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Carcinogen Assessment of Coke Oven Emissions

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CARCINOGEN ASSESSMENT

OF

COKE OVEN EMISSIONS

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PREFACE

The Carcinogen Assessment Group (CAG), located in the Office of Health and Environmental Assessment of EPA's Office of Research and Development, is a small group of scientists who perform an advisory assessment function for EPA's regulatory offices. The CAG analyzes existing scientific data and furnishes the regulatory offices with an evaluation of the carcinogenicity and levels of carcinogenic risk associated with chemicals in various exposure situations, as best can be determined from currently available scientific data.

The CAG reports are prepared primarily for internal Agency use in response to requests from the EPA regulatory offices. The scope of each evaluation varies, depending upon the nature of the request. Evaluations range in completeness from brief memoranda to extensive reports and are used by the regulatory offices for decision making, as appropriate. The reports are revised and updated based on regulatory office needs and the availability of resources.

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I. SUMMARY

The purpose of this document is to evaluate the carcinogenicity of coke oven emissions and to develop a respiratory cancer unit risk estimate, which is the cancer risk from a lifetime exposure to 1 ug/m^3 concentration of coke oven particulates.

QUALITATIVE ASSESSMENT

The production of coke by the carbonization of bituminous coal leads to the atmospheric release of chemically-complex emissions from coke ovens. The toxic constituents include both gases and respirable particulate matter of varying chemical composition. Greatest attention has been focused on the toxic effects of the particulate phase of the coal tar pitch volatiles (CTPV) emitted from coke ovens, principally because this fraction contains polycylic organic matter (POM). In addition to POM, there is concern over the potential carcinogenic and/or cocarcinogenic effects of aromatic compounds (e.g., β-naphthylamine, benzene), trace metals (e.g., arsenic, beryllium, cadmium, chromium, lead, nickel), and gases (e.g., nitric oxide, sulfur dioxide), which are also emitted from coke ovens.

Extensive epidemiological studies of coke oven workers by Lloyd (1971), Redmond et al. (1972), Redmond et al. (1976), and Redmond et al. (1979) found that workers exposed to coke oven emissions were at an increased risk of cancer. A dose-response relationship was established in terms of both length of employment and intensity of exposure according to work area at the top or side of the coke oven. The relative risk of lung, trachea, and bronchus cancer mortality was 6.94 among Allegheny County, Pennsylvania workers who had 5 or more years of experience and worked full-time topside at the coke ovens. By comparison, side oven workers employed more than 5 years had a relative

risk of 1.91, while nonoven workers employed more than 5 years had a relative risk of 1.11. Deaths from malignant neoplasms at all sites were also found to be dose-related among the Allegheny County workers. Among non-Allegheny County coke oven workers employed more than 5 years, the relative risk of cancer of the lung, trachea, and bronchus was 3.47 for full-time topside, 2.31 for mixed topside and side oven, and 2.06 for side oven. Although adequate smoking data were not available for either the Allegheny County or non-Allegheny County workers, it is not likely that differences in smoking habits could be of sufficient magnitude to negate the dose-response effect that was found. In addition to elevated mortality from cancer at all sites and elevated mortality from cancer of the lung, trachea, and bronchus, there was significant ($P < 0.05$) excess kidney cancer mortality (relative risk of 2.37) and prostate cancer mortality (relative risk of 2.45) among Allegheny County workers. A significant ($P < 0.05$) excess of prostate cancer mortality was found for the nonwhite non-Allegheny County workers (relative risk of 2.45).

Sakabe et al. (1975) observed a significant ($P < 0.05$) excess of lung cancer deaths (relative risk of 2.37) among retired iron and steel coke oven workers in Japan when compared to expected, which was derived from general population statistics. The strength of the association is weakened, however, by the lack of adequate smoking data.

British studies of coke oven workers did not show the magnitude of risk that the American studies or the Sakabe et al. study did. Davies (1977, 1978) found no excess mortality for coke oven workers when compared to the general population. However, a short observation period and the lack of evaluation according to intensity of exposure by occupational work area are shortcomings of this study. Reid and Buck (1956) did not find an excess of respiratory

cancer among British coke oven workers. They did find an excess in mortality from cancer, other than respiratory cancer, however. The authors' failure to define the study population, to adequately address latent effects, and to provide sufficient information on how expected deaths were derived, make it difficult to draw conclusions from this early study. Collings (1978) found an increase in lung cancer deaths among British coke oven workers; the increase was not statistically significant however. The period of observation was short (only 9 years), and Collings did not study the workers by work area, which might have detected a mortality difference by exposure.

Extracts of a topside coke oven sample and a sample obtained from a coke oven collecting main were found to have skin tumor initiating activity in initiation-promotion studies in SENCAR mice (Nesnow et al. 1981). The coke oven main extract sample also induced skin tumors when topically applied to SENCAR mice as a complete carcinogen or as a promoter following initiation with benzo[a]pyrene (Nesnow et al. 1981). Nesnow (1980) reported no initiating effect of topside coke oven sample extract in an initiation-promotion study in C57BL6 mice; however, this mouse strain was resistant to the positive control agent benzo[a]pyrene. The above studies on topside coke oven sample extract are weakened by contamination of the sample with particulates from ambient air. Coal tar, a condensate from coke oven emissions, has been found to be a skin carcinogen in several animal studies. Coal tar aerosols have been found to cause tumors of the lung in mice (Horton et al. 1963, Tye and Stemmer 1967, Kinkead 1973, MacEwen and Vernot 1976). Numerous animal studies have found constituents of coke oven tar and coke oven emissions to be carcinogenic.

Mutagenicity tests on the complex mixture of solvent-extracted organics of coke oven emissions were positive in bacteria. A complex mixture from the

coke oven collecting main was mutagenic in bacteria and mammalian cells in vitro. In addition, a number of components identified in coke oven emissions are recognized as mutagens and/or carcinogens. Cell transformation was found in Balb/C 3T3 mouse embryo fibroblasts and Syrian hamster embryo cells treated with solvent-extracted organics of air particulates collected topside of a coke oven; however, these studies involve possibly significant contamination of the sample with ambient air particulates.

Based on the above information, the following conclusions can be drawn: 1) Coke oven workers have been found to be at an excess risk of mortality from cancer at all sites, lung cancer, prostate cancer, and kidney cancer. 2) Sample extract from a coke oven main and coal tar, a condensate of coke oven emissions, were found to be carcinogenic in animal skin painting studies. Animals exposed to coal tar aerosol developed lung tumors. 3) Sample extracts from coke oven topside sample and a coke oven main initiated tumor formation in initiation-promotion studies in mice. 4) Coke oven door emissions were found to be mutagenic in bacteria. 5) Numerous constituents of coke oven emissions are known or suspected carcinogens. The Carcinogen Assessment Group concludes that coke oven emissions are carcinogenic.

QUANTITATIVE ASSESSMENT

A mathematical model has been developed to predict the lifetime probability of cancer death due to a continuous exposure to a carcinogen. The "minimum initiation time" and potency parameters of the model are estimated using extensive epidemiological data concerning nonwhite steelworkers exposed to coal tar pitch volatiles. These parameter estimates are then used to predict the lifetime probability of respiratory cancer death due to a lifetime exposure of 1 ugm/m^3 of coal tar pitch volatiles. This estimate was determined to be 0.9×10^{-3}, with a 95% confidence interval of 0.5×10^{-3} to 1.5×10^{-3}.

II. INTRODUCTION

Coke is a porous, cellular carbon residue produced from the carbonization of soft (bituminous) coal and used primarily in the steel industry's blast furnaces to make iron that is subsequently refined into steel. As of October 1979, the United States metallurgical coke industry was composed of 34 companies with 61 plants in 19 states. Of the industry's 61 plants, 46 are operated by iron and steel companies that produce coke primarily for use in their own blast furnaces. They are customarily referred to as "furnace" plants, in contrast to the industry's 13 "merchant" plants that generally sell their coke on the open market to foundries and other consumers. Throughout both of these industry segments, the by-product, or slot-oven process, is employed to produce what is termed "oven" coke. Currently, 93% of its output is accounted for by furnace plants and 7% by merchant plants. An alternative coking method, the beehive process, is employed by only two plants to produce relatively minor quantities of "beehive" coke, most of which is marketed for blast furnace use. The basic difference between the by-product coke oven and the beehive oven is that the former recovers vapors and other by-products from the coking process, while the latter does not. In 1979, the 59 by-product coke oven plants consisted of 199 batteries containing 11,413 ovens that produced 63,377,505 tons of coke (Hogan and Koelble 1979).

A typical by-product oven is 10 to 22 feet high, 36 to 55 feet long, and approximately 18 inches wide. A coking facility generally contains several batteries and each battery consists of 20 to 100 ovens. The coking cycle begins with the introduction of coal into the coke oven (charging) by means of a mechanical larry car which operates on rails on top of the battery. During

the charging process the lids on the charging holes are removed and the oven is placed under steam aspiration. This operation limits the escape of gases from the oven during charging so that they can be collected in the by-product gas collector main for subsequent processing. Following the heating of the coal at 1046°C (1900°F) to 1100°C (2000°F) for 16 to 20 hours, the doors on each side of the oven are removed, and the coke is pushed by a mechanically-operated ram into a railroad car called the quench car. The quench car is then moved down the battery to a quench tower where the hot coke is cooled with water.

The reactions taking place in the coke oven can be characterized in three parts (OSHA 1976). In the first step, coal breaks down at temperatures below 700°C (1296°F) to primary products consisting of water, carbon monoxide, carbon dioxide, hydrogen sulfide, olefins, paraffins, aromatic hydrocarbons, and phenolic- and nitrogen-containing compounds. The second step occurs when the primary products react as they pass through the hot coke and along the heated oven walls at temperatures above 700°C (1296°F). This results in the formation of aromatic hydrocarbons and methane; the evolution of hydrogen; and the decomposition of nitrogen-containing compounds, hydrogen cyanide, pyridine bases, ammonia, and nitrogen. The third step results in the formation of hard coke by the progressive removal of hydrogen.

Gases evolved during coking leave the coke oven through the standpipes, pass into goosenecks, and travel through a damper valve to the gas collection main that directs them to the by-product plant. These gases account for 20 to 35 percent by weight of the initial coal charge and are composed of water vapor, tar, light oils, heavy hydrocarbons, and other chemical compounds (Coy et al. 1980).

The raw coke oven gas exits at temperatures estimated at 760° to 870°C and is shock cooled by spraying recycled "flushing liquor" into the collection

main. This spray cools the gas to 80° to 100°C, precipitates tar, condenses various vapors, and serves as the carrying medium for the condensed compounds. These products are separated from the liquor in a decanter and are subsequently processed to yield tar and tar derivatives, including pyridine, tar acids, napthalene, creosote oil, and coal tar pitch. The gas is then passed either to a final tar extractor or an electrostatic precipitator for additional tar removal. On leaving the tar extractor, the gas carries three-fourths of the ammonia and 95 percent of the light oil originally present when leaving the oven.

The ammonia is recovered either as an aqueous solution by water absorption or as ammonium sulfate salt. Ammonium sulfate is crystallized in a saturator which contains a solution of 5 to 10 percent sulfuric acid and is removed by an air injector or centrifugal pump. The salt is dried in a centrifuge and packaged.

The gas leaving the saturator at about 60°C is taken to final coolers or condensers, where it is typically cooled with water to approximately 24°C. During this cooling, some naphthalene separates and is carried along with the wastewater and recovered. The remaining gas is passed into a light oil or benzol scrubber, over which is circulated a heavy petroleum fraction called wash oil or a coal-tar oil which serves as the absorbent medium. The oil is sprayed in the top of the packed absorption tower while the gas flows up through the tower. The wash oil absorbs about 2 to 3 percent of its weight of light oil, with a removal efficiency of about 95 percent of the light oil vapor in the gas. The rich wash oil is passed to a countercurrent steam stripping column. The steam and light oil vapors pass upward from the still through a heat exchange to a condenser and water separator. The light oil may be sold as crude or processed to recover benzene, toluene, xylene, and solvent naphtha.

After tar, ammonia, and light oil removal, the gas undergoes a final desulfurization process at some coke plants before being used as fuel. The coke oven gas has a rather high heating value, on the order of 20 MJ/Nm^3 (550 Btu/scf). Typically, 35 to 40 percent of the gas is returned to fuel the coke oven combustion system, and the remainder is used for other heating needs.

Typically, one ton of coal will yield the following products:

Blast Furnace Coke	545-635 kg
Large Coke Particulates	49-90 kg
Coke Oven Gas	285-345 m^3
Tar	27.5-34 l
Ammonium Sulfate	7-9 kg
Ammonium Liquor	5-135 l
Light Oil	8-12.5 l

Human exposure to coke oven emissions occurs as a result of emissions released during the charging, coking (door, topside port, and offtake system leaks), and pushing operations. During these operations large quantities of sulfur dioxide, organic vapors, particulates, and coal tar pitch volatiles adsorbed to particulates, can be emitted to the atmosphere. A detailed list of constituents found in coke oven emissions is given in Table II-1.

TABLE II-1. PARTIAL LIST OF CONSTITUENTS OF COKE OVEN EMISSIONS
(U.S. EPA 1978a)

POLYNUCLEAR AROMATIC HYDROCARBONS

Anthanthrene
Anthracene
Benzindene
Benz[a]anthracene
Benz[b]fluoranthene
Benzo[ghi]fluoranthene
Benzo[j]fluoranthene
Benzo[k]fluoranthene
Benzofluorene
Benzo[a]fluorene
Benzo[b]fluorene
Benzo[c]fluorene
Benzo[c]phenanthrene
Benzo[ghi]perylene
Benzo[a]pyrene
Benzo[e]pyrene
Benzoquinoline
Chrysene
Coronene
Dibenz[a,h]anthracene
Dibenzo[a,h]pyrene
Dihydroanthracene
Dihydrobenzo[a]fluorene
Dihydrobenzo[b]fluorene
Dihydrobenzo[c]fluorene
Dihydrobenz[a]anthracene
Dihydrochrysene
Dihydrofluoranthene
Dihydrofluorene
Dihydromethylbenz[a]anthracene
Dihydromethylbenzo[k and b]fluoranthenes
Dihydromethylbenzo[a and e]pyrenes
Dihydromethylchrysene
Dihydromethyltriphenylene
Dihydrophenanthrene
Dihydropyrene
Dihydrotriphenylene
Dimethylbenzo[b]fluoranthene
Dimethylbenzo[k]fluoranthene
Dimethylbenzo[a]pyrene
Dimethylchrysene
Dimethyltriphenylene
Ethylanthracene
Ethylphenanthrene
Fluoranthene
Fluorene
Indeno[1,2,3-cd]pyrene
Methylanthracene
Methylbenzo[a]anthracene
Methylbenzo[a]pyrene
Methylbenzo[ghi]perylene
Methylchrysene
Methylfluoranthene
Methylfluorene
Methylphenanthrene
Methylpyrene
Methyltriphenylene
Octahydroanthracene
Octahydrofluoranthene
Octahydrophenanthrene
Octahydropyrene
Perylene
Phenanthrene
Indeno[1,2,3-cd]pyrene
Pyrene
Triphenylene

POLYNUCLEAR AZA-HETEROCYCLIC COMPOUNDS

Acridine
Benz[c]acridine
Dibenz[a,h]acridine
Dibenz[a,j]acridine

AROMATIC AMINES

α-Naphthylamine
β-Naphthylamine

TRACE ELEMENTS

Arsenic
Beryllium
Cadmium
Chromium
Cobalt
Iron
Lead
Nickel
Selenium

(continued on the following page)

TABLE II-1. (continued)

OTHER AROMATIC COMPOUNDS	OTHER GASES
Benzene	Ammonia
Phenol	Carbon disulfide
Toluene	Carbon monoxide
Xylene	Hydrogen cyanide
	Hydrogen sulfide
	Methane
	Nitric oxide

III. METABOLISM

A rather brief and general discussion of the metabolism of the classes of coke oven emission components shown in Table II-1 is presented in this section. The basis of discussion, particularly for classes besides polynuclear organic matter, are reviews on metabolism in the cited documents. As shown in Table II-1, coke oven emissions can contain a wide array of chemical components. Therefore, the toxicologic significance of any single component or class of components to the carcinogenic potential of coke oven emission samples is difficult to estimate without knowledge of the chemical composition of the samples, as well as the amount of each component absorbed and metabolized by humans. Additionally, the metabolic profile of a coke oven emission sample with respect to its components considered together as a group would appear to be quite difficult to determine. Nonetheless, evidence is presented herein to indicate that chemicals or classes of chemicals described in Table II-1 can contribute to the carcinogenic potential of coke oven emissions via metabolism to active carcinogenic agents.

POLYNUCLEAR ORGANIC MATTER (POLYNUCLEAR AROMATIC HYDROCARBONS AND POLYNUCLEAR AZA-HETEROCYCLIC COMPOUNDS)

Polynuclear organic matter (POM) are metabolized via enzyme-mediated oxidative mechanisms to form reactive electrophiles (Lehr et al. 1978). For many of the POM, certain "bioactivated" metabolites are formed that have the capability for covalent interaction with cellular constituents (i.e., RNA, DNA, proteins) and ultimately leading to mutation and carcinogenesis.

The obligatory involvement of metabolic activation for the expression of POM-induced carcinogenesis has prompted the investigation of POM metabolism in numerous animal models and human tissues. From these studies has emerged an

understanding of the general mechanisms involved in POM biotransformation. It is now known that POM are metabolized by the cytochrome P-450-dependent microsomal mixed-function oxidase (MFO) system, often designated aryl hydrocarbon hydroxylase (Conney 1967, Marquardt 1976, Sims 1976, Gelboin et al. 1972). The activity of this enzyme system is readily inducible by exposure to various chemicals and is found in most mammalian tissues, although primarily studied in the liver (Bast et al. 1976, Chuang et al. 1977, Andrews et al. 1976, Cohn et al. 1977, Wiebel et al. 1975, Grundin et al. 1973, Zampaglione and Mannering 1973). The MFO system is involved in the metabolism of endogenous substrates (e.g., steroids) and the detoxification of many xenobiotics. However, the MFO system also catalyzes the formation of reactive epoxide metabolites from certain POM, possibly leading to carcinogenesis in experimental mammals (Sims and Grover 1974; Selkirk et al. 1971, 1975; Sims 1976; Thakker et al. 1977; Levin et al. 1977; Lehr et al. 1978). A second microsomal enzyme, epoxide hydrase, converts epoxide metabolites of POM to vicinal glycols, a process which may also play a critical role in carcinogenic bioactivation. Figure III-1 presents a schematic representation of the various enzymes involved in activation and detoxification pathways for B[a]P. At present this also appears to be representative of the general mechanism for POM metabolism.

A discussion of the metabolism of POM in mammalian species, including man, is best approached by examining in detail the chemical fate of the most representative and well-studied compound in the POM class, namely B[a]P. The metabolism of B[a]P has been extensively studied in rodents (for a review, see Yang et al. 1978) and the results of these investigations provide useful data which can be directly compared to and contrasted with the results of more limited studies employing human cells and tissues. Therefore, separate

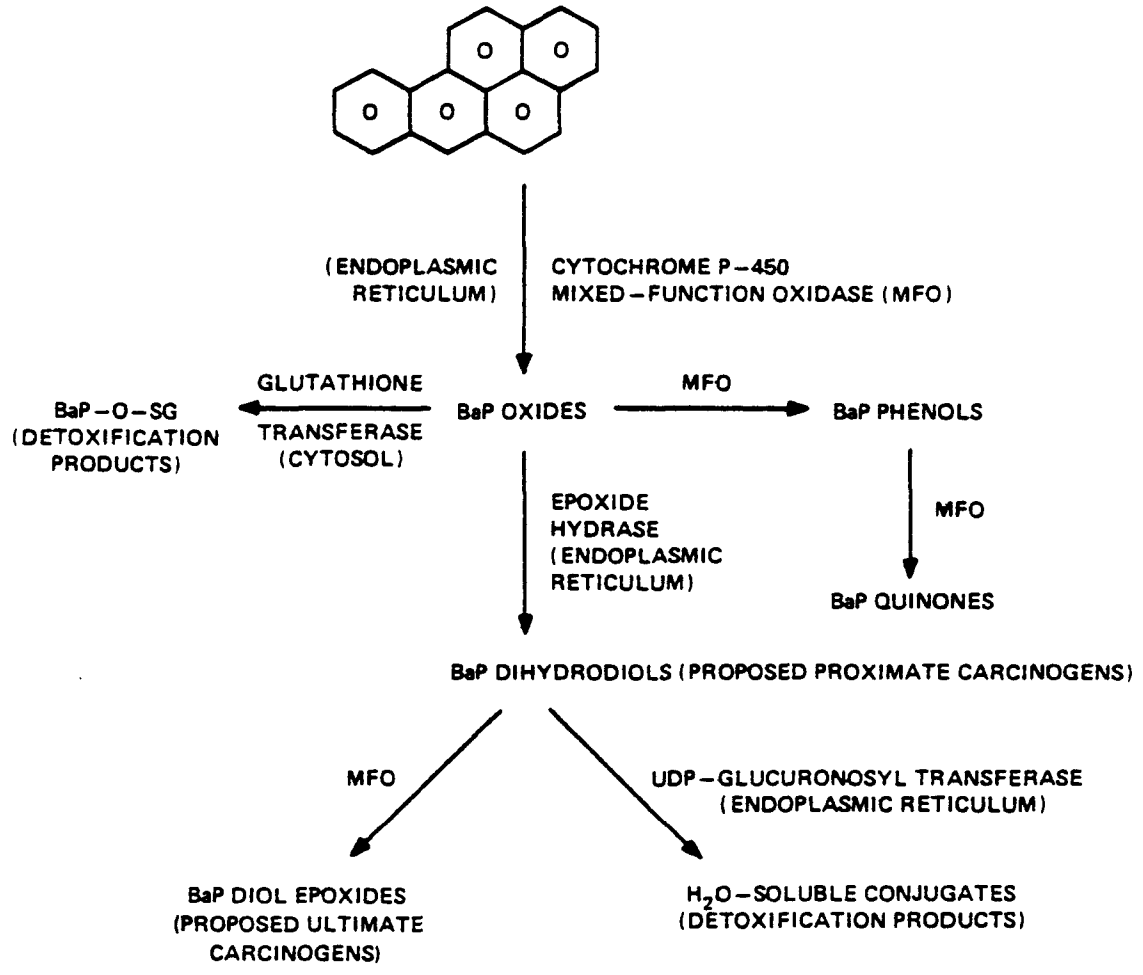


Figure III-1. Enzymatic pathways involved in the activation and detoxification of B[a]P (U.S. EPA 1979).

metabolism in general, and B[a]P metabolism in particular, in both animals and man.

The metabolites of POM produced by microsomal enzymes in mammals can arbitrarily be divided into two groups on the basis of solubility. In one group are those metabolites that can be extracted from an aqueous incubation mixture by an organic solvent. This group consists of ring-hydroxylated products such as phenols and dihydrodiols (Selkirk et al. 1974, Sims 1970), and hydroxymethyl derivatives of those POM having methyl groups, such as 7,12-dimethylbenz(a)anthracene (DMBA) (Boyland and Sims 1967) and 3-methylcholanthrene (3-MC) (Stoming et al. 1977, Thakker et al. 1978). In addition to the hydroxylated metabolites, are quinones produced by oxidation of phenols. Labile metabolic intermediates, such as epoxides, can also be found in this fraction (Selkirk et al. 1971, Sims and Grover 1974, Selkirk et al. 1975, Yang et al. 1978).

In the second group of POM metabolites are the water soluble products remaining after extraction with an organic solvent. Many of these derivatives are formed by reaction (conjugation) of hydroxylated POM metabolites with glutathione, glucuronic acid, and sulfate. Enzyme systems involved in the formation of water-soluble metabolites include glutathione S-transferase, UDP-glucuronosyl transferase, and sulfotransferases (Bend et al. 1976, Jerina and Daly 1974, Sims and Grover 1974). Conjugation reactions are believed to represent detoxification mechanisms only, although this group of derivatives has not been rigorously studied.

The metabolite profile of B[a]P, which has recently been expanded and clarified by the use of high pressure liquid chromatography (HPLC), is depicted in Figure III-2. This composite diagrams shows three groups of positional isomers, three dihydrodiols, three quinones, and several phenols.

