *Carbon blacks*

9-Nitroanthracene was detected at an undetermined level in an extract of a sample of a commercial furnace black that has not been produced since 1980 (Ramdahl & Urdal, 1982).

2.3 Analysis

Some methods used for the analysis of 9-nitroanthracene are summarized in Table 1.

Table 1. Methods for the analysis of 9-nitroanthracene

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Airborne particulates	Collect on glass-fibre filter; extract (dichloromethane); pre-chromatograph (silica gel column)	TLC (silica gel and cellulose); fluorescence quenching detection	50 ng	Jäger (1978)
	Extract (cyclohexane); liquid/liquid extraction (dimethyl sulphoxide, pentane)	GC-FID	ND	Natusch & Tomkins (1978)
	Collect in fibre bag houses; Soxhlet extract (toluene); filter	Capillary GC-FID/NPD	ND	Ramdahl *et al.* (1982b)
	Collect in fibre bag houses; Soxhlet extract (toluene); HPLC[a]	Capillary GC/MS (EI and NCI)	ND	Ramdahl *et al.* (1982a)
	Filter; Soxhlet extract (dichloromethane); HPLC[a]	Capillary GC (FID and NPD)	ND	Nielsen *et al.* (1983)
Carbon black	Soxhlet extract (toluene)	GC/MS (NCI)	1 pg	Ramdahl & Urdal (1982)
Diesel exhausts	Collect on glass-fibre filter; Soxhlet extract (dichloromethane)	Liquid chromatography; HRMS	ND	Xu *et al.* (1982)

[a] TLC, thin-layer chromatography; GC, gas chromatography; FID, flame ionization detection; NPD, nitrogen phosphorus detection; HPLC, high-performance liquid chromatography; MS, mass spectroscopy; EI, electron impact; NCI, negative chemical ionization; HRMS, high-resolution mass spectroscopy

ND, not available

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

Nitroarenes are generally synthesized or formed in the environment as mixtures of isomers by nitration of the parent hydrocarbons. They may thus be contaminated by isomers, other nitrocompounds or higher nitrated derivatives. Since such by-products often have much higher biological activities, certain experimental results may reflect the presence of trace impurities for which no analysis was performed.

3.1 Carcinogenicity studies in animals

No data were available to the Working Group.

3.2 Other relevant biological data

(*a*) *Experimental systems*

No data were available to the Working Group on toxic effects, on effects on reproduction and prenatal toxicity, or on absorption, distribution, excretion and metabolism.

Mutagenicity and other short-term tests

Reviews of the genetic effects of nitroarenes, including 9-nitroanthracene, are available (Rosenkranz & Mermelstein, 1983; Rosenkranz *et al.*, 1983).

9-Nitroanthracene was mutagenic to *Salmonella typhimurium* strains TA98 and TA100 both in the presence and absence of an Aroclor-induced rat-liver supernatant (Wang *et al.*, 1978; Ho *et al.*, 1981; Pedersen & Siak, 1981; Tokiwa *et al.*, 1981; Pitts *et al.*, 1982; Greibrokk *et al.*, 1983). An increase in mutagenic activity was observed when incubation was carried out under anaerobic conditions (Pedersen & Siak, 1981; Greibrokk *et al.*, 1983).

(*b*) *Humans*

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

No study of the carcinogenicity of 9-nitroanthracene to experimental animals was available to the Working Group.

9-Nitroanthracene was mutagenic to *Salmonella typhimurium* in the presence and absence of an exogenous metabolic system.

Overall assessment of data from short-term tests on 9-nitroanthracene[a]

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes	+			
Fungi/green plants				
Insects				
Mammalian cells (*in vitro*)				
Mammals (*in vivo*)				
Humans (*in vivo*)				
Degree of evidence in short-term tests for genetic activity : *Inadequate*				Cell transformation : No data

[a] The groups into which the table is divided and '+', '−' and '?' are defined on pp. 16-17 of the preamble; the degrees of evidence are defined on p. 17.

4.2 Human data

Environmental exposure to 9-nitroanthracene occurs, as it is a constituent of particulate matter in diesel exhaust and in urban air and has been found in one type of carbon black that is no longer produced commercially. 9-Nitroanthracene is produced only for research purposes.

No case report or epidemiological study was available to the Working Group.

4.3 Evaluation

No data were available to evaluate the carcinogenicity of 9-nitroanthracene to humans or to experimental animals.

No evaluation of the carcinogenicity of 9-nitroanthracene to humans could be made.

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6-NITROBENZO[*a*]PYRENE

1. Chemical and Physical Data

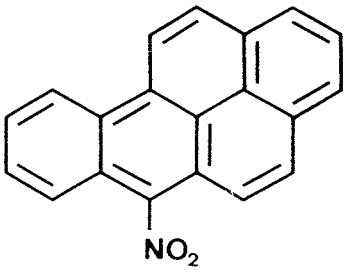
1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 63041-90-7

Chem. Abstr. Name: Benzo(a)pyrene, 6-nitro-

IUPAC Systematic Name: 6-Nitrobenzo[a]pyrene

1.2 Structural and molecular formulae and molecular weight



$C_{20}H_{11}NO_2$ Mol. wt: 297.3

1.3 Chemical and physical properties of the pure substance

From Boit (1965), unless otherwise specified

(*a*) *Description*: Orange-yellow needles (recrystallized from benzene)

(*b*) *Melting-point*: 250.5-251°C

(*c*) *Spectroscopy data*: λ_{max} 252 (E^{1}_{1} 865), 265 (E^{1}_{1} 905), 285 (E^{1}_{1} 626), 300 (E^{1}_{1} 788), 371 (E^{1}_{1} 344), 390 (E^{1}_{1} 336), 405 nm (E^{1}_{1} 249) (in ethanol) (Dewar *et al.*, 1956); nuclear magnetic resonance and mass spectra have been reported (Fu *et al.*, 1982).

(*d*) *Reactivity*: Reacts with chromic acid to form 7-oxo-7*H*-benz[*de*]anthracene dicarboxylic acid-3,4-anhydride

1.4 Technical products and impurities

No information was available to the Working Group.

2. Production, Use, Occurrence and Anaiysis

2.1 Production and use

(*a*) *Production*

6-Nitrobenzo[*a*]pyrene was first synthesized by Windaus and Rennhak in 1937 by treating benzo[*a*]pyrene with aqueous nitric acid in either glacial acetic acid or benzene and glacial acetic acid (Boit, 1965).

No evidence was found that 6-nitrobenzo[*a*]pyrene has been produced in commercial quantities.

(*b*) *Use*

No evidence was found that 6-nitrobenzo[*a*]pyrene has been used for commercial applications.

2.2 Occurrence

6-Nitrobenzo[*a*]pyrene has been detected in ambient airborne particulates (Jäger, 1978). In one study, ambient particles collected in the Detroit, MI, area during the spring and summer of 1981 contained 6-nitrobenzo[*a*]pyrene at levels of 0.9-2.5 mg/kg, corresponding to airborne concentrations of 0.04-0.28 ng/m^3 (Gibson, 1982).

Reported values for levels of 6-nitrobenzo[*a*]pyrene found in engine exhaust emissions are given in Table 1.

Table 1. 6-Nitrobenzo[*a*]pyrene levels in exhaust particulates

Sample	6-Nitrobenzo[a]pyrene concentration (mg/kg extract)	(mg/kg particulate)	Reference
Diesel			
Passenger car	--	<0.4	Gibson (1982)
6-Cylinder engine	50	5 ± 1.2[a]	Pitts *et al.* (1982)
Engine[b]	10-82	--	Schuetzle (1983)
Non-diesel			
Catalyst engine	--	0.21 ± 0.1[a]	Gibson (1982)
1980 Engine (catalyst removed, unleaded fuel)	--	17.3 ± 8.5[a]	Gibson (1982)
1974 Engine (precatalyst, leaded fuel)	--	32.8 ± 16.2[a]	Gibson (1982)

[a] Error bound is 1 standard deviation

[b] 6- and 3-Nitrobenzo[*a*]pyrenes combined

2.3 Analysis

Typical methods for the analysis of 6-nitrobenzo[*a*]pyrene are summarized in Table 2.