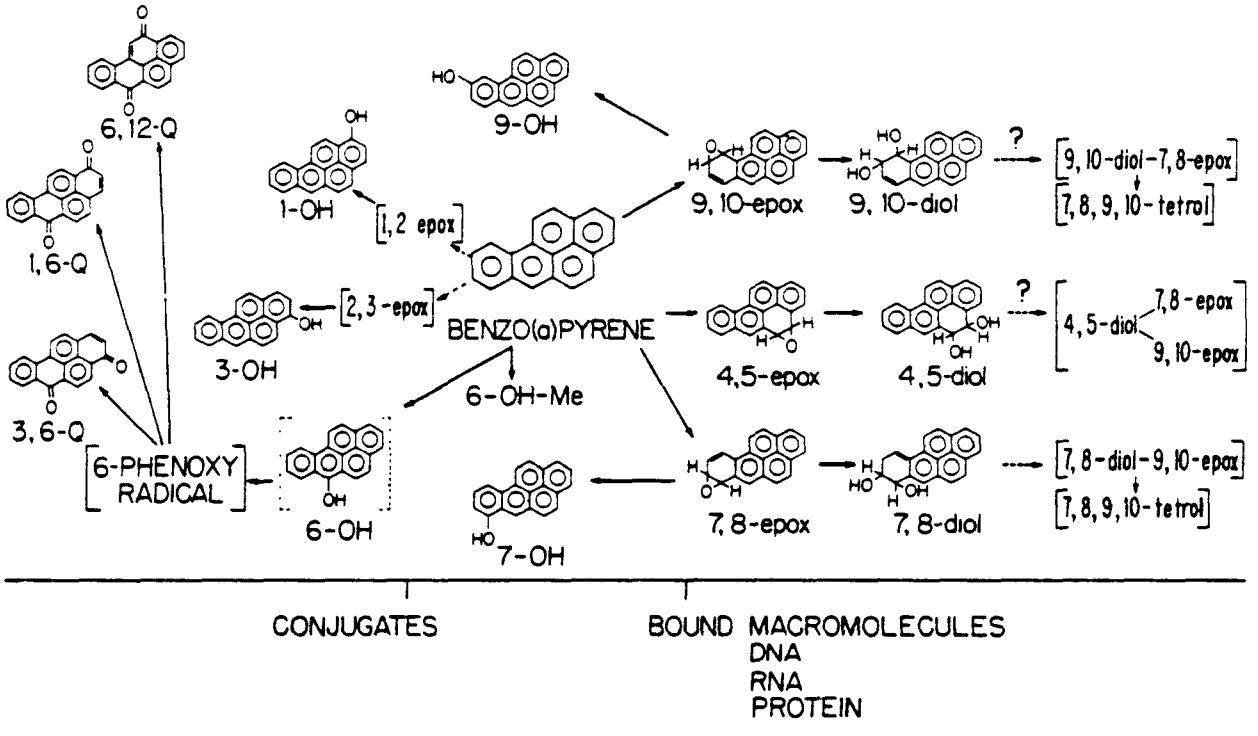


Figure III-2. Metabolites of benzo[a]pyrene (U.S. EPA 1979).

The major B[a]P metabolites found in microsomal incubations are 3-hydroxy-B[a]P, 1-hydroxy-B[a]P, and 9-hydroxy-B[a]P. The B[a]P-4,5-epoxide has been isolated and identified as a precursor of the B[a]P-4,5-dihydrodiol. Other studies indicate that epoxides are the precursors of the 7,8-dihydrodiol and 9,10-dihydrodiol as well. Considerable evidence has recently become available which implicates the stereospecific form of 7,8-dihydrodihydroxy-9,10-epoxy-B[a]P as an ultimate carcinogen derived from B[a]P (Jerina et al. 1976; Kapitulnik et al. 1977, 1978a, b; Levin et al. 1976; Yang et al. 1978).

Since the resonance properties of POM make ring openings difficult, enzymatic attack in the microsomes functions to open double bonds and add an oxygen-containing moiety, such as a hydroxyl group, to give it more solubility in aqueous media (e.g., urine) and thus facilitate removal from the body. In the formation of metabolic intermediates by oxidation mechanisms, relatively stable POM are converted to reactive metabolites (i.e., epoxides). Thus, nucleophilic attack of this reactive intermediate, through the formation of a transient carbonium ion, would be greatly enhanced. Arylations of this type are common to many classes of carcinogenic aromatic hydrocarbons. Therefore, the microsomal cytochrome P-450-containing MFO system and epoxide hydrase play a critical role in both the metabolic activation and detoxification of many constituents of POM.

Various forms of liver microsomal cytochrome P-450 can be isolated from animals treated with different enzyme inducers (Wiebel et al. 1973, Nebert and Felton 1976, Conney et al. 1977, Lu et al. 1978). Moreover, the metabolite profiles of B[a]P can be qualitatively altered depending on the type of cytochrome P-450 present in the incubation mixture (Wiebel et al. 1975). This observation has important implications in considering the carcinogenic action of certain POM toward tissues from animals of different species, sex, age,

nutritional status, and exposure to enzyme-inducing chemicals. Limited evidence is also available indicating that multiple forms of epoxide hydrase exist among animal species, which may also influence the pattern of POM metabolism with respect to carcinogenic bioactivation (Lu et al. 1978).

An important consideration in evaluating the health hazards of POM is whether metabolism in various animals tissues and species is indicative of the pattern of POM metabolism in the target organs of humans. Moreover, it is essential to determine whether differences occur in the metabolism of POM by: (a) different tissues in the same animal; and (b) different animals of the same species.

Numerous studies have shown that quantitative differences exist in the metabolism of B[a]P by different tissues and animals species (Sims 1976, Leber et al. 1976, Wang et al. 1976, Pelkonen 1976, Kimura et al. 1977, Selkirk et al. 1976). For the most part, however, interspecies extrapolation of qualitative patterns of POM metabolism appears to be a valid practice. On the other hand, marked differences in patterns of tissue-specific metabolism may prevent the reliable extrapolation of data from hepatic to extrahepatic (i.e., target organ) tissues. These differences may also exist in human tissues (Conney et al. 1976).

Freudenthal and coworkers (1978) examined the metabolism of B[a]P by lung microsomes isolated from the rat, rhesus monkey, and man. Their results confirmed previous observations regarding the existence of considerable species and intraspecies variation in B[a]P metabolism among samples from the same species. In addition, it was apparent that qualitative and quantitative interspecies variation also existed (Table III-1). Nevertheless, the qualitative differences between man and other animal species were by no means dramatic, and probably do not compromise the validity of extrapolations

TABLE III-1. METABOLITE PERCENTAGES OF B[a]P METABOLITES FROM RATS, RHESUS, AND HUMAN LUNG MICROSOMAL ASSAYS (Freudenthal et al. 1978)

	Metabolite Percentages (pmoles metabolite/pmoles total metabolites x 100)									
	Rat*			Rhesus †			Man †§			
Metabolite	1	2	3	1	2	3	1	2	3	4
Pre-9,10					3.0	5.3				
9,10-Diol	9.7	6.3	9.6	2.7	4.6	2.6		7.1	6.0	
A				1.5						
U¶	4.4	3.4	2.9	6.9		7.7	8.9	3.9	7.5	30.0
4,5-Diol	8.3	9.2	8.3	9.0	9.2	7.7	4.1			
7,8-Diol	5.3	5.2	8.0	4.2	8.6	5.1		15.0	13.3	9.9
1,6-Dione	4.4	7.5	8.3	11.4	14.8	12.8	24.9	11.6	12.6	4.4
3,6-Dione	7.8	8.0	9.9	14.5	16.0	20.5	22.5	13.8	19.2	8.5
6,12-Dione	6.8	8.6	8.6	11.8	8.0	15.3	22.5	18.3	27.4	15.7
9-OH	12.6	11.5	3.5	7.3			5.7	6.2		8.5
3-OH	40.8	40.2	41.1	30.8	35.9	23.1	11.4	24.0	13.9	22.9

*Lungs of five rats pooled for each group.

†Determinations made on lung samples from separate individuals.

§With the exception of subject 4, activity determinations were made using microsomes which had been stored at - 84°C.

¶The structural characteristics of unknown, U, may differ between species.

concerning POM metabolism.

Patterns of B[a]P metabolism in human lymphocytes and human liver microsomes are similar (Booth et al. 1974, Selkirk et al. 1975). However, in cultured human bronchus (24 hours) and pulmonary alveolar macrophages, an absence of phenols (i.e., 3-hydroxy-B[a]P) and paucity of quinones were observed (Autrup et al. 1978). Instead, a relative abundance of the trans-7,8-diol metabolite of B[a]P was demonstrated. This result is noteworthy in light of the possibility that the 7,8-diol is capable of further oxidative metabolism to an ultimate carcinogenic form of B[a]P. It is not known whether a longer incubation period would have changed the pattern of metabolite formation.

In summary, metabolism of constituents of POM is very complex although it is catalyzed by the enzyme systems involved in the metabolism of B[a]P and produces transient epoxide metabolites which, as a group, are known to be carcinogenic. Although interspecies and intraspecies variations exist in the metabolic profiles of aromatic hydrocarbons, there is evidence that similarities in the qualitative patterns of metabolism of these compounds among species allow interspecies extrapolations for the purpose of hazard assessment and risk estimation.

Several generalizations seem applicable to most unsubstituted polycyclic hydrocarbons, including the polynuclear aza-heterocyclic compounds identified in Table II-1 (U.S. EPA 1980a). Metabolic transformation may occur at saturated carbon atoms to form in sequence, alcohols, ketones, aldehydes, and carboxylic acids. More commonly, metabolic conversion at one or more aromatic double bonds (K-region and non-K-region) leads to formation of phenols or isomeric dihydrodiols through epoxide intermediates. Dihydrodiols can be further metabolized to diol epoxides. Active intermediates are removed by conjugation with glutathione or glucuronic acid or by further metabolism to

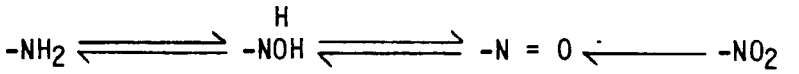
tetrahydrotetrols. Glutathione conjugates can be excreted in urine as mercapturic acid.

Jerina et al. (1977, 1980) have supported the "bay region" theory which proposes that diol epoxides can impart high biological activity when located on angular benzene rings of polycyclic (polynuclear) aromatic hydrocarbons and, furthermore, that the epoxide group forms part of the bay region in carcinogenic compounds of this class. The hindered region between the 10 and 11 positions in the benzo[a]pyrene molecule is an example of a bay region. Experimental data presented by Jerina et al. (1977, 1980) show that predicted chemical reactivity for positional isomers of benzene ring diol epoxides of specific polycyclic (polynuclear) aromatic compounds commonly correspond to their demonstrated mutagenic and tumorigenic activities. For example, Jerina et al. (1977) presented results from mutagenicity tests with Salmonella typhimurium TA 100 on diol epoxides derived from non-K-region dihydrodiols of benzo[a]anthracene to indicate a substantially greater mutagenic effect with benzo[a]anthracene 3,4-diol-1,2-epoxides (isomer 1 and 2) compared to corresponding 8,9-diol-10,11-epoxide isomers and 10,11-diol-8,9-epoxide isomers. Hence, it appears that, in aromatic hydrocarbons containing four or more benzene rings, the metabolic transformation of polycyclic (polynuclear) aromatic hydrocarbons to their ultimate carcinogenic (dihydrodihydroxyepoxy) forms is explainable by the bay region concept.

It should be noted that, according to Santodonato and Howard (1981), the metabolism of polynuclear aza-heterocyclic compounds per se largely remains to be investigated; therefore, the above generalizations on the metabolism of this class of compounds are mainly inferred from known metabolic characteristics of their homocyclic analogs, the polynuclear aromatic hydrocarbons.

AROMATIC AMINES

A general discussion on the metabolism of aromatic amines, which include α- and β-naphthylamines, is presented in a National Research Council (1981) assessment document on aromatic amines and is summarized herein. Aromatic amines are primarily metabolized by oxidation, and oxidation at the nitrogen atom or at carbon atoms in the aromatic ring may occur. Oxidation of primary amines may occur according to the following scheme:



amine hydroxylamine nitroso nitro

Little evidence is available to indicate that aromatic amines are oxidized to nitro compounds. Secondary and tertiary amines are also oxidized at the nitrogen atom. Dealkylation of tertiary to secondary amines may occur, and hydroxylamines may be formed from partial N-dealkylation of secondary amines.

Hydroxylation of the aromatic ring results from activation of the free amine group in aromatic amines. Primary hydroxylation occurs at the three position of 1-naphthylamine and the one position of 2-naphthylamine.

Transformation of aromatic amines to metabolites that can react with cellular macromolecules can occur by an initial oxidation at the nitrogen atom followed by a second activation.

Probably the main detoxification route is conjugation of the hydroxyl groups of metabolites of aromatic amines with glucuronic acid. Aromatic amines can also be conjugated with sulfate, and primary amines can be acetylated by several animal species.

OTHER AROMATIC COMPOUNDS

Benzene metabolism is summarized in a U.S. EPA (1980b) water quality criteria document. Benzene is metabolized to phenol as well as catechol and hydroquinone. The major hydroxylation product is phenol, most of which is found in urine conjugated with ethereal sulfate or glucuronic acid. Phenylmercapturic acid and muconic acid also have been found as urinary metabolites. The formation of phenol through an epoxide intermediate of benzene has been proposed. Additional metabolic transformations for the proposed epoxide intermediate of benzene include hydration and subsequent oxidation to form catechol and conjugation to form premercapturic acid. Hydroquinone production from mixed-function oxidase activity on phenol is also possible. In humans, conjugation of phenol has been found to occur largely with sulfate at low levels of benzene exposure and increasingly with glucuronide with increasing benzene exposure.

The metabolism of phenol is summarized in a U.S. EPA (1980c) water quality criteria document. Phenol is almost completely metabolized in humans with the four main metabolites as sulfate and glucuronide conjugates of phenol and hydroquinone. In rabbits, most phenol is oxidized to carbon dioxide and water plus traces of 1,2-dihydroxybenzene and 1,4-dihydroxybenzene or is excreted in urine as free or conjugated phenol.

As described in a Carcinogen Assessment Group (1980a) draft report on toluene, the major pathway for toluene metabolism involves oxidation of the methyl group to benzyl alcohol with further oxidation to benzaldehyde and benzoic acid. Benzoic acid is mainly conjugated with glycine in the liver to form hippuric acid. Small amounts of toluene may be converted to phenols (4-cresol, 2-cresol) via an epoxide intermediate.

Xylene metabolism is described in a U.S. EPA (1980d) hazard profile on

xylene. Xylene isomers (m-, o-, p-) can be oxidized to the corresponding methyl benzoic acid which is conjugated with glycine or glucuronic acid. Xylene isomers can also undergo ring hydroxylation to corresponding xylenols (dimethylphenols) which can also be conjugated to form glucuronides or ethereal sulfates. Methyl hippuric acid, a glycine conjugate of methyl benzoic acid, has been found as the main urinary metabolite in experiments on m- and p- xylenes. Paratolualdehyde has been identified as a metabolite of p-xylene.

TRACE ELEMENTS

Metabolic transformation generally does not appear to serve a major role in toxification/detoxification of the trace elements (metals) identified in Table II-1. Discussion of this issue is summarized from U.S. EPA (1980e-j) water quality criteria documents on the specific elements and from Venugopal and Luckey (1978).

Pentavalent and trivalent arsenic is metabolically transformed mainly to dimethylarsinic acid. Methylation of inorganic arsenic can serve as a detoxification mechanism. The nature of the conversion of the pentavalent form to the trivalent form, which can occur *in vivo*, remains unclear. Trivalent arsenic can readily bind to tissue macromolecules at, for example, sulfhydryl and hydroxyl groups, whereas pentavalent arsenic is less readily bound (U.S. EPA 1980e).

Beryllium can bind to inhibit several enzymes and it can be concentrated in cell nuclei. The bulk of circulating beryllium is in the form of colloidal phosphate probably absorbed on plasma α-globulin. Relatively minor amounts of beryllium can be combined in a diffusible form with organic acids such as citrate or phosphate (U.S EPA 1980f).

Circulating chromium is mainly bound in a nondiffusible form with proteins. At low levels, trivalent chromium is mainly bound to the iron-binding protein, siderophilin. Chromium can presumably penetrate cells in a hexavalent state and subsequently react with cell components. Tetravalent chromium is reduced to trivalent chromium in cells. The chemical form of chromium influences its pattern of biodistribution (U.S. EPA 1980g).

Cadmium has no known function in metabolism. It can be bound to metallothionein protein, especially in erythrocytes, liver, and kidney. Cadmium in plasma is bound to high-molecular-weight proteins (U.S. EPA 1980h).

Cobalt can be retained in several tissues. Cobalt stored in intestinal mucosa can be lost through epithelial desquamation. Cobalt can be eliminated from the body as a cobalt-histamine complex (Venugopal and Luckey 1978).

Orally administered iron is absorbed across the gastrointestinal mucosal epithelium by a mediated transfer mechanism. Most circulating iron is bound to transferrin. Iron is primarily stored as ferritin or hemosiderin in liver, bone marrow, and spleen (Venugopal and Luckey 1978).

Lead is mainly deposited in bone and smaller amounts are stored in soft tissues (Venugopal and Luckey 1978).

Nickel is stored in body tissues and can be bound to metalloprotein (U.S. EPA 1980i).

Little is known about selenium biochemistry in mammalian systems. At nutritional levels selenium is incorporated into specific functional proteins; at higher levels selenium can bind to molecules normally combined with sulfur. The main urinary metabolite of selenium is trimethylselenium ion. Inorganic selenium usually does not combine with amino acids (U.S. EPA 1980j). Selenium can also function as an inhibitor of tumor induction by chemical carcinogens.

OTHER GASES

Ammonia can be converted to urea in the liver. Ammonia is also formed endogenously by deamination of amino acids and amides and by bacterial conversion of urea in the gut (U.S. EPA 1980k).

Carbon disulfide is lipid soluble and binds to proteins. It can react reversibly with amino acids to yield thiocarbamates. Sulfur released during desulfuration of carbon disulfide can form covalent bonds with other sulfur radicals. Carbon disulfide metabolites in human urine include mainly thiourea and also mercaptothiazolinone and possibly 2-mercapto-thiazoline-4-carbamic acid. It can be desulfurated in the liver to form carbonyl sulfide which is further oxidized to form CO_2. Bivalent sulfur can also be formed which is oxidized to sulfate (World Health Organization 1979).

Carbon monoxide combines with hemoglobin to form carboxyhemoglobin, and it can also reversibly bind with cellular heme groups (U.S. EPA 1980l).

The main metabolic pathway for hydrogen cyanide is conversion to thiocyanate via rhodanase. Minor pathways include conjugation of cyanide with cysteine to form 2-iminothiazolidene-4-carboxylic acid, binding of cyanide with hydroxocobalamin, and excretion of unchanged hydrogen cyanide through the lungs. Cyanide can also be converted to formate and carbon dioxide (U.S. EPA 1980m).

Hydrogen sulfide can be detoxified by oxidation to inorganic sulfur on interaction with oxyhemoglobin. Sulfide ions can be oxidized to sulfate or thiosulfate ions (Roy and Trudinger 1970).

The nature of absorption and biodistribution of nitric oxide is presently unknown; however, nitric oxide can react with hemoglobin to form methemoglobin and nitrosylhemoglobin (Goldstein et al. 1980). Nitric acid is known to react *in vivo* with amines to yield N-nitrosamines, many of which are known animal carcinogens (Magee et al. 1976).

IV. MUTAGENICITY* AND CELL TRANSFORMATION

The objective of this mutagenicity evaluation is to determine whether or not coke oven emissions have the potential to cause somatic mutations in humans. This evaluation is a qualitative assessment based on two kinds of available information: (1) data concerning the mutagenic potential of the complex mixture of coke oven door emissions and the complex mixture from the coke oven collecting main, and (2) data concerning the mutagenic potential of the individual components that have been identified in coke oven emissions. To briefly summarize the findings, the complex mixture of organics extracted from coke oven door emissions was detected as mutagenic in bacteria. The solvent-extracted organics of the material sampled from the coke oven collecting main caused mutations in bacteria and mammalian cells in culture. Chemical analysis of coke oven emissions has revealed the presence of several components (e.g., certain polynuclear aromatic hydrocarbons, aza-heterocyclic compounds, aromatic amines, etc.) known to be genotoxic when evaluated individually in various mutagenicity tests. In addition, there are studies that show that air particulates collected topside of coke oven batteries are mutagenic in bacteria and mammalian cells in vitro. The available data concerning the mutagenicity of coke oven emissions and air particulates collected topside of coke ovens are discussed below.

STUDIES EVALUATING SOLVENT-EXTRACTABLE ORGANICS OF COKE OVEN DOOR EMISSIONS

Data concerning the potential mutagenic hazard of coke oven emissions is limited to one bacterial study sponsored by the U.S. Environmental Protection Agency's Office of Research and Development (U.S. EPA 1977b). In this study, a sealed hood was fitted over the door of a coke oven, and emissions leaking

*Prepared by the Reproductive Effects Assessment Group.

from the coke oven door were collected during an approximately 13-hour coking cycle. Particulate emissions were collected on the filter of a high volume sampler and volatile organics were collected on a Tenax-GC adsorbent column. Several samples were collected representing different time segments of the coking cycle (as shown below). Samples collected later in the coking cycle represent longer time segments because emissions from the doors decreased as time increased into the coking cycle.

Sample Extracts		Length of Sampling Segments
Absorbent	Filter	(hr)
A1	A1F	1 (represents the first hour of the coking cycle)
A3	A3F	2 (represents the beginning of the third hour up to the fifth hour)
A5	A5F	5 (represents the beginning of the ninth hour through the thirteenth hour)
A6	--	-- compressor air supply (blank)

The adsorbent column samples were soxhlet-extracted with the nonpolar solvent pentane for 24 hours and the filter samples were soxhlet-extracted sequentially with the more polar solvents methylene chloride and methanol (approximately 3 days). The seven sample extracts were evaluated at seven concentrations ranging from 5 ul to 10.0 ul of sample (in 50 ul of DMSO) in the Salmonella/mammalian microsome plate incorporation assay using the standard tester strains TA 100, TA 98, TA 1535, TA 1537, and TA 1538. Positive responses in TA 98 were observed without S-9 mix for the filter extract samples A1F, A3F, and A5F (see Figure IV-1 A). A weak positive response (twofold increase) was observed in TA 1538 (minus S-9 mix) for the filter extract A1F. The addition of S-9 mix (prepared from rat livers)

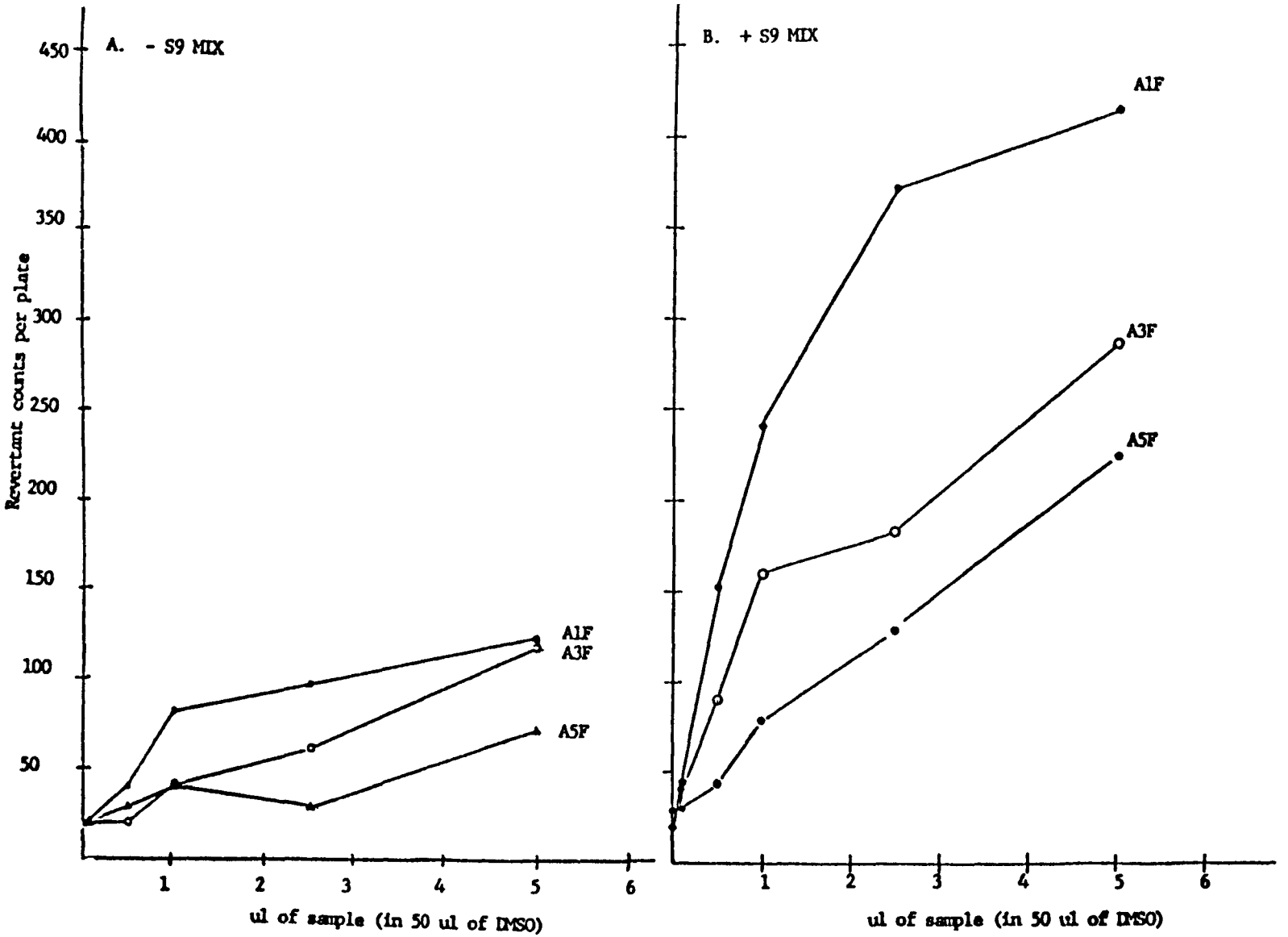


Figure IV-1 A, B. The mutagenic activity of coke oven door emissions (A, in the absence of metabolic activation; B, in the presence of metabolic activation). Emissions were collected over an approximately 13-hour coking cycle and evaluated in the Salmonella/mammalian microsome assay using TA 98. Sample A1F represents the first hour of the coking cycle, sample A3F represents a 2-hour segment from the beginning of the third hour up to the fifth hour of the coking cycle, and sample A5F represents a 5-hour segment from the beginning of the ninth hour through the thirteenth hour of the coking cycle (taken from U.S. EPA 1977b).

greatly enhanced the mutagenic response for all filter extract samples in strains TA 98, TA 100, TA 1538, and TA 1537. The filter extracts were not as active in TA 100 as they were in the other tester strains. These responses appeared as concentration-related increases in revertant colonies (see Figure IV-1 B). "Toxic effects" were reported for sample A5F at 10 ul. A1F, A3F, and A5F were not detected as mutagenic in the base-pair substitution sensitive strain TA 1535 in the absence or presence of S-9 mix.

The adsorbent column extracts A1, A3, A5, and A6 (compressor air supply) were evaluated for mutagenicity in the same manner as the filter extracts. No mutagenic activity was detected in the absence of S-9 mix. In the presence of S-9 mix, the absorbent column extracts A1 and A3 were detected as weakly mutagenic in frameshift-sensitive strains. Sample A1 was detected as positive in the frameshift-sensitive strain TA 1537, whereas in the other strains (TA 1538, TA 98, and TA 100), the responses were similar to the spontaneous revertant counts, or the positive responses that were reported either appeared as nonreproducible or not concentration-related. Sample A3 was detected as weakly positive in strains TA 1537 and TA 1538, but was not detected as mutagenic in strains TA 98 and TA 100. The mutagenicity of sample A5 was inconclusive because the positive responses reported were not reproducible. "Toxic effects" were reported for A5 at the high concentrations. The absorbent extracts were not detected as positive in TA 1535 with or without S-9 mix. The compressor air supply sample (A6) was not detected as positive under any of the treatment conditions. It should be emphasized that volatile components were collected on the absorbent column and that highly volatile components may not be effectively detected as mutagenic unless precautions are taken to prevent excessive evaporation and thus ensure exposure to the indicator organisms. Such measures were not reported to have been taken for

the absorbent extracts.

The above study of solvent-extracted organics of filter and absorbent samples demonstrated that coke oven door emissions caused frameshift mutations in bacteria. The mutagenic responses required or were enhanced by a mammalian microsomal activation system. This finding is consistent with mutagenicity studies of several individual components identified in the complex mixture as frameshift-acting mutagens requiring metabolic activation. Information on the mutagenicity of individual constitutents will be summarized later in this section.

STUDIES EVALUATING THE COMPLEX MATERIAL FROM THE COKE OVEN COLLECTING MAIN

In addition to the study on coke oven door emissions, a related complex material was sampled by EPA (Huisingh et al. 1979) from a coke oven collecting main (where the coke oven gas resulting from carbonization cools and condenses). This sample was collected from a separator collector located between the gas collector main and the primary coolers within the coke oven battery (Huisingh 1981, unpublished) at the same coke plant (located in Gadsden, Alabama) used by Huisingh et al. (1979) to sample air particulates topside of a coke oven battery referred to later. The coke oven main sample was dissolved in DMSO to test in a variety of in vitro mutagenicity assays. It should be noted that although this complex mixture is derived from coke oven emissions condensate and contains similar components, it is still qualitatively and quantitatively different in composition from coke oven emissions.

The coke oven main sample was tested twice in the Salmonella/microsome plate incorporation assay on separate days using tester strains TA 1535, TA 100, TA 98, TA 1538, and TA 1537 (Claxton and Huisingh 1981, unpublished). This coke oven condensate was not detected as mutagenic in the base-pair substitution-sensitive strain TA 1535 in the absence of S-9 mix up to a concentration of 500 ug/plate of test material (precipitate formed at this concentration) or in the presence of S-9 mix (livers were prepared from Aroclor-induced rats) up to a concentration of 100 ug/plate of test material. The frameshift-sensitive strains TA 1537, TA 1538, and TA 98 gave marginal responses in the absence of S-9 mix (twofold or less increase in revertant colonies above the spontaneous values) at the highest concentrations examined. However, these responses were interpreted as inconclusive because they did not appear as reproducible or concentration-related. Strain TA 100, a base-pair substitution-sensitive strain that is also sensitive to frameshift mutagens (McCann et al. 1975), was weakly reverted (approximately twofold increase in revertants above the solvent control counts) without metabolic activation in two different trials. When S-9 mix was incorporated in the assay, the number of revertant colonies per plate was greatly increased above the spontaneous values for strains TA 100, TA 1538, and TA 98. These positive responses appeared as concentration-related increases in revertant colonies and were reproducible. Therefore, from these studies, it appears that the coke oven main sample was primarily detected as indirect-acting in frameshift-sensitive strains.

Mitchell (1981, unpublished) evaluated the ability of the coke oven main sample to induce gene mutations in L5178Y mouse lymphoma cells with and without a rat liver microsomal activation system (S-9 mix prepared from livers of Aroclor-induced rats). The concentrations evaluated (in duplicate) in the

absence of metabolic activation ranged from 0.5 ug/ml to 50 ug/ml in one experiment, 30 ug/ml to 70 ug/ml in another, and 20 ug/ml to 150 ug/ml in a third experiment. At 50 ug/ml, 70 ug/ml, and 150 ug/ml, total relative growths* of 70%, 61%, and 21%, respectively, were reported. Concentrations above 70 ug/ml were reported to form a precipitate. Concentrations ranging from 0.5 ug/ml to 70 ug/ml did not increase the frequency of mutant colonies over that of the solvent control by more than twofold. In an assay in which the test material was evaluated up to 150 ug/ml, a fourfold increase in mutant colonies over the solvent control frequency was reported at 150 ug/ml. However, precipitates in samples from concentrations of 60 ug/ml to 150 ug/ml were reported to be "overlooked" by the investigators during the exposure and wash steps and not noticed until later. Because these precipitates may have been present during the expression and selection periods of the test, the interpretation of the dose-dependent response is difficult. Thus, based on these data, it is inconclusive whether or not the test sample was mutagenic in the absence of S-9 activation. In the presence of metabolic activation, however, the test material was mutagenic in two separate trials. Because the test material was more cytotoxic in the presence of metabolic activation than in its absence, the retesting of the material for its ability to induce mutant colonies was conducted over a narrow range of concentrations (0.5 ug/ml to 10 ug/ml). At concentrations (5 ug/ml, 6 ug/ml, and 8 ug/ml) that did not appreciably reduce total relative growth less than 30%, approximately twofold to threefold increases in mutant colonies above the spontaneous frequencies (solvent control) were reported.

The genetic effects of the coke oven main sample were also determined in a

*Percentage of relative total growth = (relative suspension growth/relative cloning efficiency) x 100.

Saccharomyces cerevisiae D3 preincubation assay for mitotic recombination (Mortelmans et al. 1980, unpublished). Prior to plating in agar, yeast cells were preincubated with the test material at a concentration range of 50 ug/plate to 5,000 ug/plate for 2 hours in the absence or presence of S-9 mix. When tested twice under the above conditions, recombinogenic activity did not differ from the solvent control and no toxic effects were reported. It should be noted that the known mutagens benzo[a]pyrene and 2-nitrofluorene were also detected as negative in this assay. The concurrent positive control 1,2,3,4-diepoxybutane, a direct-acting mutagen, greatly enhanced recombinogenic frequency, thus indicating the system was working properly without S-9 activation. Therefore, these negative results are most likely a reflection of the sensitivity of the assay.

Even though the coke oven collecting main sample is not a true representative sample of coke oven emissions, it does contain similar components that may be emitted. Thus, the mutagenic responses observed in bacteria and in mammalian cells in culture are considered as supportive evidence for the mutagenicity of coke oven emissions.

STUDIES EVALUATING SOLVENT-EXTRACTABLE ORGANICS OF AIR PARTICULATES COLLECTED ON TOP OF COKE OVENS

Although these are not studies of "pure" coke oven emissions per se, two reports discussed below have bearing on the mutagenicity of coke oven emissions. These studies show that air particulate samples collected topside of coke ovens are mutagenic in in vitro bioassays.

In a study conducted in Japan, the relative mutagenic activity was concurrently determined for air particulates from a coke mill and other industrial areas and for ambient air particulates from various residential areas (Tokiwa et al. 1977). Air particulates were collected on glass fiber

filters for 24 hours or 48 hours from six different locations in industrial areas of Ohmuta City and from six different locations in residential areas of Fukuoka City using a high air-volume sampler.*

A high air-volume sampler would collect all particle sizes, i.e., respirable (< 1.7 um in diameter), nonrespirable (> 5 um), and noninhalable (> 15 um). Information concerning sample collection (e.g., wind-direction during sampling) was not provided in the report. Although the position of the samplers also was not described in the report, Tokiwa (1981, unpublished) indicated in a letter to the Reproductive Effects Assessment Group (REAG)† that the sampler at the coke mill (sample 123) was located on top of a coke oven for 48 hours. For the other industrial samples, Tokiwa only indicated that collection points were around "several factory [sic] in the city." The residential samples were collected in heavily trafficked areas. The organics bound to the air particulates were soxhlet-extracted with methanol for 8 hours. Because methanol is a polar solvent, it will preferentially extract more polar types of organics from the air particles. It should be noted that Jungers et al. (1980) have found methanol to be less effective at extracting mutagens from air particulates than dichloromethane (the solvent used in a study by Huisingh et al. 1979, which is discussed later). The methanol extracts were evaporated to dryness and dissolved in DMSO for mutagenicity testing in the Salmonella/microsome assay using tester strains TA 1535, TA 1536, TA 1537, TA 1538, TA 100, and TA 98 with and without a mammalian activation system (S-9 mix prepared from livers of Aroclor-induced rats). The authors stated in the report that in the absence or presence of S-9 mix, the

*Ohmuta and Fukuoka are within approximately 80 miles of each other.

†A written request was made to Tokiwa to secure information concerning the location of the samplers.

solvent-extracted organics of air particulates collected topside of a coke oven were not detected as mutagenic in the base-pair substitution-sensitive strains TA 1535 and the frameshift-sensitive strain TA 1536, but were mutagenic for the frameshift-sensitive strains TA 1537, TA 1538, TA 98, and the base-pair substitution-sensitive strain TA 100, which is also sensitive to certain frameshift-acting mutagens. The data generated in the presence of S-9 mix are illustrated in Figure IV-2. The extracted organics were most active in strain TA 98. Although the authors indicate in the report that the topside coke oven sample was evaluated without S-9 mix, they do not report the results. Towika (1981, unpublished) indicated that the positive responses observed in the absence of S-9 activation "was very low." Thus, it appears that the mutagenicity of this complex mixture was primarily detected as indirect-acting. Chemical analysis (GC/MS analysis) of the topside coke oven sample revealed the presence of several polycyclic aromatic hydrocarbons known to be frameshift-acting mutagens requiring metabolic activation (e.g., chrysene, dibenzoanthracenes, benzoanthracenes, benzopyrenes, benzofluoranthenes).

In the report by Tokiwa et al. (1977), it was found that air particulates from industrial areas, particularly those collected topside of a coke oven, were more mutagenic than air particulates from residential environments. As shown in Table IV-1, the mutagenic activity in strain TA 98 (in the presence of S-9 mix) of air particulates collected topside of a coke oven in Ohmuta and other industrial sources is compared with the mutagenic activity of ambient air particulates from residential areas.* This comparison was based on data expressed as revertants per cubic meter (m^3) of air. The authors do not

*It should be noted that the mutagenic activity of ambient air may vary over time and with weather conditions.

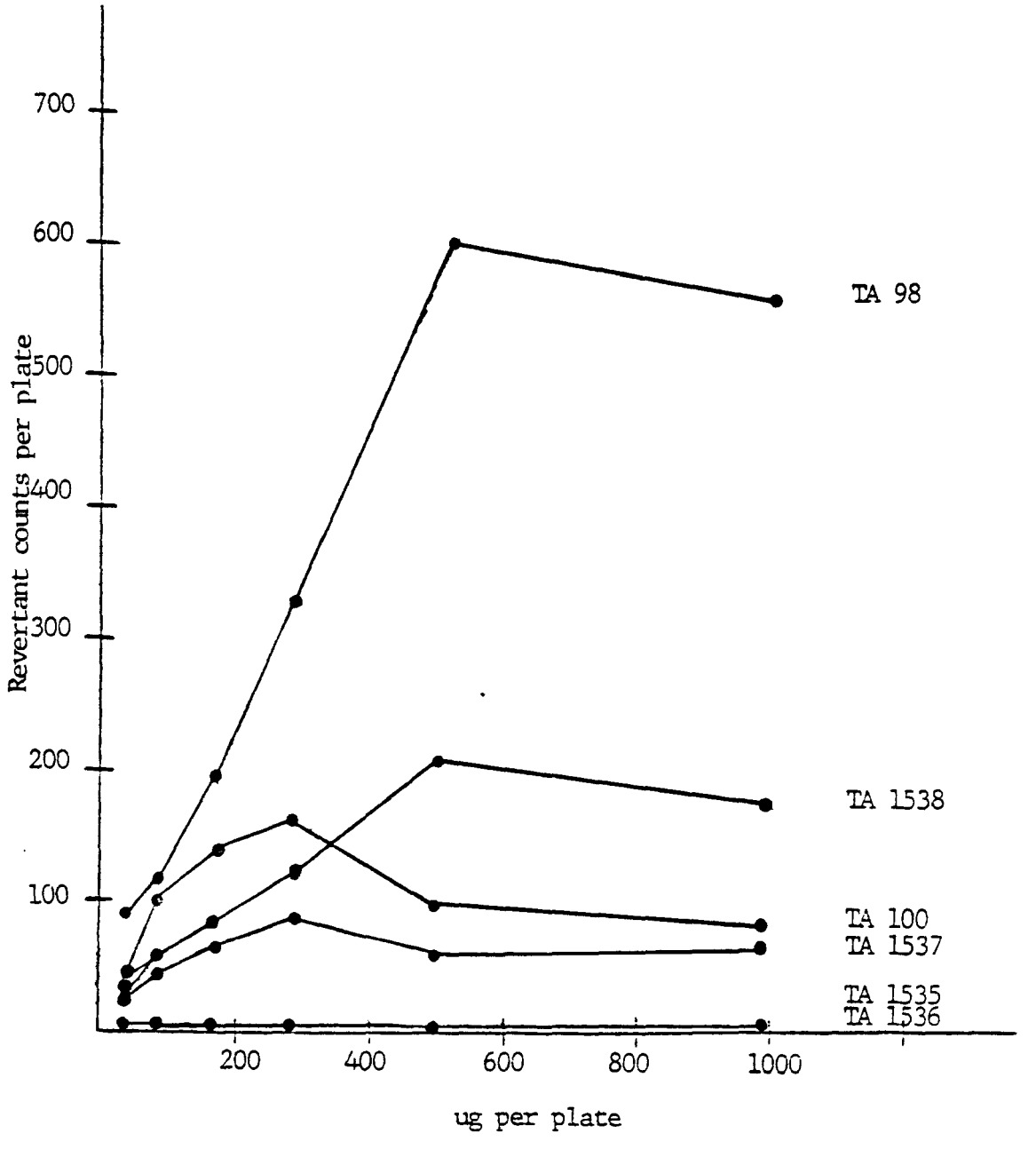


Figure IV-2. Mutagenic activity of methanol extracts of air particulates collected topside of a coke oven. The extracted sample was evaporated and diluted in DMSO for evaluation in the Salmonella/mammalian microsome assay in the presence of S-9 mix (taken from Tokiwa et al. 1977).

TABLE IV-1. SUMMARY OF THE MUTAGENIC ACTIVITY IN SALMONELLA TYPHIMURIUM OF ORGANICS EXTRACTED FROM AIR PARTICULATES COLLECTED IN INDUSTRIAL AND RESIDENTIAL AREAS OF JAPAN*

Sample Number	Revertants per m^3 air
Industrial Areast	
123 (coke mill)	445.0
160	288.0
161	94.0
162	22.2
163	138.0
164	103.0
Residential Areas§	
86	12.4
152	77.6
21	12.3
150	52.4
64	13.2
126	7.1

*Samples were collected in the industrial areas of Ohmuta and residential areas of Fukuoka. The mutagenicity of samples was evaluated with Salmonella typhimurium TA 98 in the presence of S-9 mix (taken from Towika et al. 1977).

†Sample numbers 161, 163, and 164 were not identified except as industrial areas. Sample 160 was identified as ambient air collected in the middle of factory districts. Sample 162 was identified as a sample collected far from the factory districts.

§Samples were identified only as residential areas at heavily trafficked locations.

discuss how the values for revertants/m^3 were derived. It appears from the report that the number of revertants per m^3 of air was determined only from the highest concentrations tested for each sample and that the mutagenic activities were not expressed as the slope of the dose-response curves (i.e., number of revertants per ug increase in concentration). Determination of the slopes of the dose-response curve provides a better reflection of the mutagenic potency rather than simple selection of one dose point from the dose-response curve. However, from examination of the dose-response curves illustrated in the report and reproduced in Figure IV-3, all of the samples from residential areas and the topside coke oven sample (123) caused linear dose-responses in strain TA 98. Thus, the mutagenic activity (i.e., revertants/m^3) determined from the highest concentration tested should be very similar to the mutagenic activity expressed as the slope of the linear dose-response curve. However, because some of the industrial samples follow a nonlinear response* at the high concentrations tested, regression analyses are necessary to determine if the topside coke oven sample is significantly different than some of the other industrial sources. Therefore, this study shows that, the mutagenic activity (expressed as revertants per m^3 of air)† of solvent-extracted organics of air particulates collected topside of a coke oven is 6- to 63-fold higher than the mutagenic activity of organics extracted from ambient air collected at trafficked locations in residential areas.

Air particulates also have been collected topside of a coke oven battery

*One major problem with evaluating complex environmental mixtures in the Ames test (or other short-term tests) is high toxicity. Many times the dose-response follows a nonlinear pattern at higher concentrations (Stead et al. 1981).

†The topside coke oven sample also appeared more mutagenic than residential samples (but not for the other industrial sources) when the data were expressed as revertants/ug.

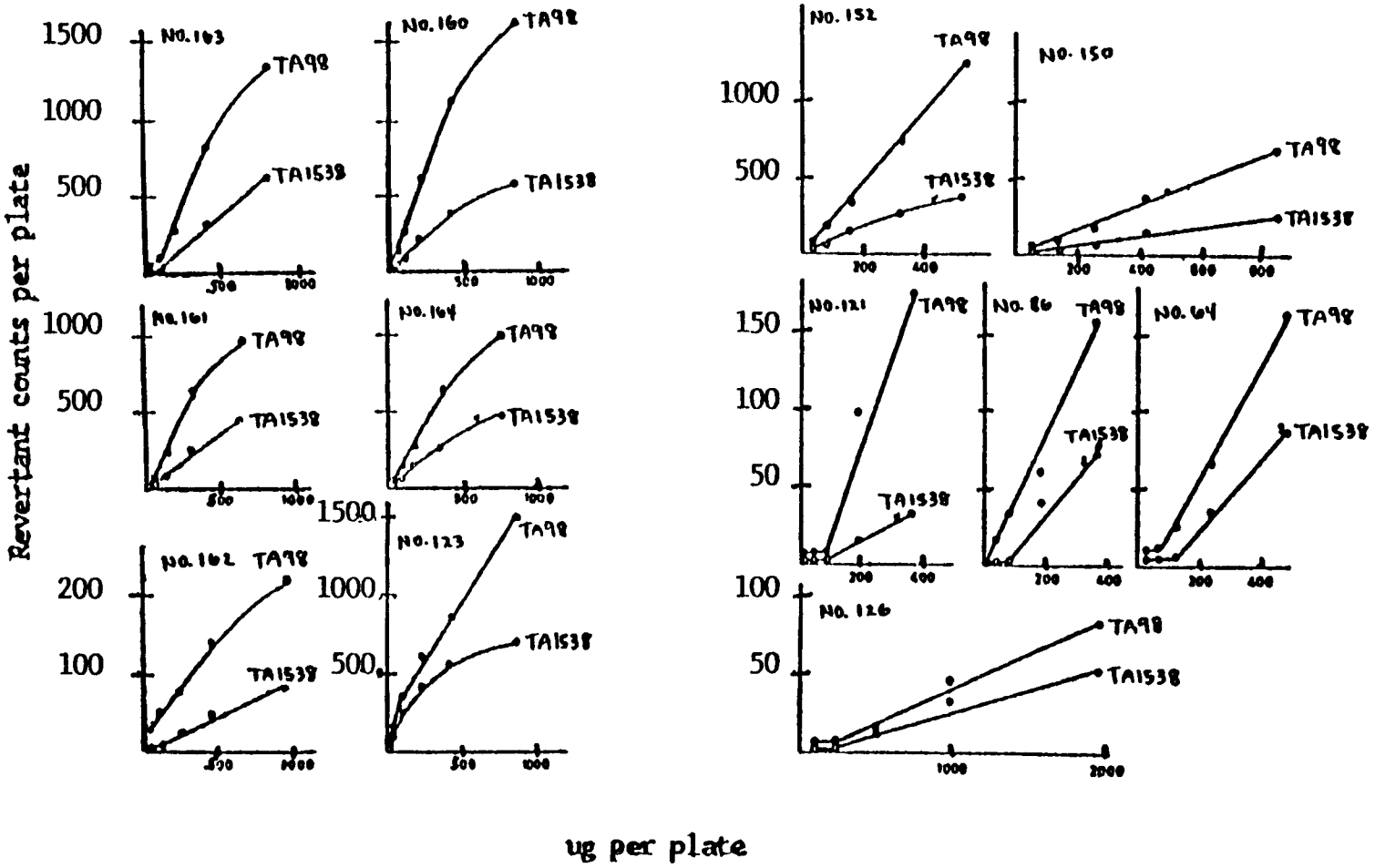


Figure IV-3. The dose-response curves from the Salmonella/mammalian microsome assay of each sample collected in industrial areas of Ohmuta (A) and in residential areas of Fukuoka (B). Sample 123 represents air particulates collected topside of a coke oven. The spontaneous revertant counts have been subtracted (taken from Towika et al. 1977).

located in Gadsden, Alabama (Huisingh et al. 1979). Huisingh (1981, unpublished) described this coke oven battery as "a newer generation of coke ovens designed to reduce fugative coke oven emissions." Air particulates (size < 1.7 um) were collected for approximately 2100 hours on electrostatic precipitator plates of two massive air volume samplers (collection rate 17.3 m^3/min each) positioned side by side at one end of a coke oven battery. The organics bound to the particulate matter were soxhlet-extracted with dichloromethane (DCM) and tested for their mutagenic potential in several *in vitro* bioassays by different investigators. This topside coke oven sample was found to cause point mutations in *Salmonella typhimurium* and gene mutations, sister chromatid exchange formation, and DNA strand breaks in mammalian cells in culture. These results are briefly described below.