Table 2. Methods for the analysis of 6-nitrobenzo[*a*]pyrene

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Airborne particulates	Collect on glass-fibre filter; extract (dichloromethane); pre-chromatograph (silica gel column)	TLC (silica gel and cellulose); fluorescence quenching detection	5 ng	Jäger (1978)
	Collect on glass-fibre filter; Soxhlet extract (toluene, dichloromethane, methanol)	TLC (silica gel); CI-MS of separated bands	ND	Pitts *et al.* (1978)
	Collect on Dexiglas filter; Soxhlet extract (benzene-ethanol); reduce to amino-PAH ($NaBH_4$-$CuCl_2$)	HPLC	ND	Gibson (1982)
Diesel exhaust	Collect on glass-fibre filter; Soxhlet extract (dichloromethane)	HPLC; GC/MS; HRMS	ND	Schuetzle *et al.* (1981)

[a] TLC, thin-layer chromatography; CI-MS, chemical ionization-mass spectroscopy; HPLC, high-performance liquid chromatography; GC/MS, gas chromatography/mass spectroscopy; HRMS, high-resolution mass spectroscopy

ND, not determined

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

Nitroarenes are generally synthesized or formed in the environment as mixtures of isomers by nitration of the parent hydrocarbons. They may thus be contaminated by isomers, other nitrocompounds or higher nitrated derivatives. Since such by-products often have much higher biological activities, certain experimental results may reflect the presence of trace impurities for which no analysis was performed.

3.1 Carcinogenicity studies in animals

Skin application

Mouse: In a study of initiating activity, two groups of 20 female CD-1 Charles River mice, aged 50-55 days, received applications of 5 μg 6-nitrobenzo[*a*]pyrene or benzo[*a*]pyrene (purity, >99%) in 0.1 ml acetone onto shaved back skin every other day for 20 days (total dose, 0.05 mg). A group of 20 female mice receiving acetone alone served as controls. Starting 10 days

after the initiation treatment was completed, all animals received thrice-weekly applications of 2.5 μg 12-*O*-tetradecanoylphorbol-13-acetate in 0.1 ml acetone for 25 weeks. At the end of this time, 5/20 of the animals treated with 6-nitrobenzo[*a*]pyrene, 18/20 benzo[*a*]pyrene-treated animals and 1/20 control animals had developed skin tumours (mainly papillomas). The difference in the incidence of papillomas between controls and nitrobenzo[*a*]pyrene-treated animals was not statistically significant [$p = 0.09$] (El-Bayoumy *et al.*, 1982).

3.2 Other relevant biological data

(*a*) *Experimental systems*

No data were available to the Working Group on toxic effects or on effects on reproduction and prenatal toxicity.

Absorption, distribution, excretion and metabolism

Two hours after a single i.p. injection of ^{3}H-6-nitrobenzo[*a*]pyrene at a dose of 4.2 mg/kg bw into male Wistar rats, the highest concentration of radioactivity (5% of the dose) was found in the liver, with lower amounts in the spleen (0.9%), kidneys (0.3%) and lungs (0.15%). Covalent binding to macromolecules, including DNA, was observed in the liver, spleen, lungs and kidneys. The order of binding per milligram of macromolecule was RNA > DNA > protein for all organs studied. Observation 24 hours after gastric intubation of a dose of 4.2 mg/kg bw of 6-nitrobenzo[*a*]pyrene showed no difference in binding to liver macromolecules between conventional Wistar and germ-free rats (Martin *et al.*, 1982).

Fu *et al.* (1982) incubated 6-nitrobenzo[*a*]pyrene with liver microsomes from 3-methylcholanthrene-induced rats. Five metabolites were identified: 1- and 3-hydroxy-6-nitrobenzo[*a*]pyrene, 6-nitrobenzo[*a*]pyrene-1,9-hydroquinone, 6-nitrobenzo[*a*]-pyrene-3,9-hydroquinone and benzo[*a*]pyrene-3,6-quinone. The major metabolite was 3-hydroxy-6-nitrobenzo[*a*]pyrene. In a later report from the same laboratory (Chou *et al.*, 1983), it was demonstrated that the 3-hydroxy-6-nitrobenzo[*a*]pyrene was formed by a rearrangement of the unstable 2,3-epoxide intermediate (NIH shift).

Hamster embryonic fibroblasts metabolized 6-nitrobenzo[*a*]pyrene to compounds designated as dihydrodiols (Tong & Selkirk, 1983).

Mutagenicity and other short-term tests

Reviews of the genetic effects of nitroarenes, including 6-nitrobenzo[*a*]pyrene, are available (Rosenkranz & Mermelstein, 1983; Rosenkranz *et al.*, 1983).

6-Nitrobenzo[*a*]pyrene was mutagenic to *Salmonella typhimurium* strains TA98 and TA100 in the presence of Aroclor-induced rat-liver supernatant; no activity was observed in the

absence of the metabolic system (Fu *et al.*, 1982; Pitts *et al.*, 1982; Greibrokk *et al.*, 1983). [The mutagenic activity of 6-nitrobenzo[*a*]pyrene in the absence of a metabolic system reported earlier (Wang *et al.*, 1978; Tokiwa *et al.*, 1981) probably resulted from contamination with 1- and 3-nitrobenzo[*a*]pyrene (Pitts *et al.*, 1982)]. A mixture of the metabolites 1- and 3-hydroxy-6-nitrobenzo[*a*]pyrene was mutagenic to strain TA98, but not to TA100, in the absence of an exogenous metabolic system. However, in the presence of Aroclor-induced rat-liver supernatant, these metabolites were mutagenic to strain TA100, and activity was further increased in strain TA98; the mutagenic activity was significantly greater than that of 6-nitrobenzo[*a*]pyrene when tested under these conditions (Fu *et al.*, 1982).

6-Nitrobenzo[*a*]pyrene (4-67 nmol/ml) was tested for transforming activity (anchorage independence) in normal human foreskin fibroblasts. When treatment was performed under anaerobic conditions, an increase in colony-forming units over background was observed. No activity was observed when treatment was aerobic. When xanthine oxidase and hypoxanthine were added to the anaerobic incubation, there was a further increase in the frequency of colony-forming units (Howard *et al.*, 1983). When tested at 3.3-34 nmol/ml in a clonal morphological transformation assay in Syrian hamster embryo cells, 6-nitrobenzo[*a*]pyrene induced a dose-dependent response (DiPaolo *et al.*, 1983).

(*b*) *Humans*

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

6-Nitrobenzo[*a*]pyrene was tested for initiating activity at only one dose level in a mouse-skin initiation-promotion experiment. The increased incidence of skin tumours was not statistically significant.

6-Nitrobenzo[*a*]pyrene was mutagenic to *Salmonella typhimurium* in the presence of an exogenous metabolic system. It induced morphological transformation of Syrian hamster embryo cells; it transformed human foreskin fibroblasts (to anchorage independence) when tested anaerobically.

Overall assessment of data from short-term tests on 6-nitrobenzo[a]*pyrene*[a]

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes		+		
Fungi/green plants				
Insects				
Mammalian cells (*in vitro*)				+
Mammals (*in vivo*)				
Humans (*in vivo*)				
Degree of evidence in short-term tests for genetic activity : *Inadequate*				Cell transformation : Positive

[a] The groups into which the table is divided and '+', '−' and '?' are defined on pp. 16-17 of the preamble; the degrees of evidence are defined on p. 17.

4.2 Human data

Environmental exposure to 6-nitrobenzo[*a*]pyrene occurs, as it is a constituent of particulate matter in diesel engine exhaust and in urban air. It is not produced commercially.

No case report or epidemiological study was available to the Working Group.

4.3 Evaluation[1]

The available data are *inadequate* to permit an evaluation of the carcinogenicity of 6-nitrobenzo[*a*]pyrene to experimental animals.

No data on humans were available.

No evaluation of the carcinogenicity of 6-nitrobenzo[*a*]pyrene to humans could be made.

[1] See the preamble, p. 15, for definitions of italicized terms.

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Tong, S. & Selkirk, J.K. (1983) Metabolism of 6-nitrobenzo[*a*]pyrene by hamster embryonic fibroblasts and its interaction with nuclear macromolecules. *J. Toxicol. environ. Health* (in press)

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6-NITROCHRYSENE

1. Chemical and Physical Data

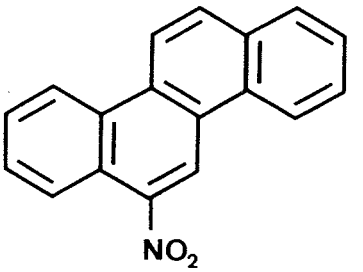
1.1 Synonyms and trade names

Chem. Abstr. Services Reg. No.: 7496-02-8

Chem. Abstr. Name: Chrysene, 6-nitro-

IUPAC Systematic Name: 6-Nitrochrysene

1.2 Structural and molecular formulae and molecular weight



$C_{18}H_{11}NO_2$ Mol. wt: 273.3

1.3 Chemical and physical properties of the pure substance

From Boit (1965), unless otherwise specified

(*a*) *Description*: Chrome-red, thick prismatic crystals (Prager & Jacobson, 1922) or orange-yellow needles (recrystallized from pyridine or xylene)

(*b*) *Boiling-point*: Sublimes without decomposition (Prager & Jacobson, 922)

(*c*) *Melting-point*: 209°C

(*d*) *Spectroscopy data*: Ultraviolet spectral data have been reported

(*e*) *Solubility*: Slightly soluble in cold ethanol, diethyl ether and carbon disulphide; somewhat more soluble in benzene and glacial acetic acid; and soluble in hot nitrobenzene (Prager & Jacobson, 1922)

(*f*) *Reactivity*: Forms 6-aminochrysene upon treatment with tin and hydrochloric acid in glacial acetic acid. Reacts with bromine to form 12-bromo-6-nitrochrysene, and reacts with fuming nitric acid to form 6,12-dinitrochrysene

1.4 Technical products and impurities

No information was available to the Working Group.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

6-Nitrochrysene was first synthesized in 1890 by heating chrysene with aqueous nitric acid in glacial acetic acid (Prager & Jacobson, 1922). It can also be synthesized by briefly heating chrysene with nitric acid and concentrated sulphuric acid in glacial acetic acid (Boit, 1965).

6-Nitrochrysene is offered for sale in research quantities by one US company (Pfaltz & Bauer, Inc., undated). However, no evidence was found that it has been produced in commercial quantities.

(*b*) *Use*

No evidence was found that 6-nitrochrysene has been used for commercial applications.

2.2 Occurrence

6-Nitrochrysene is not known to occur as such in nature. It was not found in dichloromethane extracts of airborne particulates collected in Prague, Czechoslovakia, using an analytical method with a detection limit of 100 mg (Jäger, 1978).

2.3 Analysis

A method has been described for the analysis of 6-nitrochrysene in extracts from airborne particulates using thin-layer chromatography. Particulates were collected on glass-fibre filters and extracted with dichloromethane. The extracts were pre-chromatographed on a silica gel column and then chromatographed on thin-layer plates coated with silica gel or cellulose. Fluorescence-quenching detection was used to identify components of the extract. The detection limit for 6-nitrochrysene was 100 ng (Jäger, 1978).

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

Nitroarenes are generally synthesized or formed in the environment as mixtures of isomers by nitration of the parent hydrocarbons. They may thus be contaminated by isomers, other nitrocompounds or higher nitrated derivatives. Since such by-products often have much higher biological activities, certain experimental results may reflect the presence of trace impurities for which no analysis was performed.

3.1 Carcinogenicity studies in animals

Skin application

Mouse: In a study of initiating activity, a group of 20 female CD-1 Charles River mice, aged 50-55 days, received applications of 0.1 mg 6-nitrochrysene (purity, >99%) in 0.1 ml acetone onto shaved back skin every other day for 20 days (total dose, 1 mg). A group of 20 female mice receiving acetone alone served as controls. Starting 10 days after the initiation treatment was completed, the animals received thrice-weekly applications of 2.5 μg 12-*O*-tetradecanoylphorbol-13-acetate in 0.1 ml acetone for 25 weeks. At the end of this time, 12/20 (60%) of the treated animals had developed skin tumours (mainly papillomas; with 2.1 tumours/animal) compared with 1/20 (5%) of controls ($p < 0.01$) (El-Bayoumy *et al.*, 1982).

3.2 Other relevant biological data

(*a*) *Experimental systems*

No data were available to the Working Group on toxic effects or on effects on reproduction and prenatal toxicity.

Absorption, distribution, excretion and metabolism

When ^{14}C-6-nitrochrysene was incubated with a post-mitochondrial liver supernatant from Aroclor-induced rats, the major metabolite was identified as a dihydrodiol. When incubated with the metabolic system under reduced oxygen tension (4% oxygen in nitrogen), both a dihydrodiol and 6-aminochrysene were produced (El-Bayoumy & Hecht, 1983).

Mutagenicity and other short-term tests

Reviews of the genetic effects of nitroarenes, including 6-nitrochrysene, are available (Rosenkranz & Mermelstein, 1983; Rosenkranz *et al.*, 1983).

6-Nitrochrysene was mutagenic to *Salmonella typhimurium* strains TA98 (Pederson & Siak, 1981; Tokiwa *et al.*, 1981a,b; Greibrokk *et al.*, 1983), TA1538 (Tokiwa *et al.*, 1981a) and TA100

(Tokiwa *et al.*, 1981b; Greibrokk *et al.*, 1983), both in the presence and absence of an exogenous metabolic system. Anaerobic incubation increased the mutagenicity to strain TA98 (Pederson & Siak, 1981; Greibrokk *et al.*, 1983).

When tested in a clonal morphological transformation assay in Syrian hamster embryo cells at concentrations of 3.7-73 nmol/ml, 6-nitrochrysene induced a dose-dependent response (DiPaolo *et al.*, 1983).

(*b*) *Humans*

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

6-Nitrochrysene was tested for initiating activity in a mouse-skin initiation-promotion assay and was found to be active.

6-Nitrochrysene was mutagenic to *Salmonella typhimurium* in the presence and absence of an exogenous metabolic system. It induced morphological transformation in Syrian hamster embryo cells.

Overall assessment of data from short-term tests on 6-nitrochrysene[a]

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes		+		
Fungi/green plants				
Insects				
Mammalian cells (*in vitro*)				+
Mammals (*in vivo*)				
Humans (*in vivo*)				
Degree of evidence in short-term tests for genetic activity : *Inadequate*				Cell transformation : Positive

[a] The groups into which the table is divided and '+', '−' and '?' are defined on pp. 16-17 of the preamble; the degrees of evidence are defined on p. 17.

4.2 Human data

6-Nitrochrysene has not been reported to occur in the environment. It is produced only for research purposes.

No case report or epidemiological study was available to the Working Group.

4.3 Evaluation[1]

The available data are *inadequate* to permit an evaluation of the carcinogenicity of 6-nitrochrysene to experimental animals. There is *limited evidence* for its activity as an initiator in mouse-skin carcinogenesis.

No data on humans were available.

No evaluation of the carcinogenicity of 6-nitrochrysene to humans could be made.

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Greibrokk, T., Löfroth, G., Nilsson, L. & Toftgård, R. (1983) *Nitroarenes: Mutagenicity in the Ames* Salmonella/*microsome assay and affinity to the TCDD-receptor protein*. In: Rickert, D.E., ed., *Fifth CIIT Conference on Toxicology, Toxicity of Nitroaromatic Compounds*, New York, Hemisphere Publ. Corp. (in press)

Jäger, J. (1978) Detection and characterization of nitro derivatives of some polycyclic aromatic hydrocarbons by fluorescence quenching after thin-layer chromatography: Application to air pollution analysis. *J. Chromatogr.*, *152*, 575-578

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[1] See the preamble, p. 15, for definitions of italicized terms.