Concentration-related increases in revertant counts were reported with the frameshift-sensitive strain TA 98 when the topside coke oven extract was tested at 25, 75, 125, 250, 750, and 1250 ug/plate (Claxton 1979 and unpublished data). A positive response was also reported for strain TA 100. The addition of S-9 mix (prepared from livers of Aroclor-induced rats) slightly increased the mutagenic response (an approximately twofold increase in revertant colonies above those induced in the absence of S-9 mix) in TA 98 but not in TA 100. Negative results were reported for the base-pair substitution-sensitive strain TA 1535 in either the presence or absence of S-9 mix.

Mitchell et al. (1979) examined the ability of the topside coke oven extract to cause gene mutations using L5178Y mouse lymphoma cells. Following a fixed treatment time (4 hours), a concentration-related increase in trifluorothymidine-resistant colonies was observed in three separate trials in the absence of *in vitro* metabolic activation. For example, at

concentrations that did not reduce the relative total growth* below 40% (50 ug/ml to 100 ug/ml), induced mutant frequencies up to approximately three times the spontaneous mutant frequencies were reported. The addition of S-9 Aroclor-induced rat liver enzyme activation caused an increase in cytotoxicity. Based on the results of a single experiment conducted at concentrations up to 25 ug/ml, the addition of S-9 metabolic activation appeared to enhance the response in a concentration-dependent manner; for example, at 17.5 ug/ml (45% relative total growth), a fourfold increase in mutant colonies above the spontaneous values was observed.

In a second gene mutation assay using mammalian cells in culture, Curren et al. (1979) reported that several different concentrations of the topside coke oven extract sample enhanced the frequency of ouabain-resistant colonies above the spontaneous frequency in mouse BALB/c 3T3 cells in the absence of in vitro metabolic activation; but for this response, there was no concentration-dependent increase. In the presence of metabolic activation (Aroclor-induced rat liver S-9 mix), an increase in the number of ouabain-resistant clones was also reported. However, the authors indicated that the spontaneous mutation frequency was significantly higher than the historical values observed for that cell line, thus making interpretation of the results difficult. Because of the problems described above and because neither the toxicities nor mutation frequencies of the concentrations examined were reported, the positive results of this study are considered questionable.

The ability of the topside coke oven extract to cause gene mutations in mammalian cells was also evaluated by a third laboratory using the CHO/HGPRT assay (Casto et al. 1979, 1980). Increases in variant colonies were only observed at high cell killings. For example, at 200 ug/ml (82% cell killing)

*Percentage of relative total growth = (relative suspension growth/relative cloning efficiency) x 100.

a threefold increase in 6-thioguanine (6TG) resistant colonies above the negative control was reported. It should be noted that concurrent positive controls were not included in the study design. Also, S-9 liver enzyme activation was not incorporated in the study design.

Mitchell et al. (1979) evaluated the ability of the coke oven sample to cause sister chromatid exchange (SCE) formation in Chinese hamster ovary cells with and without S-9 activation. The results of a single experiment indicated that the coke oven sample caused an increase in DNA damage in a concentration-dependent manner as measured by SCE formation. At the highest concentrations tested, an approximately twofold increase in SCE formation above the solvent control was reported for experiments in the presence and absence of S-9 mix. The percentage of cell survival or effect on mitotic induction of the concentrations tested (up to 250 ug/ml for 2 hours in the presence of S-9 mix, and up to 31 ug/ml for 21.5 hours in the absence S-9 mix) was not reported; however, the authors indicated that the highest concentration yielded a sufficient number of M_2 metaphases (i.e., cells that had divided twice) for analysis. When Casto et al. (1979) treated a culture of Syrian hamster embryo cells with 250 ug/ml or 125 ug/ml of the coke oven extract for 18 hours in the absence of exogenous metabolic activation, DNA strand breakage was detected as determined by sedimentation profiles in alkaline sucrose gradients.

Mitchell et al. (1979) reported that, in the absence of S-9 mix, recombinogenic activity in Saccharomyces cerevisiae D3 was not detected after a 4-hour fixed treatment time at concentrations of the coke sample ranging from 10 ug/ml (100% survival) to 1000 ug/ml (61% survival) or when re-tested at 100 ug/ml survival) to 1000 ug/ml (100% survival). Although a slight

increase was observed in the presence of *in vitro* metabolic activation, the results were not concentration-related or reproducible and thus are considered negative.

In the Gadsden study it should be noted that the samplers were positioned at the end of the coke oven battery with the prevailing wind direction upwind from the coke oven (Kew 1981, Huisingh 1979). Thus, the 2100-hour sample collected was diluted with ambient air. The exact extent of the dilution is not known, but it is thought to be significant (Workshop on Diesel Engine Exhaust 1981). Although dilution with ambient air occurred, chemical analysis showed that the polynuclear aromatic hydrocarbon content is not typical of ambient air (Huisingh 1981, Strup and Bjorseth 1979). (The sampler position and wind conditions during collection are not available for the 48-hour sample of the Ohmuta study.) Nevertheless, because the Gadsden sample was from a single source and was apparently diluted significantly with ambient air particulates, the mutagenic potency of this sample may not be representive of air particulates found topside of "controlled" coke ovens. Also, the Gadsden (and the Ohmuta) study did not involve a concurrent collection of samples from a moderate distance upwind and downwind from the coke oven battery to enable a determination of background mutagenic activity for the immediate vicinity.

Both the Ohmuta study by Towika et al. (1977) and the Gadsden study by Huisingh et al. (1979) show that air particulates collected topside of coke ovens are mutagenic in *Salmonella*. The Gadsden sample was also mutagenic in mammalian cells *in vitro*. These studies have bearing on the mutagenicity of coke oven emissions because the samples were collected on the top of coke ovens. Although the mutagenic activity cannot be exclusively attributed to coke oven emissions because of the ambient air contamination (particularly in

the Gadsden study), these emissions are a likely source of mutagenic air particulates.

In the aforementioned discussions on data concerning complex mixtures, it should be cautioned that there are problems associated with using short-term tests to ascertain the mutagenic potency of complex environmental mixtures which are usually comprised of hundreds of components. For example, potential mutagenic components present at low concentrations in the complex material may not be detected because their activity is overridden by the high toxicity of other components (Epler et al. 1979, 1980). Highly volatile components will not be detected as mutagenic unless precautions are incorporated into the study design to prevent excessive evaporation and thus ensure exposure of the indicator organisms. Such measures were not reported to have been taken in the studies mentioned above on coke oven-derived products and thus the results may not reflect the magnitude of the mutagenic potential of these materials. In addition, the organics screened for coke oven emissions were solvent-extracted and only those organics extracted with those particular solvents would have been evaluated for their mutagenic activity. Moreover, the activation system employed (in the cases above, the S-9 fraction was derived from livers of Aroclor-induced rats) may not effectively metabolize some potential promutagen components in the mixture (Dent 1979, Rao et al. 1978). Based on these considerations, it must be stressed that the tests to assess the mutagenicity of coke oven emissions, coke oven main sample, and air particulates collected topside of coke ovens were conducted using standard protocols and the concern is raised that the results obtained may underestimate the actual mutagenic potential of the material.

STUDIES EVALUATING URINE CONCENTRATES OF COKE PLANT WORKERS

Within a coke plant, coke oven battery workers have a high exposure to coke oven emissions, which are comprised of known mutagens and are a source of polycyclic organic matter. A method to demonstrate human exposure to mutagens is bacterial mutagenicity testing of body fluids (e.g., urine, blood, feces).

In a study conducted by Moller and Dybing (1980), urine concentrates from coke plant workers were evaluated for their mutagenic effects in the Salmonella/mammalian microsome assay. Urine was collected before and after work from 10 workers who smoked 10 to 20 cigarettes per day (workers rolled their own cigarettes) and from 10 workers who did not smoke. The personal exposure to polycyclic organic matter (POM) varied greatly among the workers within each group (i.e., smokers versus nonsmokers). As shown below, three job types were sampled: foremen, truck drivers, and coke oven battery workers.

Job Types	Smokers	Nonsmokers
coke oven battery workers	5	2
truck drivers	4	6
shift foreman	1	2

Within the job type "coke oven battery workers," there are different levels of exposure to POM or coke oven emissions. However, this general class (which includes larry car operators, door cleaners, push car operators, etc.) would have a higher exposure to POM than would the other two job types, "truck drivers" and "shift foreman." Ten nonplant workers who smoked and four nonplant workers who were nonsmokers served as control groups. The chemicals and/or their metabolites in urine samples were absorbed on a nonpolar resin

column (XAD-2) and diluted with acetone. It should be noted that the extraction and concentration methods can influence the ability to detect mutagenic metabolites in the urine. After the urine samples were evaporated to dryness, they were dissolved in DMSO for mutagenicity testing in the plate incorporation assay using the Salmonella tester strains TA 100 and TA 98. The authors stated that preliminary results showed that very little or no mutagenic activity was detected with strain TA 100 (data not reported) and thus they used strain TA 98 for further studies. The authors concluded that the mutagenic activity of urine from POM-exposed nonsmokers was not significantly different at the 95% level when compared to the mutagenic activity of nonexposed nonsmokers or to the spontaneous revertant counts. It is difficult to interpret these results because of the following deficiencies in the reporting of the data or in the study design: (1) it is not clear from the report if the authors' conclusions are based on experiments conducted in the presence or absence of S-9 mix, (2) individual revertant counts (data are illustrated in histogram) and positive control data are not reported, (3) it appears that the authors tested only one concentration of urine instead of a range of concentrations, (4) the authors used a Student's t-test to compare the POM-exposed group to the nonexposed group and did not compare individuals of a certain job type (i.e., exposure level) to the control population (The authors refer to each test person by number and do not identify the job type or exposure level of each number.), and (5) only two workers with high POM exposure job types (coke oven battery workers) are included in this nonsmoker-POM-exposed group.

The urine of the smoker-POM-exposed group was reported as mutagenic only in the presence of S-9 mix (prepared from livers of Aroclor-induced rats). It was reported that the addition of β-glucuronidase (which hydrolyzes possible

conjugates) to the urine concentrates did not enhance the mutagenic effects observed in tester strain TA 98. The authors concluded that the POM-exposed smokers did not differ at the 95% level from nonexposed smokers. Again, the authors are comparing one group with another and not individuals with certain exposure levels to the control population. They do state in the report that a suggestion of higher mutagenic activity of urine extracts was found when high POM exposure workers were compared with lower POM exposure workers. However, they indicated that a larger number of workers are needed to establish a significant difference from the control population. The results of the study by Moller and Dybing (1980) are considered inconclusive because of the problems described above.

MUTAGENICITY OF INDIVIDUAL COMPONENTS IDENTIFIED IN COKE OVEN EMISSIONS

Several polycyclic components identified in coke oven emissions have been shown to be potentially mutagenic in a variety of tests. It is not the intent of this evaluation to provide an exhaustive survey of all the mutagenicity tests that have been done with these components or with polycyclic organic matter. References concerning the mutagenicity of polycyclic compounds can be found in the Environmental Mutagen Information Center's Files, and reviews by Brookes (1977), Bruce and Berry (1980), and Kimball and Munro (1981) summarize much of this literature. Briefly, the mutagenicity of some of these components is well-established, while the mutagenicity of others is suggestive. In addition, of those components of the complex mixture known to be mutagenic, the possibility exists that mutagenic chemical substances whose activity has not been characterized may be present or that some constituents, which may act as promoters or modifers of carcinogenesis, are present. Table IV-2 is a selected list of organic components that have been reported positive

TABLE IV-2. MUTAGENIC ACTIVITY IN SALMONELLA TYPHIMURIUM OF SELECTED ORGANICS IDENTIFIED IN COKE OVEN EMISSIONS*

Chemical	S-9 Activation†	Reported Response§
Acenapthylene	A, PB	+[b]
Acridine	N.A.	+[c]
Aniline	A	-[a],+[c]
Anthracene	A, PB	-[a,b,c]
Benz[a]anthracene	A, PB	+[a,b,c]
Benzo[a]pyrene	A	+[a,b,c]
Benzo[b]fluorene	A	+[a,b,c]
Benzo[e]pyrene	A, PB	+[a,b]
Benzo[g,h,i]perylene	A, PB	+[a,b]
Carbazole	A, PB	-[b,c]
Coronene	A, PB	-[b]
Chrysene	A, PB	+[a,b,c]
Dibenz[a,j]acridine	A	+[a]
Dibenz[a,c]anthracene	A, PB	+[a,b]
Dibenz[a,h]anthracene	A	+[a,b]
Dibenzo[a,i]pyrene	A	+[a,b]

*Content of coke oven emissions extracted from reports by Bjorseth et al. (1978) and U.S. EPA (1977b).

†A, Aroclor-induced; PB, phenobarbital-induced; N.A., not available.

§Data were interpreted in the reference:
a, reported by McCann et al. (1975)
b, reported by Kaden et al. (1979)
c, reported by Epler et al. (1979)

(continued on the following page)

TABLE IV-2. (continued)

Chemical	S-9 Activation†	Reported Response§
Fluoranthene	A	+b,c
Fluorene	A, PB	-a,b
Indole	A, PB	-b
Isoquinoline	A, PB	-b,c
Naphthalene	A, PB	-a,b,c
Naphthylamine	A	+a,c
Perylene	A	+b
Phenanthrene	A, PB	-a,b,+c
Pyrene	N.A.	+c
Pyridine	A, PB	+b
Quinoline	A	+b,c
Triphenylene	A	+b,c

†A, Aroclor-induced; PB, phenobarbital-induced; N.A., not available

§Data were interpreted in the reference:
a, reported by McCann et al. (1975)
b, reported by Kaden et al. (1979)
c, reported by Epler et al. (1979)

or negative in the Salmonella/microsome assay. [A positive response in this test appears to be highly correlated with the carcinogenic potential of chemical substances (McCann et al. 1975)]. The chemicals listed in Table IV-2 may or may not be major constituents of coke oven emissions and may or may not significantly contribute to the mutagenic potential associated with simultaneous exposure to the complex mixture itself. Some of the possible organic constituents identified in coke oven emissions, which may be responsible for the potential mutagenic hazards in the complex mixture, are the polycyclic aromatic hydrocarbons (such as benzopyrenes and chrysene), the heterocyclic nitrogen compounds (such as pyridines, quinoline and substituted quinolines, acridine), or aromatic amines (such as β-naphthylamine) (Epler et al. 1977, McCann et al. 1975, Hollstein et al. 1979, U.S. EPA 1980a, Brooks 1977, Kimball and Munro 1981).

The listing above is by no means inclusive. Although several individual coke oven components have been shown to induce mutagenic responses in certain tests (e.g., bacteria, yeast, mammalian cells in vitro, animals), interactions (e.g., synergisms and antagonisms) may occur among the other components in the complex mixture to alter their mutagenic potential (Rao et al. 1979, Hass et al. 1981, Pelroy and Peterson 1979).

SUMMARY AND CONCLUSIONS

The complex mixture, coke oven emissions, has been tested for its mutagenic potential only in the Salmonella/mammalian microsome assay. The solvent-extracted organics caused mutations in a dose-dependent manner in frameshift-sensitive strains. The incorporation of an exogenous mammalian microsomal activation system greatly enhanced the mutagenic activity of this complex mixture. To confirm the positive responses reported in Salmonella,

further testing in other organisms (e.g., mammalian cells in culture) is necessary. It is important to point out that several known mutagens, identified as positive in various genetic test systems, have been identified in coke oven emissions and could contribute to the mutagenicity of the whole mixture. Like coke oven emissions, many of these components are primarily detected in Salmonella as frameshift-acting mutagens after metabolic activation. Also in support of coke oven mutagenicity, a related complex mixture, sampled from the coke oven collecting main, has been shown to be positive in two different organisms (namely, bacteria and mammalian cells in culture). This complex material was also detected in bacteria as frameshift-acting after metabolic activation.

In conclusion, the weight of evidence (i.e., in vitro data regarding the mutagenic activity of coke oven emissions and a related complex mixture and the data regarding the mutagenic activity of the individual components identified in coke oven emissions) suggests that coke oven emissions may have the potential to cause somatic mutations in humans. It should be emphasized, however, that the complex mixture itself, coke oven emissions, was evaluated only in an in vitro test; and when evaluating the risk posed by exposure to a mutagenic agent, several factors (e.g., absorption, metabolism, pharmacokinetics) may alter the mutagenic response in the whole mammal compared to the mutagenic potential determined in an in vitro test.

CELL TRANSFORMATION

Currently available studies concerning the ability of topside coke oven extract to cause cell transformation are derived from the EPA diesel research program (Huisingh et al. 1979). The sample tested was collected on top of a coke oven battery and was shown to cause cell transformation in BALB/c 3T3

cells and in primary Syrian hamster embryo cells with viral enhancement by Simian adenovirus (Curren et al. 1979, Casto et al. 1979). Negative results were reported with one test conducted in primary Syrian hamster embryo cells using the focus assay method. Because of the location of the topside air sampler and local wind conditions, an unknown portion of the topside coke oven sample contained particulate matter from other ambient air sources, as previously discussed in the mutagenicity section herein. Hence, the extent to which the results of the above cell transformation studies are representative of the topside coke oven alone appears uncertain.

V. TOXICITY

Coke oven emissions consist of a complex mixture of organic and inorganic gases and particulates (Table II-1). Only coal tar, which is produced by the condensation of coke oven emissions, will be discussed in this section. Constituents of emissions other than those producing coal tar are not considered essential to the discussion of toxicity in this document.

ACUTE TOXICITY OF COAL TAR

Experimental toxicity data on the noncarcinogenic toxic effects of coal tar are limited. In a review by Graham et al. (1940; cited in NIOSH 1978), an early study was cited in which feeding of coal tar products to pigs (6 to 15 g/day for 5 days) produced extensive liver damage and 100% mortality in the five treated animals. A second study involving the administration of liquid coal tar in capsules to pigs (three pigs receiving 3 g/day for 5 days; two pigs receiving 3 g/day for 2 days) produced similar results.

SUBCHRONIC AND CHRONIC TOXICITY OF COAL TAR AEROSOLS

In 1973, the National Institute for Occupational Safety and Health published a criteria document concerning occupational exposure to coke oven emissions. A major conclusion reached in that report was that dose-response data were lacking on the toxicity of coke oven emissions. In response to this need for more definitive information, several studies were subsequently undertaken to determine the response of experimental animals to measured concentrations of coal tar aerosols collected from coke ovens.

Kinkead (1973) prepared an aerosol of coal tar in which the solids previously had been removed by centrifugation. He exposed 64 Sprague-Dawley yearling rats (32 male and 32 female), 64 Sprague-Dawley weanling rats

(32 male and 32 female), 50 male ICR mice, and 50 male CAF-1 mice continuously for 90 days at concentrations of 0.2, 2.0, and 10 mg/m^3. In addition, 80 yearling female Sprague-Dawley rats, 9 weanling rats of each sex, 25 male CAF-1 mice, 25 male ICR mice, 24 female New Zealand white rabbits, and 100 male Syrian golden hamsters were exposed continuously for 90 days at 20 mg/m^3. Greater than 95% of the aerosol droplets were 5 um or less in diameter. Nominal and measured exposure levels were comparable.

The author stated, without reporting his data, that considerable mortality among exposed animals was encountered in this study. Mortality patterns were attributed to debilitation from exposure leading to greater susceptibility to infection, and a high incidence of chronic murine pneumonia was found in all species under study. Cumulative mortality was reported to be proportional to exposure concentration.

In all species tested, there was a remarkable effect of exposure on body weight growth curves. Weight loss was evident in exposed mice during exposure, and body weight gain was lower in treated mice compared to control mice following exposure (Figures V-1 and V-2). Trends in body weight reduction in adult rats, hamsters, and rabbits were stated (data not reported) to have been similar to those found in treated mice. Body weight loss was also evident in exposed weanling rats (Figures V-3 and V-4). However, in contrast to treated mice, decreased body weight gain rather than marked loss occurred during treatment, and a dose-response in reduced body weight gain is clearer for weanling rats. Even the lowest exposure concentration, 0.2 ug/m^3, produced some adverse effects on body weight gain. Following the termination of exposure, the inhibitory effect of coal tar aerosol on growth was still evident for at least 7 months in most species.