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3-NITROFLUORANTHENE

1. Chemical and Physical Data

1.1 Synonyms and trade names

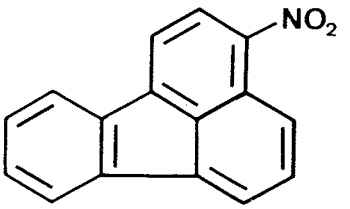
Chem. Abstr. Services Reg. No.: 892-21-7

Chem. Abstr. Name: Fluoranthene, 3-nitro-

IUPAC Systematic Name: 3-Nitrofluoranthene

Synonym: 4-Nitrofluoranthene

1.2 Structural and molecular formulae and molecular weight



$C_{16}H_9NO_2$ Mol. wt: 247.3

1.3 Chemical and physical properties of the pure substance

From Boit (1965), unless otherwise specified

(*a*) *Description:* Yellow crystals

(*b*) *Melting-point*: 159-160°C

(*c*) *Spectroscopy data*: Nuclear magnetic resonance spectral data have been reported (Shenbor & Smirnov, 1978).

(*d*) *Solubility*: Slightly soluble in diethyl ether; very soluble in acetone, benzene, dichloromethane and warm ethanol

(*e*) *Reactivity*: Reacts with chromic acid to form 2-nitro-9-oxo-fluorene-1-carboxylic acid

1.4 Technical products and impurities

No information was available to the Working Group.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

3-Nitrofluoranthene was first synthesized by Braun and Manz in 1931 by heating fluoranthene with aqueous nitric acid in glacial acetic acid (Boit, 1965).

No evidence was found that 3-nitrofluoranthene has been produced in commercial quantities.

(*b*) *Use*

No evidence was found that 3-nitrofluoranthene has been used for commercial applications.

2.2 Occurrence

3-Nitrofluoranthene has been identified in extracts of urban-air particulates from St Louis, MO (Ramdahl *et al.*, 1982), and from Prague, Czechoslovakia (Jäger, 1978). It has also been found in airborne particulates (Tokiwa *et al.*, 1981a) and in diesel-exhaust particles at a level of 1.2 mg/kg of the crude extract (Nakagawa *et al.*, 1983; Salmeen *et al.*, 1983).

2.3 Analysis

Typical methods for the analysis of 3-nitrofluoranthene are summarized in Table 1.

Table 1. Methods for the analysis of 3-nitrofluoranthene

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Airborne particulates	Collect on glass-fibre filter; Soxhlet extract (benzene-methanol); fractionate (silica gel column); convert nitro compounds to amines with HCl and Zn; extract amines and convert to acyl derivatives (heptafluorobutyric anhydride)	GC/EC	ND	Morita *et al.* (1982)
	Collect in fibre bag houses; Soxhlet extract (toluene); HPLC[a]	Capillary GC/MS (EI & NCI)	ND	Ramdahl *et al.* (1982)
	Collect on glass-fibre filter; extract (dichloromethane); pre-chromatograph (silica gel column)	TLC (silica gel and cellulose); fluorescence quenching detection	1 ng	Jäger (1978)

[a] GC/EC, gas chromatography/electron capture; HPLC, high-performance liquid chromatography; GC/MS, gas chromatography/mass spectrosocpy; EI, electron impact; NCI, negative chemical ionization; TLC, thin-layer chromatography

ND, not determined

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

Nitroarenes are generally synthesized or formed in the environment as mixtures of isomers by nitration of the parent hydrocarbons. They may thus be contaminated by isomers, other nitrocompounds or higher nitrated derivatives. Since such by-products often have much higher biological activities, certain experimental results may reflect the presence of trace impurities for which no analysis was performed.

3.1 Carcinogenicity studies in animals

Subcutaneous and/or intramuscular administration

Rat: A group of ten male F344/DuCrj Fischer rats, eight weeks old, received twice-weekly s.c. injections of 2 mg 3-nitrofluoranthene (reported to be >99% pure) dissolved in 0.2 ml dimethyl sulphoxide for 7.5 weeks; a control group of 20 male rats received injections of 0.2 ml dimethyl sulphoxide only twice weekly for ten weeks. The animals were observed for life; the last rats died on day 377. The first tumour was seen in treated animals after 277 days; 4/10 (40%) of the animals surviving beyond 162 days developed tumours described as two

dermatofibrosarcomas and two malignant fibrous histiocytomas at the injection site, one of which proved to be serially transplantable into the subcutis of the same strain over eight generations. No tumour was seen in 20 controls. The difference between tumour incidence in the control and treated groups was statistically significant ($p < 0.02$) (Ohgaki *et al.*, 1982). [The Working Group noted the small number of test animals used.]

3.2 Other relevant biological data

(*a*) *Experimental systems*

No data were available to the Working Group on toxic effects, on effects on reproduction and prenatal toxicity, or on absorption, distribution, excretion and metabolism.

Mutagenicity and other short-term tests

Reviews of the genetic effects of nitroarenes, including 3-nitrofluoranthene, are available (Rosenkranz & Mermelstein, 1983; Rosenkranz *et al.*, 1983).

3-Nitrofluoranthene was mutagenic to *Salmonella typhimurium* strains TA1537, TA1538, TA98 and TA100 in the absence of an exogenous metabolic system (Pedersen & Siak, 1981; Tokiwa *et al.*, 1981a,b; Greibrokk *et al.*, 1983). Addition of an Aroclor-induced rat-liver supernatant decreased the mutagenic activity (Tokiwa *et al.*, 1981a,b). Anaerobic incubation increased the mutagenic effect in strain TA98 (Pedersen & Siak, 1981; Greibrokk *et al.*, 1983).

When tested in a clonal morphological transformation assay in Syrian hamster embryo cells at concentrations of 4.1-16 nmol/ml, 3-nitrofluoranthene induced a dose-dependent response (DiPaolo *et al.*, 1983).

(*b*) *Humans*

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

In one limited experiment in which 3-nitrofluoranthene was tested in male rats by subcutaneous injection, sarcomas were observed at the injection site.

3-Nitrofluoranthene was mutagenic to *Salmonella typhimurium* in the presence and absence of an exogenous metabolic system. It induced morphological transformation in Syrian hamster embryo cells.

Overall assessment of data from short-term tests on 3-nitrofluoranthene[a]

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chromosomal effects	
Prokaryotes		+		
Fungi/green plants				
Insects				
Mammalian cells (*in vitro*)				+
Mammals (*in vivo*)				
Humans (*in vivo*)				
Degree of evidence in short-term tests for genetic activity : *Inadequate*				Cell transformation : Positive

[a] The groups into which the table is divided and '+', '−' and '?' are defined on pp. 16-17 of the preamble; the degrees of evidence are defined on p. 17.

4.2 Human data

Environmental exposure to 3-nitrofluoranthene occurs, as it is a constituent of particulate matter in diesel-engine exhaust and in urban air. It is not produced commercially.

No case report or epidemiological study was available to the Working Group.

4.3 Evaluation[1]

The available data are *inadequate* to permit an evaluation of the carcinogenicity of 3-nitrofluoranthene to experimentai animals.

No data on humans were available.

No evaluation of the carcinogenicity of 3-nitrofluoranthene to humans could be made.

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[1] See the preamble, p. 15, for definitions of italicized terms.

5. References

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1-NITROPYRENE

1. Chemical and Physical Data

1.1 Synonyms and trade names

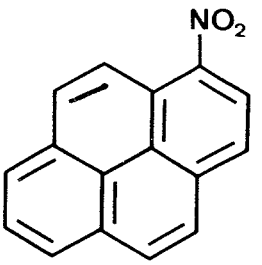
Chem. Abstr. Services Reg. No.: 5522-43-0

Chem. Abstr. Name: Pyrene, 1-nitro-

IUPAC Systematic Name: 1-Nitropyrene

Synonym: 3-Nitropyrene

1.2 Structural and molecular formulae and molecular weight



$C_{16}H_9NO_2$ Mol. wt: 247.3

1.3 Chemical and physical properties of the pure substance

(*a*) *Description*: Yellow needles or prisms (from ethanol) (Prager & Jacobson, 1922)

(*b*) *Melting-point*: 155°C (Luckenbach, 1980)

(*c*) *Spectroscopy data*: λ_{max} 233 (E_1^1 1647), 285 (E_1^1 612), 313 (E_1^1 203), 372-373 (E_1^1 533), 392 (E_1^1 475), 408 nm (E_1^1 395) [solvent unspecified] (Bavin & Dewar, 1955); nuclear magnetic resonance data have been reported (Kaplan, 1981).

(*d*) *Solubility*: Very soluble in diethyl ether (Prager & Jacobson, 1922); soluble in ethanol and benzene at 15°C (Luckenbach, 1980)

(*e*) *Reactivity*: Reacts with ethanolic potassium hydroxide to form 1,1′-azoxypyrene, also reacts with zinc powder and ethanol with catalytic amounts of ammonium chloride or ammonia to form 1,1′-azoxypyrene or, without air, 1-aminopyrene and 1-hydroxylaminopyrene (Boit, 1965)

1.4 Technical products and impurities

1-Nitropyrene produced in Japan is believed to contain pyrene and other nitropyrene isomers as impurities. No specifications were available.

2. Production, Use, Occurrence and Analysis

2.1 Production and use

(*a*) *Production*

1-Nitropyrene was first synthesized by Graebe in 1871 by heating pyrene with equal parts of nitric acid and water. It can also be obtained (in a mixture with dinitropyrenes) by the addition of potassium nitrite to a solution of pyrene in diethyl ether, followed by the slow addition of dilute sulphuric acid (Prager & Jacobson, 1922). 1-Nitropyrene has also been synthesized by heating pyrene with nitric acid in glacial acetic acid at 50°C (Boit, 1965).

Since 1972, one Japanese company has produced 1-nitropyrene by the reaction of pyrene with nitric acid.

No evidence was found that 1-nitropyrene has been produced in commercial quantities in the USA. One US company is reported to have processed an unspecified amount of 1-nitropyrene in 1977 (US Environmental Protection Agency, 1982).

(*b*) *Use*

1-Nitropyrene has been reported to be a photosensitizer, increasing the spectral sensitivity of bis-azide compounds in the long wavelength region (Tsunoda *et al.*, 1973). No evidence was found that 1-nitropyrene has been used commercially for this or other applications. However, one Japanese company uses 1-nitropyrene as an intermediate in the production of 1-azidopyrene, which is used in photosensitive printing.

2.2 Occurrence

(*a*) *Air*

A summary of the quantitative data on 1-nitropyrene levels in the particulates in exhaust emissions and in the extracts from these particulates is given in Table 1.

Table 1. 1-Nitropyrene levels in exhaust particulates and their extracts

Sample	1-Nitropyrene concentration		References
	mg/kg extract	mg/kg particulate	
Diesel	--	8.6	Morita *et al.* (1982)
	--	8.0	Gibson (1982)
4-Stroke, 6-cylinder engines typical of long-distance trucks	5-44	--	Rappaport *et al.* (1982)
6-Cylinder engine	870	93	Pitts *et al.* (1982)
Passenger vehicle	55 ± 11 150 ± 30	--	Salmeen *et al.* (1982)
1979 Passenger vehicle	2030 ± 220	--	Salmeen *et al.* (1982)
Light-duty engine	2280 ± 230	--	Schuetzle *et al.* (1982)
Passenger car	75 ± 10	--	Salmeen *et al.* (1983)
Bus	70.5	[30][a]	Nakagawa *et al.* (1983)
Passenger car	107.2-589.3	--	Nishioka *et al.* (1982)
Non-diesel			
Catalyst engine	--	0.63	Gibson (1982)
No catalyst engine	--	3.9-4.3	Gibson (1982)
Passenger car	2.5	--	Nishioka *et al.* (1982)

[a] Calculated by the Working Group for comparison purposes from data in the reference

1-Nitropyrene has been detected [at unspecified levels] in extracts of diesel exhaust emissions (Levine & Skewes, 1982; Xu *et al.*, 1982). It has been detected in extracts from urban air particulates (Ramdahl & Urdal, 1982; Ramdahl *et al.*, 1982; Sweetman *et al.*, 1982) and was detected in ambient air particles collected during the spring and summer of 1981 in the Detroit, MI, area at levels of 0.2-0.6 mg/kg (corresponding to airborne concentrations of 16-30 pg/m^3) (Gibson, 1982). A level of 20.8 pg/m^3 was detected in the air of an industrial area in Japan (Morita *et al.*, 1982).

1-Nitropyrene has also been detected in rural air particulates. Nielsen *et al.* (1983) found concentrations of 9 ± 5 pg/m^3 of 1-nitropyrene in airborne particulate samples collected in February-April 1982 in a rural area 30 km west of Copenhagen, Denmark.

(*b*) *Carbon blacks*

Toners for use in photocopy machines have been produced in quantity since the late 1950s, and are currently in widespread use. The mutagenicity of one photocopy toner was shown to be due to trace amounts of nitropyrenes which accompanied the carbon black used in the toner. This particular 'long-flow' furnace black was first used in photocopy toners in 1967. Its manufacture involved an oxidation process whereby some nitration also occurred; however, changes in the production technique reduced the total extractable nitropyrene content from an uncontrolled level of 5-100 mg/kg to below 0.3 mg/kg (Rosenkranz *et al.*, 1980; Sanders, 1981; Butler *et al.*, 1983). Toners produced from the carbon black in question after 1980 have not been found to contain detectable levels of mutagenicity and, hence, nitropyrenes (Rosenkranz *et al.*, 1980; Butler *et al.*, 1983).

1-Nitropyrene was found in an extract of carbon black (a pre-1979 sample of furnace black that had been after-treated by an oxidation-nitration process) at a level of 2.9 mg/kg (Sanders,

1981). One lot of this grade made in 1980 was found to contain 0.067 mg/kg (Giammarise *et al.*, 1982).

In a more recent study, an undetermined level of 1-nitropyrene was detected in an extract of a formerly commercial furnace black (produced before 1980)(Ramdahl & Urdal, 1982).

2.3 Analysis

Typical methods for the analysis of 1-nitropyrene are summarized in Table 2.

Table 2. Methods for the analysis of 1-nitropyrene

Sample matrix	Sample preparation	Assay procedure[a]	Limit of detection	Reference
Airborne particulates	Collect on glass-fibre filter; extract (dichloromethane); pre-chromatograph (silica gel column)	TLC (silica gel and cellulose); fluorescence quenching detection	1 ng	Jäger (1978)
Carbon black	Soxhlet extract (toluene)	Capillary GC/MS (NCI)	1 pg	Ramdahl & Urdal (1982)
	Soxhlet extract (toluene or acetone)	HPLC/UV	--	Rosenkranz *et al.* (1980)
	Soxhlet extract (chlorobenzene)	HPLC/UV	5 ng	Giammarise *et al.* (1981)
Diesel exhaust particulates	Collect on glass-fibre filter; Soxhlet extract (dichloromethane); pre-chromatograph (silica gel column)	Capillary GC/MS (EI and NCI); HRMS	ND	Newton *et al.* (1982)
	Collect on glass-fibre filter; Soxhlet extract (dichloromethane); HPLC	GC/MS (EI and NCI); HRMS	1 ng	Schuetzle *et al.* (1982)
	Collect on glass-fibre filter; Soxhlet extract (dichloromethane)	Capillary GC/MS (NCI); HPLC/UV	ND	Yergey *et al.* (1982)

[a] TLC, thin-layer chromatography; GC/MS, gas chromatography/mass spectroscopy; EI, electron ionization; NCI, negative chemical ionization; HPLC, high-perfqrmance liquid chromatography; HRMS, high-resolution mass spectroscopy; UV, ultraviolet detection

ND, not determined

3. Biological Data Relevant to the Evaluation of Carcinogenic Risk to Humans

Nitroarenes are generally synthesized or formed in the environment as mixtures of isomers by nitration of the parent hydrocarbons. They may thus be contaminated by isomers, other nitrocompounds or higher nitrated derivatives. Since such by-products often have much higher biological activities, certain experimental results may reflect the presence of trace impurities for which no analysis was performed.