Kinkead conducted a subsequent coal tar experiment in which the solid

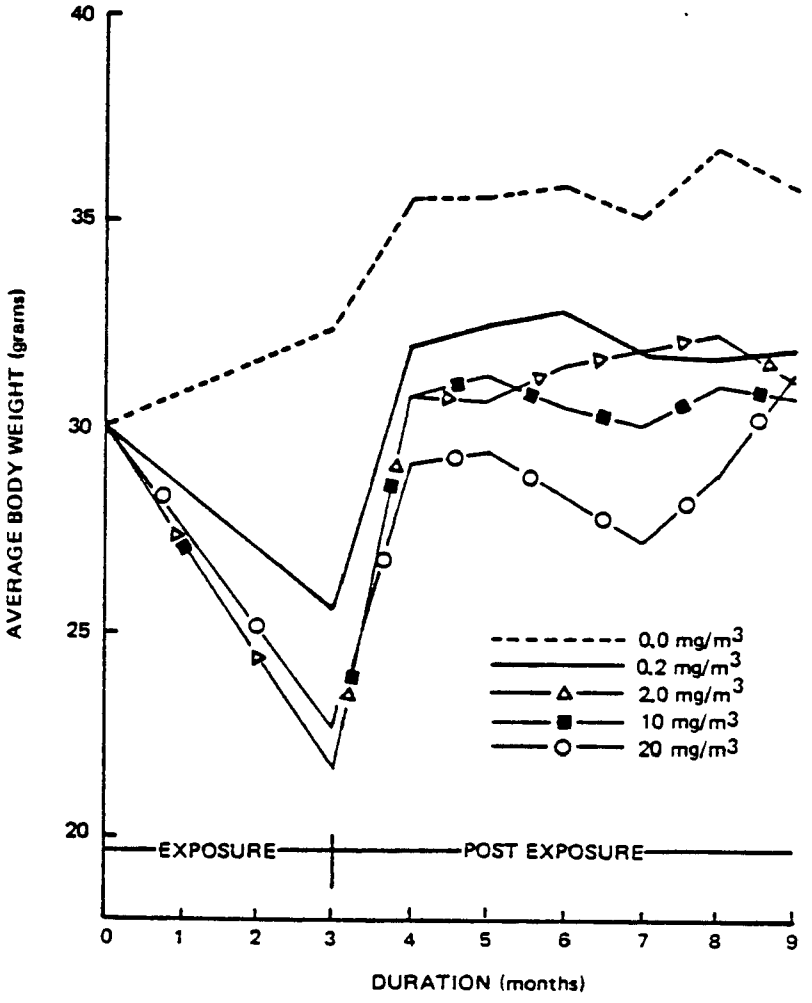


Figure V-1. Growth of male CAF-1 mice exposed to coal tar aerosol. (Kinkead 1973)

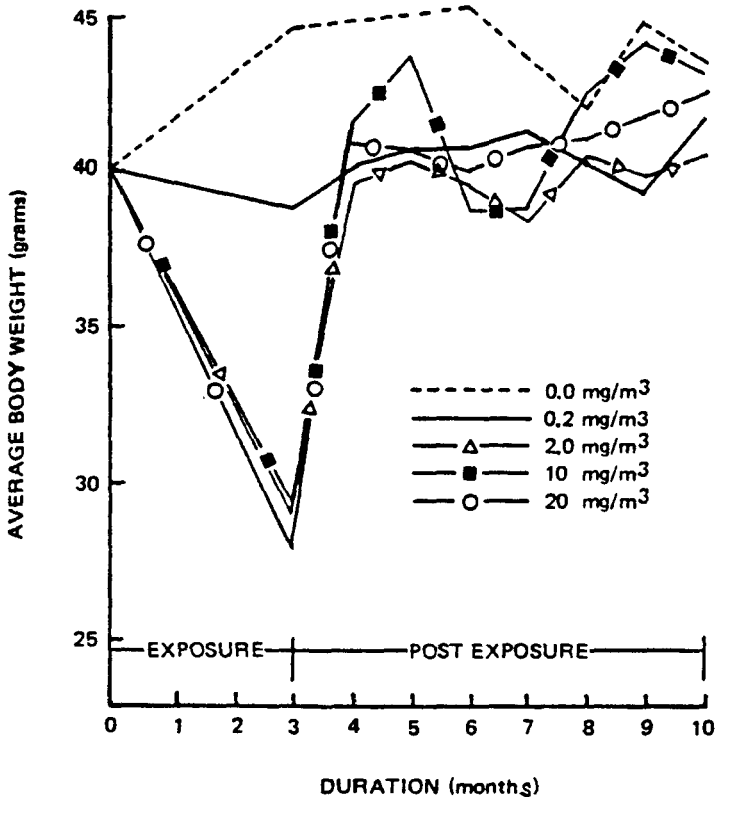


Figure V-2. Growth of male ICR mice exposed to coal tar aerosol. (Kinkead 1973)

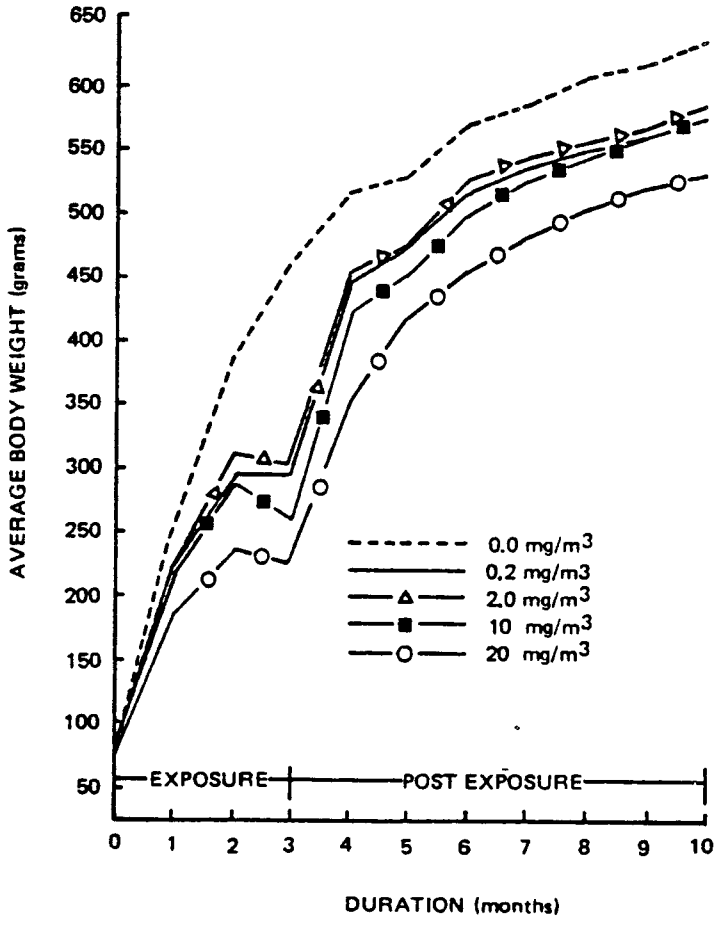


Figure V-3. Growth of male weanling rats exposed to coal tar aerosol. (Kinkead 1973)

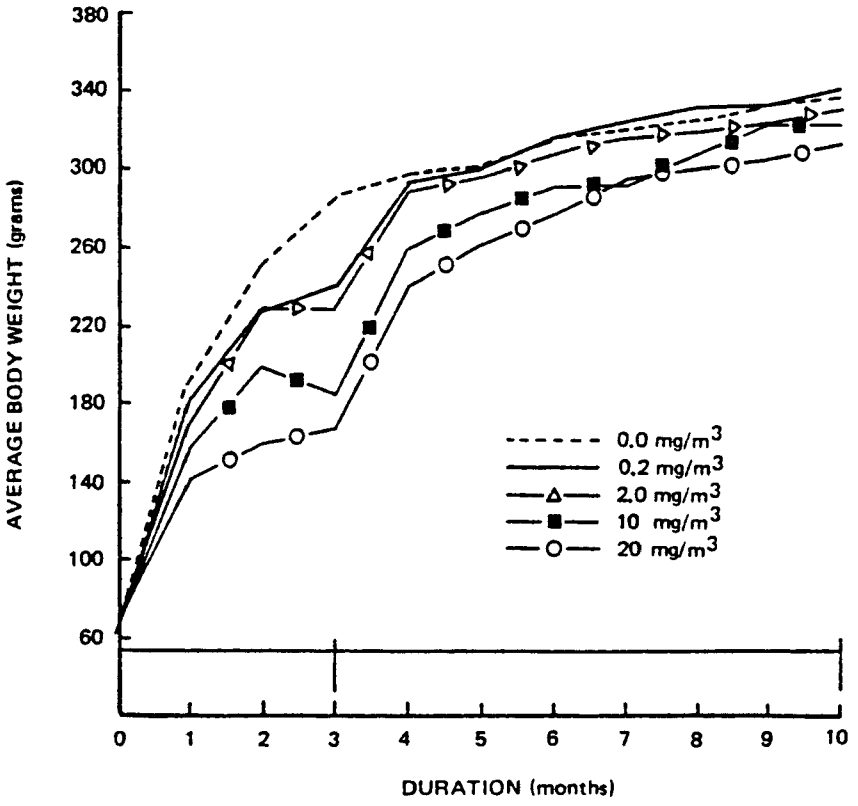


Figure V-4. Growth of female weanling rats exposed to coal tar aerosol. (Kinkead 1973)

particles and light oil fractions were retained in the experimental aerosol. Sprague-Dawley rats, New Zealand white rabbits, JAX mice, and Syrian golden hamsters (numbers not specified) were exposed continuously for 90 days to the coal tar aerosol at a concentration of 10 mg/m^3. In addition, 150 CF-1 mice were exposed to the aerosol and serially sacrificed for histopathologic analysis. Among exposed rats and hamsters, McConnell and Specht (1973) described three significant lesions occurring at the termination of exposure. These were: 1) phagocytized coal tar pigment in alveolar macrophages and in the peribronchial lymphoid tissue; 2) hepatic and renal hemosiderosis which disappeared by 100 days post-exposure; and 3) mild central lobular necrosis in the liver. Among mice sacrificed 99 days post-exposure, moderate pigmentation of alveolar macrophages was observed in 14 of 15 CF-1 mice, but in only 1 of 13 exposed JAX mice.

In a follow-up study, MacEwen and coworkers (1976) prepared a composite coal tar mixture collected from multiple coking ovens around the greater Pittsburgh area. Coal tar samples were blended together with a 20% by volume amount of the BTX (benzene, toluene, xylene) fraction of coke oven distillate. This material was believed to be more representative of that inhaled by workers on top of coke ovens. Female (75) ICR-CF-1 mice, female (50) CAF-1-JAX mice, male (40) and female (40) weanling Sprague-Dawley rats, New Zealand white rabbits (18), and male (5) and female (9) Macaca mullata monkeys were exposed to a coal tar aerosol at 10 mg/m^3, 6 hours daily, 5 days/week, for 18 months. Animals were held for an additional 6-month observation period following termination of exposure. A significant inhibition of body growth rate was observed for both male and female rats after 4 months and for rabbits by the end of the first month (Figures V-5 and V-6). Monkeys showed no significant inhibition of growth rate from exposure to the coal tar aerosol

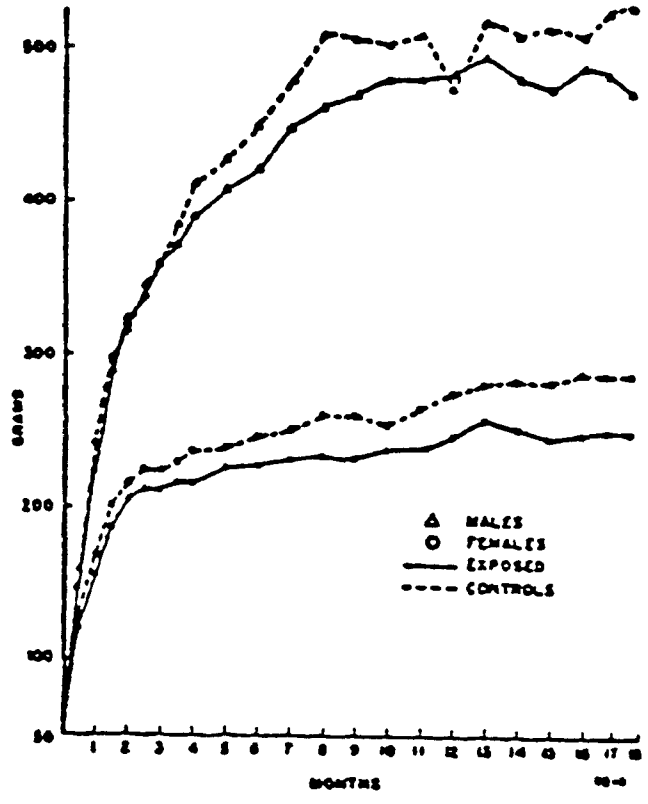


Figure V-5. The effect of repeated exposure to 10 mg/m^3 coal tar aerosol on growth of rats.
(MacEwen et al. 1976)

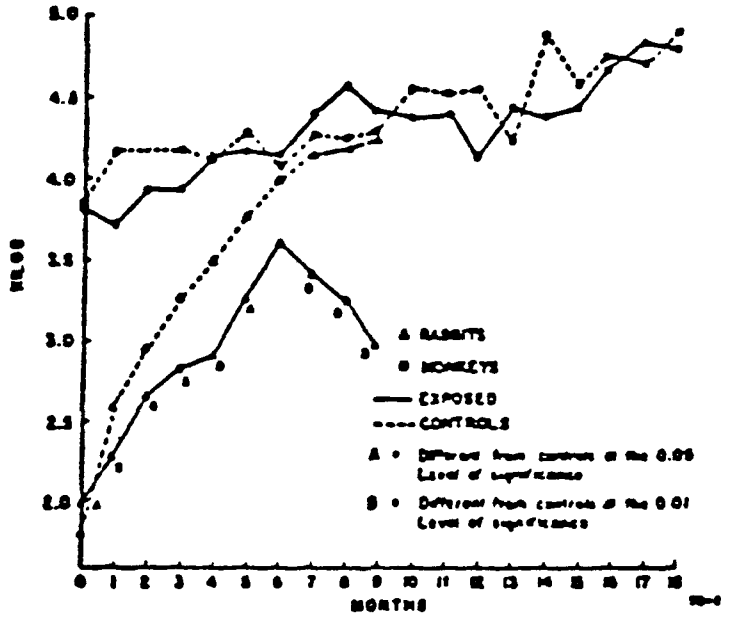


Figure V-6. The effect of repeated exposure to 10 mg/m^3 coal tar aerosol on growth of rabbits and monkeys.
(MacEwen et al. 1976)

(Figure V-6). In this study, 16 of 18 test rabbits and 6 control rabbits died during the test period.

A description of toxic effects of compounds and classes of compounds described in Table II-1 can be found in Dreisbach (1977), U.S. EPA documents (1977a, 1978a-c, 1979, 1980a-n), World Health Organization (1979), Venugopal and Luckey (1978), Roy and Trudinger (1970), National Research Council (1981), Goldstein et al. (1980), and Carcinogen Assessment Group (1980a).

VI. CARCINOGENICITY

HUMAN EPIDEMIOLOGY STUDIES

The American long-term mortality study of coke oven workers by Lloyd, Redmond, and coworkers (Lloyd and Ciocco 1969, Lloyd et al. 1970, Lloyd 1971, Redmond et al. 1972, Redmond et al. 1976, Mazumdar et al. 1975, Redmond et al. 1979) found that workers exposed to coke oven emissions have an increased risk of cancer mortality. Sakabe et al. (1975) found that coke oven workers who were retired from iron and steel plants in Japan, had an excess risk of lung cancer mortality when compared to the Japanese male population. British studies by Reid and Buck (1956), Davies (1977), and Collings (1978) have not demonstrated the cancer risk found in the American studies or the Sakabe et al. study, but the British studies had some design limitations, including short follow-up periods and lack of delineation of the coke oven workers by work area, that may have prevented the detection of any cancer risks.

American Studies

In 1969 Lloyd and Ciocco began a long-term study of the mortality of steelworkers in Allegheny County, Pennsylvania. Subsequent updates of this study focused on the mortality of coke oven workers. In 1972 Redmond et al. expanded the study to include coke plants at ten steel plants throughout the United States and Canada. Because there are several updates of the study, a summary table has been prepared and precedes the discussions of the studies (Table VI-1).

Lloyd and Ciocco (1969)--

In 1969 Lloyd and Ciocco reported on the mortality of approximately 59,000 steelworkers, including coke oven workers, employed in 1953 at seven steel plants in Allegheny County, Pennsylvania. Mortality was reported by age, race,

TABLE VI-1. SUMMARY OF COKE OVEN MORTALITY STUDY BEGUN BY LLOYD AND CIOCCO (1969)

Author and Year of Report	Study Population	Comparison Group	End of Follow-up on Vital Status	Findings
Lloyd and Ciocco (1969)	Steelworkers at seven plants in Allegheny County, Pennsylvania employed in 1953	Allegheny County male population in 1953	December 31, 1961	Average annual crude mortality rates were lower among the steelworkers than among the male population of Allegheny County.
Lloyd et al. (1970)	Different job categories within the steelworker population employed at seven plants in Allegheny County, Pennsylvania in 1953	All steelworkers employed at seven steel plants in Allegheny County in 1953	December 31, 1961	Nonwhite coke plant workers employed at least 5 years had a significantly higher total mortality rate (96 observed, 78.7 expected, $P < 0.05$), and a significantly ($P < 0.05$) higher cancer mortality rate (40 observed, 19.6 expected, $P < 0.01$); most of the excess cancer mortality was due to lung cancer mortality (25 observed, 7.3 expected).
Lloyd (1971)	Steelworkers employed in 1953 who worked or previously had worked in the coke plant at two Allegheny County, Pennsylvania steel plants	All steelworkers employed at seven steel plants in Allegheny County in 1953	December 31, 1961	An increase in respiratory neoplasm deaths was found for all coke oven workers as well as a significant excess of mortality, all causes, for workers who had worked full-time topside. The respiratory cancer excess was significant ($P < 0.01$) only among nonwhite workers. A dose-response for respiratory cancer mortality was evident by work area for workers who had worked 5 or more years.

(continued on the following page)

TABLE VI-1. (continued)

Author and Year of Report	Study Population	Comparison Group	End of Follow-up on Vital Status	Findings
Redmond et al. (1972)	Coke oven workers employed at two Allegheny County, Pennsylvania steel plants in 1953.	All men who never worked at the coke ovens at the respective Allegheny County steel plants.	December 31, 1966	A significant excess in respiratory cancer deaths was found for the non-Allegheny County plants (33 observed, 20.7 expected, $P < 0.01$); the Allegheny County plants continued to have a significant ($P < 0.01$) excess of respiratory cancer deaths. Deaths from malignant neoplasms of the genito-urinary system were found to be significantly (10 observed, 5.7 expected, $P < 0.05$) in excess among nonwhites in the non-Allegheny County plants and significantly (5 observed, observed, 0.9 expected, $P < 0.01$) in excess among whites in the Allegheny County plants. Lung cancer followed a dose-response by work area (topside, part-time topside, or side oven only) for all workers who had worked 5 years or more at the coke ovens. For nonwhites at all plants, lung cancer was found to follow a dose-response by length of time worked (< or > 5 years).
	Coke oven workers employed at 10 non-Allegheny County steel plants from 1951-55.	Nonoven workers employed at the respective non-Allegheny County steel plants from 1951-55.		

(continued on the following page)

TABLE VI-1. (continued)

Author and Year of Report	Study Population	Comparison Group	End of Follow-up on Vital Status	Findings
Mazumdar et al. (1975)	Coke oven workers employed at two Allegheny County, Pennsylvania steel plants in 1953.	All men who never worked at the coke ovens at the respective Allegheny County plants.	December 31, 1966	A considerable difference in exposure to coal tar pitch volatiles was found for different work areas. The level of exposure and length of time exposed were both found to be related to the development of cancer, particularly lung cancer.
	Coke oven workers employed at 10 non-Allegheny County steel plants from 1951-55.	Nonoven workers employed at the respective non-Allegheny County steel plants from 1951-55.		
Redmond et al. (1976)	Steelworkers employed at seven Allegheny County, Pennsylvania steel plants in 1953 who worked in the coke plant prior to or during 1953.	All steelworkers employed at the seven Allegheny County, Pennsylvania steel plants in 1953.	December 31, 1970	The statistically significant excess of respiratory cancer mortality and cancer mortality, all sites, continued. Length of exposure was divided by 5+, 10+, and 15+ years. A clear dose-response was evident both by length of exposure and by work site.

(continued on the following page)

TABLE VI-1. (continued)

Author and Year of Report	Study Population	Comparison Group	End of Follow-up in Vital Status	Findings
Redmond et al. (1979)	Steelworkers employed at seven Allegheny County, Pennsylvania steel plants in 1953 who worked in the coke plant prior to or during 1953.	All steelworkers employed at the seven Allegheny County steel plants in 1953.	December 31, 1975	Workers ever employed at the Allegheny County coke ovens through 1953 had a significant excess of deaths from "cancer-all sites" (179 observed, 144.4 expected, $P < 0.01$), prostate cancer (20 observed, 12.7 expected, $P < 0.05$), and kidney cancer (7 observed, 2.6 expected, $P < 0.05$). The elevated lung, trachea, and bronchus cancer mortality seen in the earlier updates continued.
	Coke oven workers employed at 10 non-Allegheny County steel plants from 1951-1955.	Non-coke oven workers employed at the respective non-Allegheny County steel plants from 1951-1955.		Among non-Allegheny County coke oven workers, a significant excess of cancer mortality at all sites (194 observed, 162.56 expected, $P < 0.01$) and a significant excess of prostate cancer mortality among nonwhite workers (15 observed, 9.44 expected, $P < 0.05$) was found. As in the Redmond et al. (1972) update, a significant ($P < 0.05$) excess of lung, trachea, and bronchus cancer mortality existed for both whites and nonwhites. Excesses increased for workers employed 5 or more years.

and cause of death. Mortality was not divided by work area (e.g., coke oven workers, etc.), however. Records of the workers were collected between July 1962 and December 1964 at the personnel offices of the plants by teams of four people assigned to each plant. Information on workers who still worked at the plant in 1962 included a complete work history from time of first employment with the specific company through 1961, birthplace of employee and his parents, race, marital status, and identifying information for follow-up. For men leaving employment before January 1, 1962, the follow-up schema consisted of references to death lists and city directories, as well as inquiries to local, state, and federal agencies. When no determination could be made through these sources, mail and telephone contacts were made to the next of kin. The average annual mortality rates for the steelworkers were found to be lower than that of the male population of the county in which the plants are situated. For the steelworkers, the crude mortality rate among whites was 911.0 per 100,000 person-years at risk and among nonwhites was 994.2 per 100,000 person-years at risk. In the county where the steel plants are located, the crude mortality rate among whites was 1578.2 per 100,000 population and among nonwhites was 1880.6 per 100,000 population. Comparison by age category found that for both whites and nonwhites, the mortality rates were higher in the county than among the steelworkers.

Lloyd et al. (1970)--

In a continuation of the Lloyd and Ciocco (1969) study, Lloyd et al. (1970) calculated the expected deaths for each of 53 work areas by applying the death rate of the total steelworkers population to the number at risk in the work area. A Standard Mortality Ratio (SMR)* was calculated for each area. The

*$SMR = \frac{\text{Observed Deaths}}{\text{Expected Deaths}} \times 100$

overall SMR for coke plant workers was 104. Since disease response may be a function of length of exposure, an SMR using person-years was calculated for those who had attained 5 years of exposure. For each man who had attained 5 years in a work area, the time at risk was calculated as the time of completion of the 5 years to the end of observation (date of death or December 1961). For men attaining 5 years prior to 1953, the initial date at risk was January 1, 1953. The comparison group was all steelworkers who had attained 5 years of employment in the industry prior to or during the period 1953-1961. The number of expected deaths in each work area for specified race, age, nativity (country of origin), and residence was calculated by applying the specific rate of the total steelworker population to the person-years at risk in the work area. For coke plant workers, the SMR for white workers was 99 while the SMR for nonwhite workers was 122, which was significant (96 observed, 78.7 expected, $P < 0.05$) using a summary chi-square with one degree of freedom. When Lloyd et al. looked at cause-specific mortality among workers exposed 5 years or more, the SMR for malignant neoplasms among white coke plant workers was 102 while that among nonwhite workers was 204 (40 observed, 19.6 expected, $P < 0.05$). The authors reported that a more detailed analysis of the deaths from malignant neoplasms revealed that the excess for nonwhite workers was due to malignant neoplasms of the respiratory system (25 observed vs. 7.3 expected). SMR's for other causes of death (vascular lesions affecting the central nervous system, heart disease, accidents, all other causes) were not significant.

Lloyd (1971)--

Lloyd (1971) further delineated the source of the respiratory cancer excess within the coke plant environment and clarified the apparent differential in mortality for white and nonwhite workers. All of the coke oven workers in the

steelworker study worked at by-product coke ovens. Prior to World War I, the main source of metallurgical coke in the United States was the beehive coke oven. Since World War I, the by-product plant, which allows for recovery of tar, oils, and chemicals from the volatiles, has increasingly predominated. The by-product coke plant is divided into three rather distinct areas in terms of function and potential exposure to environmental hazards. These are: 1) the coal handling area where coal is received by rail or barge and where provision is made for the handling, storage, and blending of several types of coal before transfer to the coke ovens; 2) the coke ovens, grouped into batteries, with equipment for charging and discharging the ovens and the quenching of coke; and 3) the by-product plants for recovery of gas and chemical products. Because of the reports by Kawai et al. (1967) and Doll et al. (1965) of higher lung cancer rates for men engaged primarily in the coal-carbonization process, Lloyd decided to focus on the men employed at the coke ovens or in their immediate vicinity. Occupational titles indicating employment some distance from the coke ovens were assigned to a nonoven group. The coke oven group included all job titles requiring that some part of the working day be spent at the topside of the ovens or the side of the ovens, including the quenching station, the coke wharf, and the coke screening station.

Of the 58,828 steelworkers employed in 1953, 2,552 worked in the coke plant. However, an additional 978 steelworkers employed in other work areas in 1953 had previously been employed in the coke plant. The distribution of these workers by race, work area, and period of employment (1953 or prior years) is given in Table VI-2.

Expected mortality for the coke oven workers was derived from mortality for the entire steelworker population. A significant excess of observed to expected deaths from malignant neoplasms of the respiratory system was found (Table

TABLE VI-2. DISTRIBUTION OF COKE PLANT WORKERS EMPLOYED IN ALLEGHENY COUNTY, PENNSYLVANIA IN 1953 BY WORK AREA AND RACE
(adapted from Lloyd 1971)

	Coke Plant	Coke Oven		Nonoven	
		Number	Per Cent	Number	Per Cent
Employed in 1953 or Prior Years					
Total	3,530	2,048	58.0	1,482	42.0
White	2,369	993	41.9	1,376	58.1
Nonwhite	1,161	1,055	90.9	106	9.1

VI-3). Although there was an increase in respiratory cancer deaths among white workers, this increase was not significant. Respiratory cancer deaths among nonwhite workers was significantly ($P < 0.01$) elevated. The author reported that of the 25 deaths from malignant neoplasms of the respiratory system among workers employed in 1953, 23 of them were attributed to neoplasm of the lung. The author did not present any data on the specific site of the respiratory neoplasm deaths among workers employed in years prior to 1953. Coke oven worker mortality from diseases other than malignant neoplasm of the lung was little different from expected.