3.1 Carcinogenicity studies in animals

(*a*) *Skin application*

Mouse: In a study of initiating activity, a group of 20 female CD-1 Charles River mice, aged 50-55 days, received applications of 0.1 mg 1-nitropyrene (purity, >99%) in 0.1 ml acetone onto shaved back skin every other day for 20 days (total dose, 1 mg). A group of 20 female mice receiving acetone alone served as controls. Starting 10 days after the initiation had been completed, the animals received thrice-weekly applications of 2.5 μg 12-*O*-tetradecanoylphorbol-13-acetate in 0.1 ml acetone for 25 weeks. At the end of this time, 16% of the treated animals and 5% of the control animals had developed skin tumours (mainly papillomas). This difference was not statistically significant (El-Bayoumy *et al.*, 1982).

(*b*) *Subcutaneous and/or intramuscular administration*

Rat: A group of 20 male F344/DuCrj Fischer rats, eight weeks old, received twice-weekly s.c. injections of 2 mg 1-nitropyrene (purity reported to be >99% [nature of impurities not stated]) dissolved in 0.2 ml dimethyl sulphoxide for 10 weeks; a control group of 20 male rats received injections of 0.2 ml dimethyl sulphoxide only according to the same schedule. The animals were observed for life; the last rats died on day 377. The first tumour in the treated group was seen after 162 days; 8/17 (47%) of the animals surviving beyond this time developed tumours, described as one extraskeletal osteosarcoma and seven malignant fibrous histiocytomas at the site of injection. Two of these proved to be serially transplantable into the subcutis of the same strain over 14 generations. No tumour was seen in controls. The difference between tumour incidence in the control and treated groups was statistically significant ($p < 0.003$) (Ohgaki *et al.*, 1982).

In another study, 1-nitropyrene was injected s.c. into newborn CD rats and subsequently at 'seven weekly' intervals. After 62 weeks a dose-dependent induction of tumours at the site of injection in both males and females was seen; induction of mammary tumours in females was also reported (Hirose *et al.*, 1983). [The Working Group noted that this study was reported only as an abstract, and no further detail was available.]

3.2 Other relevant biological data

(*a*) *Experimental systems*

Toxic effects

No data on LD_{50} were available to the Working Group.

Small groups of male and female SPF Fischer 344 rats received single oral doses of up to 5 g/kg bw of 1-nitropyrene (purified by thin-layer chromatography) as a fine powder suspension in 2% gelatin. These animals showed no mortality or histological damage in a wide range of organs examined when killed 4 or 14 days after administration (Marshall *et al.*, 1982).

No data were available to the Working Group on effects on reproduction and prenatal toxicity.

Absorption, distribution, excretion and metabolism

Urine and faeces from two male and two female, 15-week-old, Fischer 344 rats, administered 1-nitropyrene, 5.0 g/kg bw, as a 170 mg/ml suspension in 2% gelatin by oral gavage were collected and analysed. Approximately 70% of the dose was excreted as unchanged 1-nitropyrene in the faeces over four days, 80% of which was excreted in 24 hours. [This suggests that the dose was in large excess of that which could be absorbed.] Free 1-aminopyrene constituted 2% of the administered dose, 28% of the dose being unaccounted for. Sulphate and glucuronide esters of 1-aminopyrene (<1%) but little or no free 1-nitropyrene and 1-aminopyrene were detected in the urine (Marshall *et al.*, 1982).

In a review (McClellan, 1983) it was reported that in rats exposed by 'nose-only' inhalation to radiolabelled 1-nitropyrene, three-quarters of the deposited radioactivity was excreted in the urine.

When 1-nitropyrene was incubated anaerobically with human faeces or the bacteria derived therefrom, 1-aminopyrene was produced (Kinouchi *et al.*, 1982; El Bayoumy *et al.*, 1983). 1-Aminopyrene has also been detected following incubation of 1-nitropyrene with cultures of intestinal anaerobic bacteria (Kinouchi *et al.*, 1982; Howard *et al.*, 1983a; El-Bayoumy *et al.*, 1983). When conventional and germ-free Fischer 344 rats were administered 1-nitropyrene by gavage, 1-aminopyrene was detected in the faeces of the conventional animals only (El-Bayoumy *et al.*, 1983).

El-Bayoumy and Hecht (1983) incubated 1-nitropyrene with an Aroclor-induced rat-liver supernatant for 60 min at 37°C. Six peaks were identified: unchanged 1-nitropyrene, 1-nitropyren-3-ol, 1-nitropyren-6-ol, 1-nitropyren-8-ol, *trans*-4,5-dihydro-4,5-dihydroxy-1-nitropyrene and a small amount of 1-aminopyrene. When incubation was carried out under reduced oxygen tension (4% oxygen in nitrogen), the major metabolite detected was 1-aminopyrene.

When 1-nitropyrene was incubated anaerobically with either rat-liver supernatant, cytosol or microsomes, a slow reduction to 1-aminopyrene occurred. The rate of reduction was increased in each case following addition of either flavin mononucleotide or nicotinamide-adenine dinucleotide phosphate (reduced form) (Nachtman & Wei, 1982).

Mutagenicity and other short-term tests

Reviews of the genetic effects of nitroarenes, including 1-nitropyrene, are available (Rosenkranz & Mermelstein, 1983; Rozenkranz *et al.*, 1983).

When 1-nitropyrene was incubated with calf thymus or plasmid DNA in the absence of an exogenous metabolic system, there was no evidence of covalent binding or intercalation [details not given] (Rosenkranz *et al.*, 1980; Mermelstein *et al.*, 1981; Rosenkranz & Mermelstein, 1983).

Following incubation of ^{3}H-1-nitropyrene with calf thymus DNA, bovine xanthine oxidase and hypoxanthine at 37°C, covalent binding to DNA was shown to be proportional to the amount of reducing enzyme present (Howard & Beland, 1982). The major covalent DNA adduct was identified as *N*-(deoxyguanosin-8-yl)-1-aminopyrene. Two minor peaks were not characterized (Howard *et al.*, 1983b)

^{3}H-1-Nitropyrene was incubated at 37°C with growing cultures of *Salmonella typhimurium* strain TA98. Dichloromethane extracts of a cell-free supernatant revealed the presence of unchanged 1-nitropyrene, 1-aminopyrene, *N*-acetyl-1-aminopyrene and other unidentified metabolites. 1-Nitropyrene adducts were detected in the bacterial DNA after isolation but were not identified (Messier *et al.*, 1981; Quilliam *et al.*, 1982).

When *S. typhimurium* strain TA1538 was incubated with ^{3}H-1-nitropyrene, *N*-(deoxyguanosin-8-yl)-1-aminopyrene was identified as the major DNA adduct (Howard *et al.*, 1983b).

1-Nitropyrene was mutagenic to *S. typhimurium* strains TA1537, TA1538, TA98 and TA100 in the absence of an exogenous metabolic system (Pitts, 1979; Rosenkranz *et al.*, 1980; Wang *et al.*, 1980; Löfroth, 1981; Mermelstein *et al.*, 1981; Pederson & Siak, 1981a; Rosenkranz *et al.*, 1981; McCoy & Rosenkranz, 1982; Salmeen *et al.*, 1982; Greibrokk *et al.*, 1983). When tested under anaerobic conditions, mutagenicity was increased by between two- (Pederson & Siak 1981b) and seven-fold (Greibrokk *et al.*, 1983).

The effect of Aroclor-induced rat-liver supernatant on the mutagenicity of 1-nitropyrene remains unclear, as both potentiating (Pitts *et al.*, 1982) and inhibitory (Tokiwa *et al.*, 1981a,b; Mermelstein *et al.*, 1982; Griebrokk *et al.*, 1983) effects have been observed.