The author next considered differential mortality within the several work divisions of the coke ovens. To do this he divided the coke oven workers into full-time topside (larry car operator, lidman, and standpipe man), part-time topside (foreman, heater, and occassional maintenance men such as pipefitters), and side oven, which was the remainder of the coke oven work force (including workers at the quenching station, coke wharf, and the screening station). Mortality for malignant neoplasms of the lung for each of these subdivisions is reported by race in Table VI-4. As can be seen in Table VI-4, there is a significant excess of total coke oven worker lung cancer mortality. Nonwhite lung cancer mortality is significantly increased; white lung cancer mortality is in excess but not significant. The excess mortality is associated primarily with employment at the full-time topside occupations. The total mortality experience of men employed only at the side ovens does not differ significantly ($P < 0.05$) from that expected. The observed deaths from malignant neoplasms of the lung are seven times that expected (19 observed, 2.6 expected, $P < 0.01$) for full-time topside workers; the risk for nonwhite topside workers is eight times that expected (18 observed, 2.2 expected, $P < 0.01$). The limitation of small

TABLE VI-3. OBSERVED AND EXPECTED RESPIRATORY CANCER DEATHS AND STANDARDIZED MORTALITY RATIOS (SMR's) OF COKE OVEN WORKERS EMPLOYED IN ALLEGHENY COUNTY, PENNSYLVANIA IN 1953 AND PRIOR YEARS BY RACE
(adapted from Lloyd 1971)

	Coke Plant			Coke Oven			Nonoven		
	Observed Deaths	Expected Deaths	SMR	Observed Deaths	Expected Deaths	SMR	Observed Deaths	Expected Deaths	SMR
Total	37	21.8	170*	33	13.3	248*	4	8.5	47
White	11	12.2	90	8	5.0	160	3	7.3	41
Nonwhite	26	9.6	271*	25	8.4	298*	1	1.2	---†

*Significant at $P < 0.01$.

†Less than five deaths in both observed and expected; statistical significance not calculated.

TABLE VI-4. OBSERVED AND EXPECTED LUNG CANCER DEATHS AND STANDARDIZED MORTALITY RATIOS (SMR's) FOR MEN EMPLOYED IN SELECTED COKE OVEN SUBDIVISIONS IN ALLEGHENY COUNTY, PENNSYLVANIA IN 1953 AND PRIOR YEARS BY RACE (adapted from Lloyd 1971)

	Observed	Expected	SMR
Total Coke Oven	31	12.3	252*
White	8	4.7	170
Nonwhite	23	7.6	303*
Side Oven	10	8.0	125
White	5	2.7	185
Nonwhite	5	5.4	93
Partial Topside	2	1.7	---†
White	2	1.6	---†
Nonwhite	0	0.1	---†
Full Topside	19	2.6	731*
White	1	0.5	---†
Nonwhite	18	2.2	818*

*Significant at $P < 0.01$.

†Less than five deaths in both observed and expected; significance not calculated.

numbers precludes the calculation of significance of the lung cancer excess for white workers. Causes of death other than malignant neoplasm of the lung were not significantly ($P < 0.05$) greater than expected.

Lloyd also looked at observed and expected lung cancer deaths by length of employment (Table VI-5). Lung cancer mortality among coke oven workers having worked 5 or more years was significantly ($P < 0.01$) increased. Although an excess was found for both white and nonwhite workers, only the excess among the nonwhite workers having worked 5 or more years was significant. Deaths from causes other than lung cancer were not significantly ($P < 0.05$) increased above that expected.

When the lung cancer mortality of men employed 5 years or more at coke ovens was analyzed by work area, it was found that full-time topside workers had ten times the expected number of lung cancer deaths (Table VI-6). The combination of work area and length of exposure to produce a higher SMR than that found by either work area or length of exposure alone suggests that both length of exposure and intensity of exposure are important respiratory cancer risk factors.

Other causes of death among the coke oven workers were found to be similar to expected except for a significant ($P < 0.05$) excess of "nonrespiratory tumors" among "side and topside (less than 5 years-topside)" workers (9 observed vs. 4.3 expected and a SMR of 209), and a significant excess ($P < 0.05$) of "all other causes" (11 observed vs. 6.1 expected and a SMR of 180) among nonwhite full-time topside workers. Most of the excess in "other causes" is accounted for by deaths from vascular lesions of the central nervous system and tuberculosis.

A primary criticism of the Lloyd (1971) study is the fact that smoking, a potential confounding variable in any study of lung cancer, was not adequately addressed primarily due to the nature of the study design. Obtaining smoking

TABLE VI-5. OBSERVED AND EXPECTED LUNG CANCER DEATHS AND STANDARDIZED MORTALITY RATIOS (SMR's) FOR MEN EMPLOYED AT COKE OVENS IN ALLEGHENY COUNTY, PENNSYLVANIA IN 1953 AND PRIOR YEARS BY LENGTH OF EMPLOYMENT (AS OF JANUARY 1, 1953)
(adapted from Lloyd 1971)

	Observed	Expected	SMR
Less Than 5 Years	4	4.7	---†
White	3	2.2	---†
Nonwhite	1	2.6	---†
5 or More Years	27	7.6	355*
White	5	2.6	192
Nonwhite	22	5.1	431*

*Significant at $P < 0.01$.

†Less than five deaths in both observed and expected; significance not calculated.

TABLE VI-6. OBSERVED AND EXPECTED LUNG CANCER DEATHS AND STANDARDIZED MORTALITY RATIOS (SMR's) FOR MEN EMPLOYED AT COKE OVEN SUBDIVISIONS IN ALLEGHENY COUNTY, PENNSYLVANIA FOR MORE THAN 5 YEARS (AS OF JANUARY 1, 1953) BY WORK AREA AND RACE
(adapted from Lloyd 1971)

	Observed	Expected	SMR
Side Oven Only	6	4.1	146
White	2	1.1	---†
Nonwhite	4	3.0	---†
Side and Topside (less than 5 years full topside)	6	2.1	286*
White	2	1.3	---†
Nonwhite	4	0.8	---†
Full-time Topside	15	1.5	1000*
White	1	0.2	---†
Nonwhite	14	1.3	1077*

*Significant at $P < 0.01$.

†Less than five deaths in both observed and expected; significance not calculated.

histories in a study of historic prospective design is nearly impossible. However, the dose-response is so pronounced in this study, particularly for nonwhite workers, that it is improbable that the significant excess seen in lung cancer mortality could have been caused by smoking alone. Certainly, however, the possibility of a synergistic effect of smoking and coke oven emissions cannot be ruled out.

Lloyd (1974) compared age-specific lung cancer mortality rates of the steelworkers including the coke oven workers with lung cancer rates for smokers and nonsmokers (Table VI-7). While the total steelworker population showed a lung cancer mortality somewhat like that observed for all cigarette smokers and coke oven workers who never worked topside showed rates not too different from those for heavy cigarette smokers, the rates for topside workers and for those employed more than 5 years topside are far beyond what would have been predicted by differential cigarette smoking experience. Again, a synergistic effect of coke oven emissions and smoking cannot be ruled out.

TABLE VI-7. ESTIMATES OF AVERAGE ANNUAL LUNG CANCER MORTALITY RATES (PER 100,000 PERSON-YEARS) FOR SELECTED U.S. SMOKING GROUPS, 1954-1962, AND STEELWORKER GROUPS, 1953-1961
(Lloyd 1974)

	AGE				
	U.S. Smokers	35-44	45-54	55-64	65-74
	Steelworkers	<45	45-54	≥55	
Never smoked or occasional only		-	-	12	29
Current cigarette smokers - total		5	39	158	258
Current cigarette smokers, 1-9/day		-	-	69	119
Current cigarette smokers, over 39/day		-	104	321	559
Steelworkers		12	126	160	
Coke oven, never topside		-	130	387	
Coke oven, topside		228	1,058	1,307	
Coke oven, ≥ 5 years topside		265	1,587	1,961	

Redmond et al. (1972)--

Redmond et al. (1972) expanded the investigation of coke oven workers to include ten selected steel plants in diverse parts of the United States and Canada. Study subjects included men who had worked at the coke ovens at these plants at any time in the 5-year period 1951 through 1955. Criteria used to determine eligibility for inclusion in the study as a coke oven employee were as follows: 1) the man must have had at least 30 consecutive days of employment at the coke ovens, and 2) individuals listed strictly as vacation replacements were not eligible. The comparison group of men was chosen in one of two ways. First, at plants where permanent numbers were assigned sequentially at time of first employment, the nonoven workers were selected by examining the records of the men closest in number to the coke oven workers. The first two men who were employed at the same plant during the period 1951 through 1955, of the same race, and of similar date of initial employment of the coke workers were chosen for the comparison group (i.e., two nonoven workers for each oven worker). At four plants no sequential number was assigned on the basis of starting date; therefore, a second method for selecting the comparison group was devised. A systematic sampling of one out of every five records was made and two nonoven workers were selected for each oven worker on the basis of closest starting date, race, and other study criteria which included the following: 1) the man must have been actively employed sometime in the period 1951 through 1955; 2) the man must never have held a job at the coke ovens, but could have worked in the coal, coke handling, or by-products areas; 3) the man must have had at least 30 days consecutive employment; and 4) vacation replacements were excluded.

Since occupational terminology varied from plant to plant, personnel at the plant were consulted to clarify whether the job in question was at the coke ovens. Follow-up of the workers was through December 31, 1966. For workers who

had left employment prior to December 31, 1966, the method of ascertaining vital status was similar to that of Lloyd and Ciocco (1969). Among all coke plant (oven and nonoven) workers there was a loss to follow-up of only 18 of 2,888 (0.6%) for white employees and 62 workers out of 3,587 (1.7%) for nonwhite employees. In addition to the investigation of the ten non-Allegheny County steel plants, follow-up of all workers who had worked during 1953 at the two Allegheny County steel plants that had coke plants (reported by Lloyd 1971) was updated to 1966. The comparison group for the Allegheny County steel plants consisted of all men who had never worked at the coke ovens.

Expected mortality and relative risk for the coke oven workers were derived in the following manner:

> Tables have been constructed for the coke oven workers and controls by first classifying each plant's cohort by race, age at entry to the study, and the calendar years of follow-up: 1951-1957, 1958-1962, 1963-1966. An expected number of deaths for the coke oven workers was calculated for each of these subgroups with the underlying assumption that both coke oven workers and controls have the same rate within each subgroup. The total expected number of deaths for each plant is the sum of the specific rates for each subgroup multiplied by the number of coke oven workers at risk in the subgroup, while the expected number of deaths for coke oven workers at all plants is the sum of the expected number of deaths for the individual plants. The relative risk is a weighted average of the observed and expected number of deaths for each subgroup, where the weights used are approximately proportional to the precision within each subgroup. The reader should note that, because the relative risk is a weighted average, it cannot be obtained directly by dividing the total observed deaths by the total expected deaths.

Comparison of observed and expected deaths for all workers revealed an excess of malignant neoplasms of the lung, trachea, and bronchus and of the genitourinary organs (Table VI-8). Among the non-Allegheny County workers, a significant excess in lung, trachea, and bronchus cancer deaths occurred in both white and nonwhite workers. In addition, a significant ($P < 0.05$) excess in genitourinary cancer was found among nonwhite workers. As Lloyd (1971) had found, mortality from cancer of the lung, trachea, and bronchus among Allegheny County workers was significant ($P < 0.01$) for nonwhites only. Genitourinary

TABLE VI-8. OBSERVED AND EXPECTED DEATHS AND RELATIVE RISKS FOR MALIGNANT NEOPLASMS OF THE LUNG, TRACHEA, AND BRONCHUS AND THE GENITOURINARY ORGANS FOR COKE OVEN WORKERS EMPLOYED FROM 1951 TO 1955 AT TEN NON-ALLEGHENY COUNTY STEEL PLANTS AND FOR COKE OVEN WORKERS EMPLOYED DURING 1953 AT TWO ALLEGHENY COUNTY, PENNSYLVANIA STEEL PLANTS BY RACE
(adapted from Redmond et al. 1972)

	Non-Allegheny County			Allegheny County			All Plants		
	Observed Deaths	Expected Deaths	Relative Risk	Observed Deaths	Expected Deaths	Relative Risk	Observed Deaths	Expected Deaths	Relative Risk
					WHITE				
Malignant Neoplasms Lung, trachea, and bronchus	13	7.5	3.02*	4	3.4	---§	17	10.8	2.06†
Malignant Neoplasms Genitourinary organs	2	1.8	---§	5	0.9	6.99	7	2.7	3.49†
					NONWHITE				
Malignant Neoplasms Lung, trachea, and bronchus	23	13.4	2.99†	29	17.3	3.77†	52	30.7	3.35†
Malignant Neoplasms Genitourinary organs	10	5.7	3.02†	4	4.9	---§	14	10.6	1.60
					TOTAL				
Malignant Neoplasms Lung, trachea, and bronchus	36	20.9	3.00†	33	20.7	2.69†	69	41.5	2.85†
Malignant Neoplasms Genitourinary organs	12	7.5	2.42*	9	5.8	1.76	21	13.3	2.05†

*Significant at $P < 0.05$ as calculated by a summary chi-square statistic with one degree of freedom.

†Significant at $P < 0.01$ as calculated by a summary chi-square statistic with one degree of freedom.

§Less than five deaths in both observed and expected; significance not calculated.

cancer mortality among Allegheny County workers was significant ($P < 0.01$) for whites only. All other causes of death (other malignant neoplasms, tuberculosis of the respiratory system, other diseases of the respiratory system, cardiovascular-renal diseases, accidents, and all other causes) for both Allegheny and non-Allegheny County workers, were not significantly ($P < 0.05$) different from that expected.

As in the Lloyd (1971) study, the authors delineated the mortality experience by work area and length of exposure. When the cancer mortality for all plants combined (Allegheny County and non-Allegheny County plants) was analyzed by work area, a significant ($P < 0.05$) excess of malignant neoplasms of the lung, trachea, and bronchus was evident in full-time topside workers with most of this excess occurring among nonwhite workers. Additionally, there was a significant ($P < 0.05$) excess of genitourinary cancer in side oven workers. Mortality from other causes was not significantly ($P < 0.05$) different from expected except for cardiovascular renal disease which was significantly less than expected among white topside workers and total (white and nonwhite) side oven workers.

When deaths were analyzed by time spent at the coke ovens, a significant ($P < 0.01$) increase in malignant neoplasms of the lung, trachea, and bronchus and for workers having worked 5 years or more was found, with most of this excess among nonwhite workers. A significant ($P < 0.05$) excess of genitourinary cancer deaths occurred among workers having worked 5 or more years with most of the excess occurring among white workers (6 observed, 2.2 expected, $P < 0.01$ for white workers; 11 observed, 8.4 expected, $P > 0.05$ for nonwhite workers). Mortality from other causes was not significantly different from expected except for "other malignant neoplasms," which was significantly ($P < 0.01$) less than expected among workers having worked less than 5 years.

As Lloyd (1971) had done, Redmond et al. analyzed the combined effect of length of employment and work area. Similar to Lloyd's (1971) findings, malignant neoplasms of the lung, trachea, and bronchus were found to be elevated for all oven workers having worked 5 years or more, and this excess was found to follow a dose-response relationship (Table VI-9). Men employed at full-time topside jobs (subjecting the employee to the greatest exposure) 5 years or more have a relative risk of cancer of the lung, trachea, and bronchus of 6.87 ($P < 0.01$), compared with a lesser risk of 3.22 ($P < 0.01$) for men with 5 years or more of mixed topside and side oven experience, and 2.10 ($P < 0.05$) for men with more than 5 years of side oven experience.

A significant excess (8 observed, 2.6 expected, $P < 0.01$) of kidney cancer was found for total oven workers. Lloyd (1971) had found an excess of kidney cancer, but this excess had not been statistically significant.

Mazumdar et al. (1975)--

Mazumdar et al. (1975) used the mortality data from the Lloyd and Redmond et al. studies and data compiled by the Pennsylvania Department of Health on ambient levels of benzene soluble organic (BSO) material for the topside and side oven areas of the coke oven to analyze cancer mortality dose-response among the coke oven workers. The authors determined an exposure level in mg/m^3-month of BSO material for the workers by multiplying the exposure for the area where the person worked (mg/m^3) times the length of time in months that the person worked there. Cumulative exposure (mg/m^3-months) was divided into four categories: $\leq$ 199, 200-499, 500-699, and $\geq$ 700 mg/m^3-months. Age-adjusted data for the total number of nonwhite workers showed a clear dose-response relationship for lung cancer mortality and cancer at all sites mortality above 200 mg/m^3-month. A dose-response was not seen for white

TABLE VI-9. OBSERVED AND EXPECTED DEATHS AND RELATIVE RISK FOR NEOPLASMS OF THE LUNG, TRACHEA, AND BRONCHUS AND KIDNEY FOR COKE OVEN WORKERS EMPLOYED FROM 1951 to 1955 AT TEN NON-ALLEGHENY COUNTY STEEL PLANTS AND FOR COKE OVEN WORKERS EMPLOYED DURING 1953 AT TWO ALLEGHENY COUNTY, PENNSYLVANIA STEEL PLANTS BY LENGTH OF EMPLOYMENT
(adapted from Redmond et al. 1972)

Malignant Neoplasm	Total Oven			Five Years or More Coke Oven			Five Years or More Full-Time Topside		
	Observed Deaths	Expected Deaths	Relative Risks	Observed Deaths	Expected Deaths	Relative Risks	Observed Deaths	Expected Deaths	Relative Risks
Lung, trachea, and bronchus	69	41.5	2.85*	55	28.0	3.48*	25	7.4	6.87*
Kidney	8	2.6	7.49*	5	1.6	5.69	0	0.1	---§

	Five Years or More Topside and Side Oven Exposure			Five Years or More Side Oven, Never Topside			Less Than Five Years Coke Oven		
Lung, trachea, and bronchus	15	5.5	3.22*	15	8.7	2.10†	14	9.9	1.70
Kidney	3	0.4	---§	2	0.7	---§	0	0.2	---§

*Significant at $P < 0.01$, significance based on a summary chi-square with one degree of freedom.

†Significant at $P < 0.05$, significance based on a summary chi-square with one degree of freedom.

§Less than five deaths in both observed and expected; significance not calculated.

workers. Fewer white workers than nonwhite workers worked at the topside of the coke ovens, however, which would have reduced the probability of detecting a cancer risk for whites in the high exposure group and thus would have reduced the probability of detecting a cancer mortality dose-response. Also, the authors stated that "since time, as well as level of concentration, is necessary to achieve a high-value exposure index, any oven worker dying from lung cancer within a moderate or small period of time from first exposure can, obviously, no longer accumulate additional exposure. Consequently, if the total exposure doses required to increase the risk of lung cancer in a white individual are less than in the nonwhite individual and/or the average latent period is shorter than that of the nonwhite worker, the same strong association between total exposure and increasing risk of lung cancer will not be demonstrated by a time dependent index such as the one employed here."

Mazumdar et al. found that lung cancer mortality was less than expected for workers exposed to $\leq$ 200 mg/m^3-month benzene-soluble material. This should not be construed as a no effect level, however, because as the authors themselves stated, a diluting effect may result from inclusion in the study group of coke oven workers with too few years of observation to allow for the appearance of a latent effect. The workers in this study were followed for a period of only 14 years and, as the authors themselves indicate, the average latent period for occupational lung cancers may range from 15 to 25 years.

Redmond et al. (1976)--

Redmond et al., in an update of the historical prospective cohort study begun by Lloyd, confirmed earlier findings of a statistically significant excess of lung cancer in coke oven workers. Follow-up was extended through December 31, 1970, on 58,828 men employed at seven Allegheny County steel plants in 1953

and was more than 99.9% complete with some 12,818 men reported deceased. Expected deaths and relative risk were calculated in the same manner as in the Redmond (1972) study.

The excess of respiratory cancer found in the Redmond et al. (1972) study continued. With the longer period of follow-up and the aging of the cohort, the greater number of deaths made it possible to consider 10+ and 15+ years of exposure as well as 5+ years. Observed deaths from cancer of the respiratory system and the relative risks for coke oven workers are shown in Table VI-10. As can be seen from the table there was a pronounced dose-response both by length of exposure and by work site. A strong dose-response for cancer mortality, all sites, was also found by length of exposure and by work site (Table VI-11).

TABLE VI-10. OBSERVED DEATHS AND RELATIVE RISKS OF DEATH FROM CANCERS OF THE RESPIRATORY SYSTEM, 1953-1970, FOR COKE OVEN WORKERS BY WORK AREA AND LENGTH OF EMPLOYMENT THROUGH 1953 (adapted from Redmond et al. 1976)

Work Area	Years Employed Through 1953					
	5+		10+		15+	
	Obs.	R.R.	Obs.	R.R.	Obs.	R.R.
Coke Oven	54	3.02*	44	3.42*	33	4.14*
Oven Topside Full-time	25	9.19*	16	11.79*	8	15.72*
Oven Topside Part-time	12	2.29*	16	3.07*	18	4.72*
Oven Side Only	17	1.79†	12	1.99*	7	2.00

*Significant at $P < 0.01$.
†Significant at $P < 0.05$.

TABLE VI-11. OBSERVED DEATHS AND RELATIVE RISKS OF DEATH FROM MALIGNANT NEOPLASMS, 1953-1970, FOR COKE PLANT WORKERS BY WORK AREA AND LENGTH OF EMPLOYMENT THROUGH 1953 (adapted from Redmond et al. 1976)

Work Area	Years Employed Through 1953					
	5+		10+		15+	
	Obs.	R.R.	Obs.	R.R.	Obs.	R.R.
Total Coke Plant	166	1.47*	136	1.50*	108	1.62*
Coke Oven	101	1.66*	85	1.95*	63	2.40*
Oven Topside Full-time	35	3.70*	22	5.12*	12	7.63*
Oven Topside Part-time	26	1.59†	31	1.85*	32	2.73*
Oven Side Only	40	1.17	32	1.46	19	1.51
Nonoven	65	1.28	48	1.10	39	1.13
No One Coke Plant Area	0	---§	3	---§	6	1.34

*Significant at $P < 0.01$.
†Significant at $P < 0.05$.
§Less than five deaths.

Redmond et al. (1979)--

The most recent update of mortality data on the coke plant workers cohort (Lloyd and Ciocco 1969, Lloyd et al. 1970, Lloyd 1971, Redmond et al. 1972, Redmond et al. 1976, and Mazumdar et al. 1975) extends the analysis through 1975 (Redmond et al. 1979). The vital status of the approximately 59,000 steelworkers in the Allegheny County study and the vital status of the steelworkers in the ten non-Allegheny County steel plants were updated in order to determine the expected cause-specific deaths. Work histories were not updated because of lack of funding. Expected deaths and relative risk were derived in the same manner as in the Redmond et al. (1972) study.

Among the coke oven workers in Allegheny County, excess mortality from malignant neoplasms of the lung, trachea, and bronchus continued (Table VI-12). As in earlier studies, this excess was significant ($P < 0.01$) among nonwhite workers. Excess mortality of cancer of the kidney became significant ($P < 0.05$) for white workers. Also, excess mortality from prostate cancer among total oven workers became significant for the first time (20 observed, 12.74 expected, $P < 0.05$). For workers ever having been employed at the coke ovens through 1953, excess mortality from all cancers; cancer of the lung, trachea, and bronchus; kidney; and prostate is reported in Table VI-12. In addition to the tumor sites listed in Table VI-12, the relative risk of mortality for "all other cancers" for full-time topside workers was significantly ($P < 0.05$) elevated (relative risk = 2.50). "All other cancers" include neoplasms other than of the respiratory system, digestive organs and peritoneum, genitourinary organs, buccal and pharyngeal organs, lymph and hematopoietic tissues, and skin. Among coke oven workers employed for "five or more years through 1953," observed and expected mortality and relative risk from all cancers and from cancer of the lung, trachea, and bronchus; kidney; and prostate is reported in Table VI-13.

TABLE VI-12. OBSERVED AND EXPECTED LUNG, TRACHEA, AND BRONCHUS; KIDNEY; AND PROSTATE CANCER DEATHS, 1953-75, AND RELATIVE RISKS FOR ALLEGHENY COUNTY, PENNSYLVANIA STEELWORKERS EVER EMPLOYED AT THE COKE OVENS THROUGH 1953 BY RACE AND PLACE OF EMPLOYMENT (adapted from Redmond et al. 1979)

Cause of Death	Place of Employment														
	Total Coke Oven			Oven Topside Full-time			Oven Topside Part-time			Side Oven			Nonoven		
	Obs.	Exp.	R.R.	Obs.	Exp.	R.R.	Obs.	Exp.	R.R.	Obs.	Exp.	R.R.	Obs.	Exp.	R.R.
Malignant Neoplasm															
all sites	179	144.38	1.29*	56	25.91	2.37*	25	21.86	1.15	98	92.89	1.06	115	102.75	1.13
white	63	62.47	1.01	4	5.55	0.72	24	20.97	1.15	35	35.91	0.97	94	90.15	1.05
nonwhite	116	81.91	1.55*	52	20.37	2.90*	1	0.89	--§	63	56.97	1.13	21	12.60	1.76†
Lung, Trachea, and Bronchus	86	47.43	2.05*	35	8.56	4.87*	8	6.84	1.17	43	28.70	1.58*	28	30.61	0.91
white	23	19.02	1.22	2	1.78	--§	8	6.58	1.22	13	10.60	1.23	26	27.54	0.94
nonwhite	63	28.41	2.87*	33	6.78	6.17*	0	0.25	--§	30	18.10	1.83*	2	3.07	--§
Kidney	7	2.61	2.88†	2	0.51	--§	3	0.40	--§	2	1.61	--§	1	1.79	--§
white	6	1.20	5.42*	1	0.11	--§	3	0.38	--§	2	0.65	--§	1	1.54	--§
nonwhite	1	1.41	--§	1	0.40	--§	0	0.02	--§	0	0.96	--§	0	0.25	--§
Prostate	20	12.74	1.67†	4	2.54	--§	3	1.41	--§	13	8.48	1.60	9	7.82	1.16
white	8	4.13	1.99	0	0.30	--§	3	1.29	--§	5	2.49	2.04	4	5.73	0.69
nonwhite	12	8.62	1.49	4	2.23	--§	0	0.12	--§	8	6.00	1.39	5	2.10	2.53

*Significant at $P < 0.01$.

†Significant at $P < 0.05$.

§Less than five deaths in both observed and expected; significance not calculated.

TABLE VI-13. OBSERVED AND EXPECTED LUNG, TRACHEA, AND BRONCHUS; KIDNEY; AND PROSTATE CANCER MORTALITY, 1953-75, AND RELATIVE RISKS FOR ALLEGHENY COUNTY, PENNSYLVANIA STEELWORKERS EMPLOYED FOR 5 YEARS OR MORE AT THE COKE OVENS THROUGH 1953 BY RACE AND PLACE OF EMPLOYMENT
(adapted from Redmond et al. 1979)

Cause of Death	Place of Employment														
	Total Coke Oven			Oven Topside Full-time			Oven Topside Part-time			Side Oven			Nonoven		
	Obs.	Exp.	R.R.	Obs.	Exp.	R.R.	Obs.	Exp.	R.R.	Obs.	Exp.	R.R.	Obs.	Exp.	R.R.
Malignant neoplasm															
all sites	123	89.02	1.46*	37	14.24	2.90*	34	24.05	1.44†	52	47.39	1.11	88	71.54	1.25
white	32	32.70	0.98	2	2.53	--§	18	16.31	1.11	12	13.87	0.86	73	62.70	1.18
nonwhite	91	56.32	1.81*	35	11.71	3.45*	16	7.74	2.18*	40	33.53	1.22	15	8.83	1.81†
Lung, Trachea, and Bronchus	63	28.30	2.63*	25	4.38	6.94*	14	7.50	1.91†	24	13.45	1.91*	23	20.84	1.11
white	12	10.02	1.20	2	0.76	--§	5	5.23	0.96	5	4.00	1.26	20	18.83	1.06
nonwhite	51	18.28	3.82*	23	3.62	8.10*	9	2.27	4.38*	19	9.45	2.24*	3	2.00	--§
Kidney	6	1.83	3.55*	0	0.27	--§	4	0.52	--§	2	0.98	--§	2	1.28	--§
white	5	0.64	8.50*	0	0.04	--§	3	0.32	--§	2	0.25	--§	2	1.09	--§
nonwhite	1	1.19	--§	0	0.22	--§	1	0.20	--§	0	0.73	--§	0	0.19	--§
Prostate	12	8.73	1.43	3	1.56	--§	3	1.83	--§	6	5.12	1.19	7	5.94	1.19
white	3	2.25	--§	0	0.18	--§	2	0.98	--§	1	1.09	--§	4	4.42	--§
nonwhite	9	6.48	1.47	3	1.37	--§	1	0.85	--§	5	4.03	1.27	3	1.51	--§

*Significant at $P < 0.01$.

†Significant at $P < 0.05$.

§Less than five deaths in both observed and expected; significance not calculated.

For coke oven workers employed for "five or more years through 1953," the relative risks of mortality from neoplasms of the lung, trachea, and bronchus, as well as from kidney cancer, were higher than that for workers "ever employed through 1953."

Among non-Allegheny County coke oven workers ever employed during 1951-55, significant ($P < 0.05$) excess mortality from cancer of the lung, trachea, and bronchus continued for both white and nonwhite workers. In addition, total deaths from cancer at all sites was significantly in excess (194 observed, 162.56 expected, $P < 0.01$). Among nonwhites, a significant excess of prostate cancer mortality (15 observed, 9.44 expected, $P < 0.05$) was found (Tables VI-14 and VI-15). These risks increased among workers employed for 5 years or more. As in the Redmond et al. (1972) update, a dose-response was also evident by work area. For workers employed for more than 5 years during 1951-55, the relative risk of cancer of the lung, trachea, and bronchus was 3.47 ($P < 0.01$) for full-time topside, 2.31 ($P < 0.05$) for mixed topside and side oven, and 2.06 ($P < 0.05$) for side oven experience. Kidney cancer mortality, which was significantly ($P < 0.05$) elevated among the white Allegheny County workers, was not significantly elevated among the non-Allegheny County workers. Cancer of sites other than lung, trachea, and bronchus and prostate was not significantly ($P < 0.05$) in excess; neither were causes of death other than cancer.

Among the 10 non-Allegheny County plants there was a considerable variation from plant to plant in the relative risks for all causes, and one plant had excessive risks for nearly every major cause of death. Although the amount of risk for lung cancer varied among plants, there was a consistent pattern of the number of observed deaths exceeding the number of expected deaths.

TABLE VI-14. OBSERVED AND EXPECTED LUNG, TRACHEA, AND BRONCHUS; KIDNEY; AND PROSTATE CANCER MORTALITY, 1951-1975, AND RELATIVE RISKS FOR NON-ALLEGHENY COUNTY STEELWORKERS EVER EMPLOYED DURING 1951-1955, BY RACE AND PLACE OF EMPLOYMENT
(adapted from Redmond et al. 1979)

Cause of Death	Total Coke Oven			Place of Employment Oven Topside Full-time			Oven Topside Part-time			Side Oven		
Malignant Neoplasm	Obs.	Exp.	R.R.	Obs.	Exp.	R.R.	Obs.	Exp.	R.R.	Obs.	Exp.	R.R.
All sites	194	162.56	1.36*	71	45.56	1.79*	14	18.34	0.69	109	92.30	1.28†
White	63	56.92	1.18	12	10.82	1.13	12	13.76	0.83	39	31.70	1.35
Nonwhite	131	105.64	1.47*	59	34.75	2.04*	2	4.58	----§	70	60.60	1.24
Lung, Trachea, and Bronchus	82	53.66	2.20*	39	16.23	3.52*	8	4.76	1.96	35	25.99	1.55
White	28	18.64	2.16*	6	3.41	2.15	7	3.90	2.22	15	9.37	2.07
Nonwhite	54	35.02	2.23*	33	12.82	3.98*	1	0.86	----§	20	16.62	1.30
Kidney	5	4.13	1.36	1	0.95	----§	1	0.47	----§	3	2.51	----§
White	2	1.40	----§	0	0.14	----§	1	0.32	----§	1	0.71	----§
Nonwhite	3	2.73	----§	1	0.81	----§	0	0.15	----§	2	1.80	----§
Prostate	17	12.23	1.81	5	2.94	1.94	0	0.68	----§	12	7.75	2.03
White	2	2.79	----§	0	0.44	----§	0	0.59	----§	2	2.19	----§
Nonwhite	15	9.44	2.45†	5	2.50	2.43	0	0.18	----§	10	5.56	2.65†

*Significant at $P < 0.01$.
†Significant at $P < 0.05$.
§Less than five deaths (observed and expected).

TABLE VI-15. OBSERVED AND EXPECTED LUNG, TRACHEA, AND BRONCHUS; KIDNEY; AND PROSTATE CANCER MORTALITY, 1951-1975, AND RELATIVE RISKS FOR NON-ALLEGHENY COUNTY STEELWORKERS EMPLOYED FOR 5 OR MORE YEARS AT TIME OF ENTRY TO STUDY BY RACE AND PLACE OF EMPLOYMENT (adapted from Redmond et al. 1979)

Cause of Death	Place of Employment: Total Coke Oven			Oven Topside Full-time			Oven Topside Part-time			Side Oven		
Malignant Neoplasm	Obs.	Exp.	R.R.*	Obs.	Exp.	R.R.*	Obs.	Exp.	R.R.*	Obs.	Exp.	R.R.*
All sites	118	96.04	1.45†	42	26.03	1.99†	27	24.92	1.11	49	39.61	1.35
White	33	29.25	1.23	1	1.78	----¶	14	13.74	1.03	18	13.50	1.54
Nonwhite	85	66.79	1.57†	41	24.25	2.16†	13	11.18	1.20	31	26.11	1.27
Lung, Trachea, and Bronchus	50	31.75	2.49†	19	8.51	3.47†	13	6.87	2.31§	18	11.23	2.06§
White	14	9.42	2.15	0	0.57	----¶	6	3.86	1.83	8	4.06	3.48§
Nonwhite	36	22.33	2.66†	19	7.94	4.00†	7	3.01	2.90§	10	7.16	1.59
Kidney	3	2.73	----¶	0	0.63	----¶	1	0.79	----¶	2	1.33	----¶
White	2	0.98	----¶	0	0.00	----¶	1	0.38	----¶	1	0.39	----¶
Nonwhite	1	1.74	----¶	0	0.63	----¶	0	0.42	----¶	1	0.94	----¶
Prostate	13	7.92	2.63§	6	2.39	3.71§	2	1.41	----¶	5	2.75	2.40
White	1	1.38	----¶	0	0.16	----¶	0	0.65	----¶	1	0.79	----¶
Nonwhite	12	6.54	3.59§	6	2.23	4.21§	2	0.76	----¶	4	1.96	----¶

*Relative risks that are statistically significant were not indicated in Redmond et al. (1979). These were obtained by personal communication with Redmond (1981).

†Significant at $P < 0.01$.

§Significant at $P < 0.05$.

¶Less than five deaths (observed and expected).

British Studies

Reid and Buck (1956)--

Reid and Buck (1956) studied the causes of death of men dying while "on the books" of the British National Coal Board coking plants during the period 1949-54. This included both retired and actively employed workers. Causes of death were ascertained through the funeral fund of the National Union of Mineworkers or through a vital statistics search of the General Register Office. The authors analyzed mortality for the currently employed and retired workers separately.

For the actively employed, information on age and job distribution was obtained from a special census taken in 1952. Additional information on the nature and duration of different jobs held in the plants was obtained from a sample of 10% of the workers. Total man-years of exposure over the period 1949-54 were divided proportionally according to the age and job distributions found in the 1952 special census. Expected deaths were derived by multiplying the accumulated man-years in each age and job category by the comparable cause and age-specific death rates derived from a "large industrial organization" during the period 1950-54. Although the authors did not disclose the identity of this large industrial organization, they do state that the derived death rates for this industry were similar to those of civil servants of the General Post Office, 60 years of age or younger, during the same period. Data on civil servants were not available beyond the usual retiring age of 60.

The coking plant workers generally fell into four main groups. The first group consisted of men involved in operating the coking ovens, driving the ram, filling the oven, clearing the hydraulic main, etc. The second group was involved in the recovery of by-products such as tar, ammonia, and benzole. The

third group was composed of laborers whose duties and contacts with the processes varied greatly. The fourth group included maintenance men and craftsmen who occasionally were in contact with the processes. The number of workers falling into each of these four job groups was not reported. Mortality by cause and occupational exposure is reported in Table VI-16.

There was a significant difference between observed and expected mortality for all other cancer combined (minus respiratory cancer) for coke workers (24 observed vs. 16 expected; $P < 0.05$, two-tailed test). For respiratory cancer, however, there was no increase in observed mortality over that expected. If the occupational classifications are divided* according to whether the men were ever employed at any time as oven workers or never employed as oven workers, oven workers would have a significantly elevated risk from cancers at all sites (40 observed vs. 32 expected; $P < 0.05$, one-tailed test) and an elevated risk (14 observed vs. 10 expected) of respiratory cancer, which is not statistically significant. A significant excess risk of death (except respiratory cancer) is apparent in men who never worked at the coke oven (205 observed vs. 162 expected; $P < 0.01$, one-tailed test). Men employed at any time as by-product workers do not appear to be subject to an excess risk of respiratory cancer, "cancer all sites combined" or "deaths all causes combined except respiratory cancer." By contrast, men who were never by-product workers have a significantly elevated risk of death excluding respiratory cancer (254 observed vs. 218 expected; $P < 0.01$, one-tailed test).

Twenty workers who died from lung cancer while still on the company payroll, and for whom detailed occupational histories were available, spent an average of

*This division was proportionally distributed according to the work histories of the 10% random sample (800 workers).

TABLE VI-16. MORTALITY* IN COKING PLANT WORKERS ACCORDING TO OCCUPATIONAL EXPOSURE
(adapted from Reid and Buck 1956)

	Mortality by Last Job Held								Mortality by Work History					
	Oven Workers		By-product Workers		Maintenance Workers		Men Employed at Any Time as Oven Workers		Men Never Employed as Coke Oven Workers		Men Employed at Any Time as By-product Workers		Men Never Employed as By-product Workers	
	O	E	O	E	O	E	O	E	O	E	O	E	O	E
Respiratory cancer	4	5	3	3	14	14	14	10	7	13	4	6	17	17
All cancers†	24§	16	9	9	38	48	40¶	32	31	41	16	18	55	55
Other causes	50	49	29	26	166	141	71	95	174	121	46	53	199	163
Total excluding respiratory cancer	74	65	38	35	204	189	111	127	205¶	162	62	71	254	218

*O = observed deaths, E = expected deaths (adjusted for age) based on an unspecified industry for the period 1949-1954.

†"All cancers" was probably meant to be reported by Reid and Buck as "all other cancers." Otherwise the number for the "total excluding respiratory cancer" is in error.

§Significantly in excess of expected ($P < 0.05$, two-tailed test).

¶Significantly in excess of expected ($P < 0.05$, one-tailed test).

23.0 years in the coking plants and 16.3 as coke oven workers. These figures are not appreciably different from the average duration of employment for men of the same age included in the random sample of 800 (25.3 years in the coking plants and 16.7 years as oven workers). Comparison of "average" employment duration may not reflect differences in length of employment between the lung cancer cases and the total random group, however. It is possible that a number of older workers in either group may have worked for only a short period of time which might bias any comparison of averages.

The number of retired workers was not known; only the number of retirees who died was known. Therefore, for retired workers, the proportion of respiratory cancer deaths to all cancer deaths and the proportion of all cancer deaths to total deaths were compared among occupational groups (oven workers, by-product workers, laborers, maintenance workers, and foremen) by last job worked. They were also compared by whether or not they had ever worked as oven workers and whether or not they had ever worked as by-product workers. No differences were found by either comparison. Since the ages of death of the retired workers were not known, mortality was not compared by age.

The authors reported a significant ($P < 0.05$, one-tailed test) excess in other than respiratory cancer mortality for workers whose last job was at the coke ovens. No excess in respiratory cancer was seen however. For workers who had ever worked at the coke ovens, there was no significant ($P < 0.05$) increase in either respiratory or other cancer. For retired workers, no difference was seen in the proportions of cancer deaths. The amount of confidence that can be placed in the validity of the results of this study is in question, however, because of the superficiality and lack of details in the description given by the author regarding the methodology and conduct of the study. The authors fail to adequately define the basic study population. It is unclear whether the

study population includes all men who ever had a record of employment in the coke plant during the period 1949-54, since the author refers to an "average" of 8,000 men employed in National Coke Board (NCB) coking plants or just those found through the special 1952 census. If the cohort consisted of workers employed in 1952, and since there was little or no follow-up of any of these members, it appears that this study is little more than a cross-sectional study of mortality in a conglomerate of several different coke plants. As much as can be determined, the observed deaths are only those deaths of members of the study group who were employed in the period 1949-54. Also, it should be noted that the number of lung cancer deaths observed may have been deficient since only men dying while "on the books" of the coking plants during the period 1949 to 1954 were included. Lloyd (1971) reported (apparently from communication with Reid and Buck) that men were removed from the books after prolonged absence from work.

Since follow-up after 1954 was nonexistent, latent effects were not adequately considered. Furthermore, the death rates utilized in calculating expected deaths were those prevailing in an unknown "large industrial organization." It is not known how they were derived or defined. Therefore, it cannot be said with any certainty that they are compatible with whatever definition the authors utilized to derive the study population. Regarding the retired workers, comparison of proportionate mortality without any age-adjustment must be viewed with some skepticism. In short, this study leaves many unanswered questions and is so ambivalent that it is difficult to place any confidence in the study results.

Davies (1977, 1978)--

Davies (1977, 1978) reported on the mortality experience from May 1954 until

June 1965 of 610 coke oven workers at two South Wales coke works (Works A and B). The 610 workers employed at the two plants had 6261.5 man-years of follow-up; eighty-eight had died during the follow-up period. Male mortality rates for England and Wales (average for 4 years, 1958-61) were multiplied times the person-years of follow-up in each age category to obtain the expected deaths for the coke workers. Observed and expected deaths were for total mortality from malignant neoplasms of different sites, cardiovascular mortality, respiratory disease mortality, and mortality from other causes. The Standard Mortality Ratio for the two coke works was 92. There was no significant ($P < 0.05$) excess in mortality for any of the diseases evaluated including cancer of the lung (8 observed vs. 8.94 expected), cancer of the bladder and kidney (3 observed vs. 1.9 expected), and respiratory disease (14 observed vs. 12.6 expected). There was a significant ($P < 0.05$, one-tailed test) negative difference between the observed and expected deaths from cardiovascular disease (29 observed vs. 41.36 expected).

The follow-up period as reported in this study was 11 years (1954-1965). The follow-up period would have been longer, of course, for those workers who started work before 1954. Without further information, however, the follow-up period in the Davies study may not be considered adequate to detect differences in lung cancer mortality since the latency period from exposure to the start of lung cancer may be as long as 20 to 30 years.

Davies did not describe the degree of environmental exposure of the coke workers (e.g., topside of ovens, side of ovens, nonovens) as has been done in other studies (Lloyd 1971, Redmond et al. 1972, Redmond et al. 1976, Redmond et al. 1979). Extremely high risk has been found to be limited to a small proportion of the coke oven population. A comparison of coke oven workers to non-coke oven workers, without any further delineation, may not be able to detect differences in lung cancer risk.

Collings (1978)--

Collings (1978) conducted a follow-up study of 2,854 male coke workers employed in 14 coke works scattered throughout Great Britain. To be included in the study, these workers had to have attained a minimum of 1.5 years continuous employment at the plant ending in July 1967. They were subsequently followed 9 years from August 1, 1967 to August 1976 and their mortality experience was tabulated. The cohort was derived from lists provided by the coke works. For each person in the cohort, a questionnaire was submitted to the respective coke works asking personal information, work since joining the coke industry, and work prior to date of entry; completion of the questionnaire was arranged by a senior medical officer familiar with the works. Three distinct occupational groups, nonovens, part-ovens, and ovens were designated. The "nonovens" category included 392 men who had no contact with the ovens. "Part-ovens" included 742 men with some occasional contact with oven work. "Ovens" was comprised of 1,615 men who had at least one specialized oven job prior to August 1, 1967. Length of employment was tabulated for the "ovens" group but not for the other groups.

For comparison, expected deaths were derived in two separate ways. In the first method, the mortality experience of men in the study cohort was compared to that of all men in Great Britain. Person-years at risk were accumulated in the appropriate age, calendar-time period, cancer latency period, and occupational groups. Standard population death rates were applied to the comparable person-years categories to derive expected deaths and finally Standard Mortality Ratios (SMRs). In the second method, the author derived a "comparative mortality figure" (CMF) for each occupational category (ovens, nonovens, and part-ovens). The CMF was derived as the ratio of the sum of the observed mortality across all age categories to that of the sum of the expected mortality.

Expected mortality was derived in the following manner:

$$\frac{\text{Number in age group of occupational category} - \text{Number of deaths for the particular cause in the age group of the occupational category}}{\text{Number in age group for all occupational categories} - \text{Number of deaths for the particular cause in the age group of the occupational category}} \times \text{All deaths for the particular cause in the age group}$$

= Expected deaths for the occupational category by age group.

With regard to latency and specific job within the coke works, only lung cancer mortality appears to be somewhat excessive but not significant when contrasted with rates in Great Britain (45.0 observed vs. 35.7 expected, P = 0.12). If only the coke oven workers in England and Wales (not Scotland) are considered and population mortality data from those two countries are used to derive expected deaths, then lung cancer mortality is significantly elevated (41 observed vs. 32.4 expected mortality, $P < 0.05$). However, lung cancer mortality is not significant when manually-skilled (40.8 expected), partly-skilled (39.5 expected), or unskilled (44.5 expected) workers in England and Wales are used to derive expected lung cancer deaths. The author notes that most workers in the study cohort would be considered partly-skilled and the lung cancer mortality in that group is almost identical to that of the partly-skilled in England and Wales. However, overall mortality is 17% lower (254 observed vs. 306.4 expected) compared to partly-skilled workers. This observation led the author to comment that the high proportion of lung cancers in the study cohort may be related to occupational factors.

A smoking history questionnaire was submitted to a limited subgroup of study members who were still employed at the works during data collections (1973 to 1975), and who attended the works medical center at that time. This

represented only 41% of the workforce. Based on such limited data, the author concluded that the 26.7% excess lung cancer mortality could not be due to excessive tobacco consumption on the part of members of the study population. Cigarette consumption in 4 of 14 coke works was, according to the author, "above average," while in the remainder it was below average.

With respect to the three occupational groups, i.e., ovens, part-ovens, and nonovens, the comparative mortality figure computed for each occupational group for certain selected causes, including lung cancer, revealed no statistically significant excesses. However, the author reports that when SMRs were calculated for the same occupational groups (utilizing the male population of Great Britain), lung cancer was excessive in all three groups, but no tabular data is provided to support this assertion.

The risk of lung cancer as well as the risk of all malignant neoplasms apparently increases with increasing lengths of employment on the coke ovens, although not significantly so. The population of employees who had worked on the ovens for more than 10 years had an SMR of 127 and a CMF of 1.24 based on 17 observed lung cancers. Additionally, the SMR and CMF for the cause "all malignant neoplasms" was 126 and 1.30, respectively, based upon 30 observed cancer deaths in the same workers. Had the author looked at latency and length of employment together, the contribution of both to the increase in risk may have been better defined.

The findings above, the author concludes, tend to support American studies that show an excessive risk of lung cancer in coke workers, although overall mortality in general is "favorable." The fact that none of the findings are statistically significant may be a consequence of the short 9-year period of observation.

Another 6 to 10 years of observation may be needed before a statistically significant excess risk of lung cancer is found. Secondly, the author did not differentiate between topside and side oven workers. The earlier American studies have pinpointed the highest risk mainly to topside workers. Thirdly, to measure the impact of length of employment on risk in coke ovens work is meaningless unless latent factors are considered simultaneously. What the author perceives as a correlation of length of exposure to risk may well be only a veiled manifestation of a latent effect.

Sakabe et al. 1975 --

Sakabe et al. (1975) studied lung cancer mortality and cancer mortality (all sites) for the years 1949-1973* among retired coke oven workers from 11 companies in Japan. At the time of the study there were 36 companies producing coke in Japan. No explanation was provided as to why the other companies did not participate in the study. Mortality was ascertained by a questionnaire to the industrial physician or chief health inspector of each industry. The expected mortality was calculated from the vital statistics for the general Japanese male population for the corresponding period of time. Coke ovens in Japan are categorized as those for blast furnace coke, those for casting coke, and those for general coke, depending on the purpose for which the coke is manufactured. The furnace temperature of coke ovens is about 1300°C for blast furnace coke, 1000°C for casting coke, and 1200°C for general coke.