1-Nitropyrene was not mutagenic to *S. typhimurium* strain TA1535 (Rosenkranz *et al.*, 1980; Mermelstein *et al.*, 1981) or to *Escherichia coli* WP2 *uvr* A (Mermelstein *et al.*, 1981).

This compound did not induce mitotic gene conversion in the yeast *Saccharomyces cerevisiae* D4 (McCoy *et al.*, 1983).

Sugimura and Takayama (1983) showed that 1-nitropyrene at a concentration of 10^{-4} μmol/ml induced unscheduled DNA synthesis in the epithelial cells of human explants; only one concentration was tested. [The source of the explant, i.e., bronchial or tracheal, is unclear.] It was reported in an abstract that this compound induced unscheduled DNA synthesis in primary rat hepatocytes (Ball *et al.*, 1983).

1-Nitropyrene was reported to be weakly mutagenic to Chinese hamster ovary cells in the presence or absence of Aroclor-induced rat-liver supernatant (Marshall *et al.*, 1982). [The Working Group considered that the data did not show a positive effect.] Li and Dutcher (1983) showed a marginal effect when mutation at the hypoxanthineguanine phosphoribosyl transferase (HGPRT) gene locus was measured in Chinese hamster ovary cells. Upon addition of a liver supernatant from Aroclor-induced rats, a significant and dose-related response was observed. Ball *et al.* (1983) reported in an abstract that 1-nitropyrene was active in the mouse lymphoma L5178Y TK$^{+/-}$ system, but only in the presence of Aroclor-induced rat-liver preparation.

1-Nitropyrene was neither cytotoxic nor mutagenic to Chinese hamster lung fibroblasts at concentrations of up to 20 μg/ml, in the presence or absence of rat-liver supernatant from polychlorinated biphenyl-induced rats, using diphtheria toxin as a selective marker (Nakayasu *et al.*, 1982). 1-Nitropyrene did not induce significant mutation to ouabain resistance at concentrations of up to 10 μg/ml in Chinese hamster V79 cells in the presence or absence of irradiated Syrian hamster embryo feeder cells (Takayama *et al.*, 1983) [The Working Group noted that a low toxicity was reported at the highest dose used.]

1-Nitropyrene (3-30 nmol/ml) induced sister chromatid exchanges in Chinese hamster ovary cells. Upon addition of supernatant from livers of Aroclor-induced rats there was a further increase (Nachtman & Wolff 1982).

Following intubation of 1-nitropyrene (0.5, 1.5 and 5.0 g/kg bw in 2% gelatin) into three groups of three female Fischer 344 rats, sister chromatid exchanges in bone-marrow cells were induced to a small but significant extent, with a dose-related increase at the two lower doses (Marshall *et al.*, 1982).

Concentrations of 1-nitropyrene of up to 4 nmol/ml induced a dose-dependent response in a clonal morphological transformation assay in Syrian hamster embryo cells (DiPaolo *et al.*, 1983). In an abstract, Tu *et al.* (1983) reported no evidence for transforming activity of 1-nitropyrene in BALB/c-3T3 cells. 1-Nitropyrene (3-33 nmol/ml) was tested for transforming activity (anchorage independence) in normal human foreskin fibroblasts. When treatment was performed under anaerobic conditions, an increase in anchorage-independent clones was observed; addition of xanthine oxidase and hypoxanthine caused a further increase. No activity was observed when incubation was aerobic (Howard *et al.*, 1983c).

1-Nitrosopyrene, a putative intermediate in the reductive activation process, was more mutagenic to *S. typhimurium* TA98 than the parent compound (Massaro *et al.*, 1983).

(*b*) *Humans*

No data were available to the Working Group.

3.3 Case reports and epidemiological studies of carcinogenicity in humans

No data were available to the Working Group.

4. Summary of Data Reported and Evaluation

4.1 Experimental data

1-Nitropyrene was tested in a mouse-skin initiation-promotion assay; no significant increase in skin tumour incidence was observed. In one experiment in which 1-nitropyrene was tested in rats by subcutaneous injection, tumours were observed at the injection site.

1-Nitropyrene bound covalently to DNA *in vitro* and to cellular DNA in the presence of appropriate activation enzymes. It was mutagenic to *Salmonella typhimurium* in the presence and absence of an exogenous metabolic system. In the one available study, it did not induce mitotic gene conversion in the yeast *Saccharomyces cerevisiae*. Both positive and negative results were observed in studies of mutagenicity in mammalian cells. 1-Nitropyrene induced unscheduled DNA synthesis and sister chromatid exchange in mammalian cells in culture, and sister chromatid exchange *in vivo* in bone-marrow cells of rats. It induced transformation of human foreskin fibroblasts (to anchorage independence) under anaerobic conditions and morphological transformation of Syrian hamster embryo cells.

Overall assessment of data from short-term tests on 1-nitropyrene[a]

	Genetic activity			Cell transformation
	DNA damage	Mutation	Chomosomal effects	
Prokaryotes	+	+		
Fungi/green plants		?		
Insects				
Mammalian cells (*in vitro*)	?	?	+	+
Mammals (*in vivo*)			+	
Humans (*in vivo*)				
Degree of evidence in short-term tests for genetic activity : *Sufficient*				Cell transformation : Positive

[a] The groups into which the table is divided and '+', '−' and '?' are defined on pp. 16-17 of the preamble; the degrees of evidence are defined on p. 17.

4.2 Human data

Environmental exposure to 1-nitropyrene occurs, since it is a constituent of particulate matter in diesel engine exhaust and in urban air. It was also found as a trace contaminant of one type of furnace black. It is produced commercially in very small quantities for use as a chemical intermediate.

No case report or epidemiological study was available to the Working Group.

4.3 Evaluation[1]

There is *limited evidence* for the carcinogenicity of 1-nitropyrene in experimental animals.

No data on humans were available.

No evaluation of the carcinogenicity of 1-nitropyrene to humans could be made.

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[1] See the preamble, p. 15, for definitions of the italicized terms.

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SUPPLEMENTARY CORRIGENDA TO VOLUMES 1-32

Corrigenda covering Volumes 1-6 appeared in Volume 7; others appeared in Volumes 8, 10-13, 15-32.

Supplement 4

p. 47	A, last line	*replace footnote* 9 *by footnote* 3.
p. 53	A, lines 3-6	*replace* An increased risk of bladder cancer was reported to be associated with the manufacture of auramine in two further studies[3,4]. No information on exposure to auramine alone was available to the Working Group. *by* Data reported in two further studies[3,4] of workers involved in the manufacture of auramine were judged to show an increased risk of bladder cancer; however, workers had also been exposed to other chemicals, induding ß-naphthylamine. Data on exposure to auramine alone were considered inadequate for evaluation.
p. 65	B, 1st line	*add* to mice *after* administration
p. 122	A, 2nd line	*replace* 8.74 *by* 7.28 [data pooled by the Working Group]
	A, 3rd line	*delete* This difference is significant.
p. 268		*replace* Indenó [1,2-*cd*] pyrene *by* Indeno [1,2,3-*cd*] pyrene
p. 288		*replace* Nivalenol *by* Nivalenol*

CUMULATIVE INDEX TO IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS

Numbers in italics indicate volume, and other numbers indicate page. References to corrigenda are given in parentheses. Compounds marked with an asterisk(*) were considered by the working groups, but monographs were not prepared becaused adequate data on carcinogenicity were not available.

IARC MONOGRAPHS ON THE EVALUATION OF THE CARCINOGENIC RISK OF CHEMICALS TO HUMANS

Some Inorganic Substances, Chlorinated Hydrocarbons, Aromatic Amines, *N*-Nitroso Compounds, and Natural Products	Volume 1, 1972; 184 pages (out of print)
Some Inorganic and Organometallic Compounds	Volume 2, 1973; 181 pages US$ 3.60; Sw. fr. 12.-- (out of print)
Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds	Volume 3, 1973; 271 pages (out of print)
Some Aromatic Amines, Hydrazine and Related Substances, *N*-Nitroso Compounds and Miscellaneous Alkylating Agents	Volume 4, 1974; 286 pages US$ 7.20; Sw. fr. 18.--
Some Organochlorine Pesticides	Volume 5, 1974; 241 pages US$ 7.20; Sw. fr. 18.-- (out of print)
Sex Hormones	Volume 6, 1974; 243 pages US$ 7.20; Sw. fr. 18.--
Some Anti-thyroid and Related Substances, Nitrofurans and Industrial Chemicals	Volume 7, 1974; 326 pages US$ 12.80; Sw. fr. 32.--
Some Aromatic Azo Compounds	Volume 8, 1975; 357 pages US$ 14.40; Sw. fr. 36.--
Some Aziridines, *N*-, *S*- and *O*-Mustards and Selenium	Volume 9, 1975; 268 pages US$ 10.80; Sw. fr. 27.--
Some Naturally Occurring Substances	Volume 10, 1976; 353 pages US$ 15.00; Sw. fr. 38.--
Cadmium, Nickel, Some Epoxides, Miscellaneous Industrial Chemicals and General Considerations on Volatile Anaesthetics	Volume 11, 1976; 306 pages US$ 14.00; Sw. fr. 34.--
Some Carbamates, Thiocarbamates and Carbazides	Volume 12, 1976; 282 pages US$ 14.00; Sw. fr. 34.--
Some Miscellaneous Pharmaceutical Substances	Volume 13, 1977; 255 pages US$ 12.00; Sw. fr. 30.--
Asbestos	Volume 14, 1977; 106 pages US$ 6.00; Sw. fr. 14.--
Some Fumigants, the Herbicides 2,4-D and 2,4,5-T, Chlorinated Dibenzodioxins and Miscellaneous Industrial Chemicals	Volume 15, 1977; 354 pages US$ 20.00; Sw. fr. 50.--
Some Aromatic Amines and Related Nitro Compounds - Hair Dyes, Colouring Agents and Miscellaneous Industrial Chemicals	Volume 16, 1978; 400 pages US$ 20.00; Sw. fr. 50.--
Some *N*-Nitroso Compounds	Volume 17, 1978; 365 pages US$ 25.00; Sw. fr. 50.--
Polychlorinated Biphenyls and Polybrominated Biphenyls	Volume 18, 1978; 140 pages US$ 13.00; Sw. fr. 20.--
Some Monomers, Plastics and Synthetic Elastomers, and Acrolein	Volume 19, 1979; 513 pages US$ 35.00; Sw. fr. 60.--
Some Halogenated Hydrocarbons	Volume 20, 1979; 609 pages US$ 35.00; Sw. fr. 60.--
Sex Hormones (II)	Volume 21, 1979; 583 pages US$ 35.00; Sw. fr. 60.--
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Some Pharmaceutical Drugs	Volume 24, 1980; 337 pages US$ 25.00; Sw. fr. 40.--
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Some Anticancer and Immunosuppressive Drugs	Volume 26, 1981; 411 pages US$ 30.00; Sw. fr. 62.--
Some Aromatic Amines, Anthraquinones and Nitroso Compounds and Inorganic Fluorides Used in Drinking-Water and Dental Preparations	Volume 27, 1982; 341 pages US$ 25.00; Sw. fr. 40.--
The Rubber Industry	Volume 28, 1982; 486 pages US$ 35.00; Sw. fr. 70.--
Some Industrial Chemicals and Dyestuffs	Volume 29, 1982; 416 pages US$ 30.00; Sw. fr. 60.--
Miscellaneous Pesticides	Volume 30, 1983; 424 pages US$ 30.00; Sw. fr. 60.--
Some Feed Additives, Food Additives and Naturally Occurring Substances	Volume 31, 1983; 314 pages US$ 30.00; Sw. fr. 60. --
Chemicals and Industrial Processes Associated with Cancer in Humans (IARC Monographs 1-20)	Supplement 1, 1979; 71 pages (out of print)
Long-term and Short-term Screening Assays for Carcinogens: A Critical Appraisal	Supplement 2, 1980; 426 pages US$ 25.00; Sw. fr. 40.--
Cross Index of Synonyms and Trade Names in Volumes 1 to 26	Supplement 3, 1982; 199 pages US$ 30.00; Sw. fr. 60.--
Chemicals, Industrial Processes and Industries Associated with Cancer in Humans (IARC Monographs Volumes 1 to 29)	Supplement 4, 1982; 292 pages US$ 30.00; Sw. fr. 60.--
Polynuclear Aromatic Compounds, Part 1, Chemical, Environmental and Experimental Data	Volume 32, 1983 ; 477 pages US $ 35.00 ; Sw.fr. 70
Polynuclear Aromatic Compounds, Part 2, Carbon Blacks, Mineral Oils and Some Nitroarenes	Volume 33, 1984; 245 pages US$ 25.00; Sw. fr. 50.--

IARC SCIENTIFIC PUBLICATIONS

Liver Cancer	No. 1, 1971; 176 pages US$ 10.000; Sw. fr. 30.—
Oncogenesis and Herpesviruses	No. 2, 1972; 515 pages US$ 25.00; Sw. fr. 100.—
N-Nitroso Compounds, Analysis and Formation	No. 3, 1972; 140 pages US$ 6.25; Sw. fr. 25.—
Transplacental Carcinogenesis	No. 4, 1973; 181 pages US$ 12.00; Sw. fr. 40.—
Pathology of Tumours in Laboratory Animals—Volume I—Tumours of the Rat, Part 1	No. 5, 1973; 214 pages US$ 15.00; Sw. fr. 50.—
Pathology of Tumours in Laboratory Animals—Volume I—Tumours of the Rat, Part 2	No. 6, 1976; 319 pages US$ 35.00; Sw. fr. 90.— (OUT OF PRINT)
Host Environment Interactions in the Etiology of Cancer in Man	No. 7, 1973; 464 pages US$ 40.00; Sw. fr. 100.—
Biological Effects of Asbestos	No. 8, 1973; 346 pages US$ 32.00; Sw. fr. 80.—
N-Nitroso Compounds in the Environment	No. 9, 1974; 243 pages US$ 20.00; Sw. fr. 50.—
Chemical Carcinogenesis Essays	No. 10, 1974; 230 pages US$ 20.00; Sw. fr. 50.—
Oncogenesis and Herpesviruses II	No. 11, 1975; Part 1, 511 pages US$ 38.00; Sw. fr. 100.— Part 2, 403 pages US$ 30.00; Sw. fr. 80.—
Screening Tests in Chemical Carcinogenesis	No. 12, 1976; 666 pages US$ 48.00; Sw. fr. 120.—
Environmental Pollution and Carcinogenic Risks	No. 13, 1976; 454 pages US$ 20.00; Sw. fr. 50.—
Environmental *N*-Nitroso Compounds—Analysis and Formation	No. 14, 1976; 512 pages US$ 45.00; Sw. fr. 110.—
Cancer Incidence in Five Continents—Volume III	No. 15, 1976; 584 pages US$ 40.00; Sw. fr. 100.—
Air Pollution and Cancer in Man	No. 16, 1977; 331 pages US$ 35.00; Sw. fr. 90.—
Directory of On-Going Research in Cancer Epidemiology 1977	No. 17, 1977; 599 pages US$ 10.00; Sw. fr. 25.— (OUT OF PRINT)
Environmental Carcinogens—Selected Methods of Analysis, Vol. 1: Analysis of Volatile Nitrosamines in Food	No. 18, 1978; 212 pages US$ 45.00; Sw. fr. 90.—
Environmental Aspects of *N*-Nitroso Compounds	No. 19, 1978; 566 pages US$ 50.00; Sw. fr. 100.—
Nasopharyngeal Carcinoma: Etiology and Control	No. 20, 1978; 610 pages US$ 60.00; Sw. fr. 100.—
Cancer Registration and Its Techniques	No. 21, 1978; 235 pages US$ 25.00; Sw. fr. 40.—
Environmental Carcinogens—Selected Methods of Analysis, Vol. 2: Methods for the Measurement of Vinyl Chloride in Poly(vinyl chloride), Air, Water and Foodstuffs	No. 22, 1978; 142 pages US$ 45.00; Sw. fr. 75.—
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