The 11 companies surveyed included four iron and steel plants, four city gas companies, and three "coke manufacturing chemical companies and coke manufacturing companies." Coke ovens in the iron and steel plants in Japan are used solely for manufacturing blast furnace coke, and coke ovens of city gas plants are used for manufacturing coke for blast furnaces, casting furnaces, and general use. No description of the purpose of the coke production was given for the three "coke manufacturing chemical companies and coke manufacturing companies." There was no statistical difference between the observed and expected cancer (all sites) mortality or lung cancer mortality when the study population consisted of retired workers from all 11 companies combined.

Sakabe et al. then compared the observed cancer mortality for the 674 retired workers from the four iron and steel plants and the 1,261 retired

*Although 2,201 workers who retired between 1947 and 1973 were traced, only the cancer deaths from 1949 to 1973 were included in the study. The authors provided no explanation for the period 1947 to 1949.

workers at the four city gas companies with the expected cancer mortality for those companies. The number of retired workers among the "coke manufacturing chemical companies and coke manufacturing specialized companies" was too small for statistical comparison of observed and expected cancer mortality. Cancer mortality (all sites) was not significantly ($P < 0.05$) different from that expected for either the iron and steel plants (36 observed, 31.87 expected) or the city gas companies (51 observed, 69.77 expected). Lung cancer mortality among the iron and steel plants coking companies was significantly greater than expected however (8 observed, 3.38 expected, $P \leqq 0.022$). No statistical difference between the observed and expected lung cancer mortality was found for the city gas companies.

When Sakabe et al. looked at proportionate cancer mortality, the proportion of lung cancer cases to all cancers was significantly greater ($P \leqq 0.05$) than expected for the iron and steel plants but not for the city gas companies.

Sakabe et al. also studied the age of lung cancer onset and working period at the coke ovens. For all coke oven (including both city gas and iron and steel plants) workers, lung cancer was found to occur after 5 years of working and at the age of 50 or over (except for one individual whose age was reported as 44). Among coke oven workers of the iron and steel plants, lung cancer occurred after 10 years of working and at the age of over 50 years. Smoking data for the lung cancer cases was incomplete. Of the 18 coke oven workers who died from lung cancer, 10 were smokers, 2 were nonsmokers, and no information was available for 6. Reliable information concerning the amount of smoking for each smoker could not be obtained.

In conclusion, Sakabe et al. found a statistically significant ($P \leqq 0.022$) excess of lung cancer mortality among workers retired from plants that produce coke for blast furnaces, but not among retired coke oven

workers from city gas companies. The strength of this association is weakened, however, by the lack of adequate smoking data. An excess of lung cancer mortality among the coke oven workers at the city gas companies was not found perhaps because the coke ovens at the gas companies may be operated from 100°C to 300°C lower than the coke ovens at the iron and steel plants.

The authors also found that the proportion of lung cancer mortality to all cancer mortality was significantly ($P < 0.05$) in excess among retired coke oven workers of iron and steel plants, but not among retired coke oven workers of city gas industries.

Summary

Lloyd (1971) and Redmond et al. (1972, 1976, 1979) found an excess of total cancer mortality and respiratory organ cancer mortality among workers employed at coke works. Both were found to be dose-related. Workers exposed to low (side oven), medium (side oven and topside), and high (topside only) exposure had increasingly greater excesses of total cancer mortality rates and lung cancer mortality rates. Not only was there an increase in excess lung cancer mortality by occupation site, but there was an increase by length of exposure as well. Workers exposed 5 years or more had a greater excess of lung cancer than workers exposed less than 5 years.

As indicated earlier, one criticism of the Lloyd (1971) and Redmond et al. (1972, 1976, 1979) studies is that smoking data were not taken. An analysis of lung cancer mortality is generally not considered adequate without smoking data. However, the dose-responses seen in the Lloyd and Redmond et al. studies is so striking that it is improbable that the excess in lung cancer mortality could be explained by differences in smoking habits.

An apparent discrepancy in the Lloyd and Redmond et al. studies is that the excess lung cancer mortality among nonwhite workers in Allegheny County was significant while that among white workers was not significant. Several explanations have been offered for this phenomenon. Perhaps the most obvious explanation is that more nonwhites than whites were employed at the coke ovens in Allegheny County, particularly as full-time topside workers, and the excess among nonwhites may have been significant because of their larger sample size. Redmond et al. (1979) suggested that the difference may be because, within the respective subsites at the coke ovens, whites and nonwhites may have had different jobs and consequently different exposure to volatile hydrocarbon effluents. Redmond et al. (1979) also suggested that the difference may be

because mortality rates for lung cancer have been shown in other studies to be inversely correlated with educational qualifications and occupational category. As Redmond et al. (1979) noted, however, the expanded studies of non-Allegheny County coke oven workers found that the lung cancer risk was significant for both whites and nonwhites. In addition, Mancuso (1977) has suggested that the difference in cancer mortality risk between the nonwhites and whites in the Allegheny County plants may have resulted because a majority of the nonwhites were migrants from the South.* Since Mancuso did not report how many of the total steelworker population (from which the expected mortality data were derived) were also migrants from the South, it would be premature to conclude that being a nonwhite worker from the South predisposes one to cancer. Also, it would be difficult to separate the effects of place of origin and race from the effects of industrial exposure. Impoverished migrant workers may well take any job that is offered including those jobs that place persons at an excess risk of cancer. Finally, as noted above, the Redmond et al. studies of non-Allegheny County coke oven workers found that excess risk of lung cancer was significant for both whites and nonwhites.

Prostate cancer mortality was significantly ($P < 0.05$) increased among all Allegheny County coke oven workers ever employed in 1953. For workers having worked 5 or more years, however, the excess was not significant. Similar to the apparent discrepancy between whites and nonwhites above, an excess of prostate cancer mortality did exist among workers employed 5 years or more, but possibly because of small sample size, the excess was not significant. Among the non-Allegheny County workers, the excess in

*In 1974, Mancuso and Sterling reported that migrants in Ohio, particularly migrants from the South, had higher death rates for various cancer sites than did persons born in Ohio.

prostate cancer was significant for nonwhite workers only.

Kidney cancer mortality was significantly increased ($P < 0.01$) among white workers in the Allegheny County study. Small excesses in kidney cancer were seen for both whites and nonwhites in the non-Allegheny County plants, but these excesses were not significant ($P < 0.05$).

Sakabe et al. (1975) found that there was a significant excess of lung cancer mortality among retired Japanese coke oven workers at iron and steel coking plants when compared to cancer mortality among the general population. Sakabe et al. did not divide the retired workers into exposure categories as had been done in the American studies. Coke oven workers from the low exposure groups would have been mixed with persons from high exposure groups. It is likely that persons in the high exposure groups would have been at an even greater lung cancer risk. A lack of smoking data, however, weakens the findings of the study.

Reid and Buck (1956) found a significant ($P < 0.05$, one-tailed test) difference between the observed and expected mortality for cancer, other than respiratory cancer, for coke plant workers whose last job was listed as "coke ovens." No excess was found for respiratory cancer deaths. When mortality was analyzed by whether the workers had ever worked at the coke ovens, no significant excess in respiratory or other cancer mortality was found. The Reid and Buck study had a number of deficiencies, however. The study population was poorly defined and the "observed deaths" may not have included deaths of workers "not on the books." Furthermore, the study did not sufficiently address the issue of a cancer latency period since little or no follow-up of vital status occurred. Analysis of mortality among retired workers was not adequate since there was no adjustment for age.

Davies (1977, 1978) did not find any significant difference between the

observed and expected cancer mortality of the coke oven workers at two coke works in South Wales. Davies followed his cohort for only 11 years, however. Also, Davies did not consider the degree of environmental exposure among the coke oven workers. Extremely high risk has been found to be limited to only a small proportion of the coke oven population. The comparison of coke oven to non-coke oven workers may not have been able to detect any differences especially considering the relatively short follow-up period.

Collings (1978) found an excess of lung cancer among the coke oven workers when compared to rates for Great Britain (45.0 observed vs. 35.7 expected); this excess was not significant ($P < 0.05$), however. Like the Davies study, Collings followed his cohort for a relatively short period of time (9 years). Also, similar to Davies, the author did not evaluate the degree of environmental exposure of the coke workers (i.e., he failed to differentiate between topside and side oven workers). It should also be noted that coke ovens are operated at lower temperatures in Great Britain than they are in the United States (Doherty and DeCarlo 1967), which may contribute to the lack of positive findings in the three British studies on coke workers (Reid and Buck 1956, Davies 1977, and Collings 1978).

The update by Redmond et al. of the study begun by Lloyd consistently showed a significant excess of lung, trachea, and bronchus cancer mortality. In the Redmond et al. studies, there was a dose-response both by working area (topside, side oven and part-time topside, and side oven) and by length of exposure. Prostate cancer and kidney cancer also appeared to be in excess in the Redmond et al. (1979) update. Because the British studies did not follow the workers as long as the American studies did, and because neither the British studies nor the Sakabe et al. study considered occupational categories

within the coke works, the positive results of the American studies are considered a better evaluation of the cancer risk to coke oven workers. Therefore, based on results of the American studies, it is concluded that exposure to coke oven emissions increases the risk of cancer of the lung, trachea, and bronchus; kidney; and prostate, as well as cancer at all sites combined.

ANIMAL STUDIES

Topside Coke Oven and Coke Oven Main

Topside coke oven sample extract has been tested as a tumor initiator in initiation-promotion skin treatment studies in two strains of mice (Nesnow et al. 1981, Nesnow 1980). An extract of material from a coke oven collecting main has also been evaluated for activities as a whole carcinogen, an initiator, and a promoter [in skin treatment studies with one strain of mouse (Nesnow et al. 1981)].

Initiation-Promotion Studies--

Nesnow et al. (1981) have evaluated the effects of extracts of topside coke oven emission and coke oven main samples in initiation-promotion and complete carcinogenicity studies in mice. The methods for obtaining the test samples from coke ovens has been described by Huisingh (1981) and Huisingh et al. (1979). Topside coke oven samples were collected as particulate matter with a Massive Air Volume Sampler, and coke oven main samples were obtained from a separator located between the gas collector and the primary coolers within the coke oven battery. The samples were soxhlet-extracted with dichloromethane, which was subsequently removed by evaporation under dry nitrogen gas. All test materials used in this study were prepared under yellow light immediately before application, in 0.2 ml spectral grade acetone, onto test sites.

Mice of the SENCAR strain, derived from mating female Charles River CD-1 mice with male skin tumor sensitive (STS) mice, were selected as the test animals in this study.

Each control and treatment group consisted of 40 male and 40 female mice which were 7 to 9 weeks old at the start of the study. Animals were caged in

groups of 10 under yellow light. Test sites on the skin were shaved 2 days before initial treatment, and only mice in the resting phase of the hair cycle were used. In the initiation-promotion experiments, initiating agents were applied as single doses except for the 10 mg (highest) dose which was given as five daily doses of 2 mg each. At 1 week following application of initiator, 2 ug of the promoter 7,12-dimethylbenz[a]anthracene-12-O-tetradecanoylphorbol-13-acetate (TPA) was topically applied twice per week. In tests for complete carcinogenicity, test material was applied once weekly, or twice weekly at the highest dose, for 50 to 52 weeks. Test substances evaluated as promoting agents were applied to the skin once each week, or twice each week at the highest dose, for 34 weeks following skin treatment with a 50.5 ug dose of the initiator benzo[a]pyrene (B[a]P).

Animals were observed weekly for tumor formation, and papillomas over 2 mm in diameter and carcinomas were included in cumulative totals if they persisted for at least 1 week. Papillomas were scored at 6 months or, in the test for promoting activity, 34 weeks, and carcinomas were totaled after 1 year. The authors indicate that examination of animals by necropsy and tissues and tumors by histopathology was being done and that pathologic data would be presented in a separate forthcoming report.

Results of initiation-promotion experiments on topside coke oven sample extract, coke oven main sample extract, and B[a]P as initiating agents are compared in Table VI-17. The stronger effect of the coke oven main sample compared to the topside coke oven sample reflects the greater concentration of ingredients contributing to the initiating activity of the former sample. Responses to the coke oven main sample and B[a]P in the study for complete carcinogenesis are shown in Table VI-18. Promoting activity was found with the coke oven main sample and TPA following initiation with B[a]P

TABLE VI-17. SENCAR MOUSE SKIN TUMORIGENESIS
(Nesnow et al. 1981)

Dose (ug/mouse)		No. Mice Surviving	Mice with Papillomas* (%)	Papillomas per mouse*	Mice with Carcinomast (%)	Carcinomas per Mouset
			BENZO[A]PYRENE - TUMOR INITIATION			
0	(M)	37	8	0.08	5	0.05
0	(F)	39	5	0.05	0	0
2.52	(M)	40	45	0.50	5	0.07
2.52	(F)	39	31	0.44	5	0.05
12.6	(M)	40	73	1.8	20	0.20
12.6	(F)	37	57	1.1	23	0.23
50.5	(M)	39	100	5.8	25	0.25
50.5	(F)	40	75	2.8	20	0.20
101	(M)	38	95	10.2	30	0.33
101	(F)	38	97	7.9	25	0.25
			TOPSIDE COKE OVEN - TUMOR INITIATION			
100	(M)	40	13	0.13	0	0
100	(F)	40	10	0.20	8	0.08
500	(M)	40	73	1.6	5	0.05
500	(F)	40	70	1.8	15	0.15
1000	(M)	37	95	2.6	15	0.15
1000	(F)	39	72	2.0	3	0.03
2000	(M)	39	95	4.0	13	0.13
2000	(F)	38	90	3.5	10	0.10
10,000	(M)	39	100	7.1	13	0.15
10,000	(F)	40	100	7.7	20	0.23
			COKE OVEN MAIN - TUMOR INITIATION			
100	(M)	38	50	0.63	10	0.10
100	(F)	39	31	0.38	25	0.25
500	(M)	39	90	3.7	54	0.59
500	(F)	39	82	2.2	54	0.54
1000	(M)	39	87	3.3	53	0.53
1000	(F)	39	90	3.1	48	0.48
2000	(M)	40	78	3.1	48	0.48
2000	(F)	40	100	5.3	45	0.45
10,000	(M)	38	100	8.9	55	0.55
10,000	(F)	37	100	8.1	65	0.65

*Scored at 6 months.
†Cumulative score after one year.

TABLE VI-18. SENCAR MOUSE SKIN TUMORIGENESIS
(adapted from Nesnow et al. 1981)

Dose (ug/mouse/week)	Mice with Carcinomas* (%)	Carcinomas per Mouse*
BENZO[A]PYRENE - COMPLETE CARCINOGENESIS		
12.6 (M)	10	0.10
12.6 (F)	8	0.08
25.2 (M)	63	0.63
25.2 (F)	43	0.43
50.5 (M)	93	0.93
50.5 (F)	98	0.98
101 (M)	80	0.83
101 (F)	90	0.98
202 (M)	80	0.80
202 (F)	93	0.98
0 (M)	0	0
0 (F)	0	0
COKE OVEN MAIN - COMPLETE CARCINOGENESIS		
100 (M)	5	0.05
100 (F)	5	0.05
500 (M)	36	0.36
500 (F)	30	0.30
1000 (M)	48	0.55
1000 (F)	60	0.60
2000 (M)	82	1.00
2000 (F)	78	0.78
4000 (M)	98	0.98
4000 (F)	75	0.85

*Cumulative score after one year.

(Table VI-19). Spontaneous tumor formation in the control groups was not evident in the studies for complete carcinogenesis and promoting activity (Tables VI-18 and VI-19) and was below 10% incidence for papillomas and was 5% (males) or 0% (females) incidence for carcinomas in the experiment for initiating activity (Table VI-17).

Results of the study by Nesnow et al. (1981) show that coke oven main sample extract contained ingredients capable of producing skin tumors in SENCAR mice either as an initiator, a promoter, or a complete carcinogen. Topside coke oven sample extract was also active as an initiating agent; however, according to Nesnow et al. (1981), an unknown portion of the topside sample was contaminated with particulate matter from ambient air due to the location of the Massive Air Volume Sampler and local wind conditions (this issue is further discussed on pages 39, 41, and 44 of the mutagenicity section herein). Hence, the extent to which the topside coke oven sample extract used in the initiation-promotion experiment is representative of topside coke oven sample per se appears uncertain.

Data in Tables VI-17 and VI-18 show that the tumorigenic responses to the coke oven sample extracts and B[a]P tended to be constant at all doses above the lowest dose in the dose ranges used. The nature of these dose-responses indicates that the doses used were in the range capable of producing maximal effects in relation to the sensitivity of the SENCAR strain to the initiating and complete carcinogenic properties of these test materials. The authors proposed that a lack of a monotonic dose-response across a dose range may be due to a toxic effect of the test material being tested which damages the epidermis to yield a reduced tumorigenic response. Forthcoming results of the histopathologic examination of skin test sites may provide evidence in favor of this possibility. However, although not identified as an experimental

TABLE VI-19. SENCAR MOUSE SKIN TUMORIGENESIS
COKE OVEN MAIN - TUMOR PROMOTION
(adapted from Nesnow et al. 1981)

Dose (ug/mouse)	Mice with Papillomas*	Papillomas per mouse*
0 (M)†	0	0
0 (F)	0	0
100 (M)§	3	0.02
100 (F)	10	0.10
500 (M)	26	0.44
500 (F)	38	0.83
1000 (M)	53	1.2
1000 (F)	68	1.2
2000 (M)	84	2.5
2000 (F)	85	3.1
4000 (M)¶	100	8.2
4000 (F)	100	8.8
TPA, 4 ug (M)#	86	3.1
TPA, 4 ug (F)	97	5.9

*Scored at 34 weeks.

†Mice initiated with 50.5 ug benzo[a]pyrene (B[a]P) and subsequently treated weekly with acetone.

§Mice initiated with 50.5 ug (B[a]P) and subsequently treated weekly with coke oven main.

¶Mice initiated with 50.5 ug (B[a]P) and subsequently treated twice weekly with 2 mg coke oven main.

#Mice initiated with 50.5 ug (B[a]P) and subsequently treated twice weekly with 2 ug TPA.

problem in the study report, it is possible that the rather constant response over the dose ranges used may be due to incomplete solubility of the test samples in acetone, which in turn actually might have resulted in the application of rather similar doses throughout the dose ranges. Nonetheless, although the responses in Tables VI-17 and VI-18 were generally not monotonic throughout the entire dose ranges used, the data clearly show positive activity for the indicated test materials. As shown in Table VI-19, a clearer indication of a dose-related effect was obtained in the evaluation of coke oven main sample extract as a promoter.

In summary, coke oven main sample extract was positive as a complete carcinogen, an initiator, and a promoter on the skin of SENCAR mice, and topside coke oven sample extract was positive as an initiator on the skin of SENCAR mice.

Nesnow (1980) reported results of an additional initiation-promotion experiment with the topside coke oven extract on C57BL/6 mice done for comparison with the experiment on SENCAR mice. Similar protocols were used for the two studies except that the C57BL/6 mice were on study for 52 weeks. Tumor-initiating activity at the application site was not observed with coke oven emission sample extract at doses as high as 10 mg/mouse; however, tumor-initiating activity was also not demonstrated with the positive control chemical, benzo[a]pyrene, at doses as high as 403.68 ug/mouse. Thus, results obtained in the experiment on C57BL/6 mice are considered inconclusive as indicated by the resistance of this mouse strain to tumor-initiating activity by the positive control agent.

Coal Tar

Carcinogenicity studies on aerosols of coal tar and coal tar fractions in laboratory animals were reported by Horton (1961), Horton et al. (1963), Tye and Stemmer (1967), MacEwen and Vernot (1972-1976), Kinkead (1973), McConnell and Specht (1973), and MacEwen et al. (1976). These studies provide evidence for a carcinogenic effect of coal tar aerosol test samples as discussed herein.

Numerous carcinogenicity studies on coal tar samples applied topically to the skin of laboratory animals have been reported. Studies discussed herein, which show an ability of coal tar samples to produce local tumors following skin treatment, include those reported by Bonser and Manch (1932), Hueper and Payne (1960), Horton (1961), and Wallcave et al. (1971). Horton (1961) and Wallcave et al. (1971) tested coal tar samples from coking operations.

Inhalation Exposure Studies--

Horton et al. (1963) examined C3H mice (a strain that was reported to have a low historical incidence of spontaneous pulmonary adenomas) for lung tumors following inhalation exposure to coal tar aerosol, gaseous formaldehyde, or gaseous formaldehyde followed by coal tar aerosol. In the first part of the experiment, groups of 60, 60, and 42 mice were exposed to concentrations of 0.5, 0.10, or 0.20 mg/liter, respectively, of gaseous formaldehyde for three 1-hour periods per week. The control group consisted of 59 untreated mice. After 35 weeks, none of the animals that were sectioned of those that died (118 of 221) during the period had developed lung tumors. The surviving animals were used to conduct further experiments with coal tar and formaldehyde. The surviving 33 mice from the control group in the first part of the experiment and the surviving 26 mice from the group that had been

exposed to 0.10 mg/liter of gaseous formaldehyde in the first part of the experiment were exposed to 0.30 mg/liter of coal tar aerosol for three 2-hour periods per week for up to 36 weeks. The surviving 36 mice from the group that had been exposed to 0.05 mg/liter of formaldehyde in the first part of the experiment were exposed to 0.15 mg/liter of formaldehyde for three 1-hour periods each week for up to 35 weeks. Also, the untreated control group* was observed for 82 weeks.

The test animals were exposed to the test substances until death. The first death occurred 1 to 11 weeks after exposure and the longest time until death was 36 weeks. Serial sections of the trachea, large bronchi, and lung of the exposed animals and sections of the lung of 30 unexposed mice were examined (Table VI-20).

Five mice inhaling coal tar aerosol and one mouse inhaling formaldehyde followed by coal tar developed squamous cell tumors in the periphery of the lung, involving one-third to one-half of the lobe. In two mice from the former group, several lobes were involved. A sixth mouse in the former group that died after 20 weeks of exposure had an invasive squamous cell carcinoma, which was described as "unquestionably a squamous cell carcinoma, whereas, those occurring in the other five animals probably represented an earlier stage of development at the time of death." One mouse in each group had adenoma of the lung. Tumors of the lung were not observed in mice breathing formaldehyde only or in untreated controls.

There were other changes produced in the tracheobronchial epithelium as the result of the inhalation of coal tar. The most striking was a necrotizing tracheobronchitis in the majority of mice; the incidence was not reported. In

*The initial size of the untreated group was not reported. At the termination of the experiment at 82 weeks, the group consisted of 30 mice.

TABLE VI-20. TUMORS OF THE LUNG IN MICE INHALING FORMALDEHYDE AND/OR AEROSOL OF COAL TAR
(adapted from Horton et al. 1963)

Treatment	Squamous Cell Tumors		Adenomas		Total	
Untreated Controls	0/30	(0%)	0/30	(0%)	0/30	(0%)
Coal Tar	6/33*	(18%)	1/33	(3%)	7/33	(21%)
Formaldehyde and Coal Tar	1/26	(4%)	1/26	(4%)	2/26	(8%)
Formaldehyde	0/36	(0%)	0/36	(0%)	0/36	(0%)

*A squamous cell carcinoma was found in one animal.

addition, squamous cell metaplasia extended into the smaller bronchi. Hyperplasia of the bronchial epithelium occurred frequently, sometimes with papillary infolding. The epithelium of untreated mice was normal, showing neither metaplasia nor hyperplasia.

Epithelial changes in mice inhaling formaldehyde involved mostly the trachea; extension into the major bronchi was infrequent and did not occur at all in the smaller bronchi. In general, the inhalation of formaldehyde resulted in an acute tracheobronchitis ranging from slightly to severely necrotizing, or developing into a chronic type with proliferation of fibrous tissue. This was sometimes complicated by bronchopneumonia. In summary, mice inhaling coal tar aerosol developed squamous cell carcinomas of the lung, as well as hyperplastic and metaplastic epithelial changes.

Tye and Stemmer (1967) separated two different coal tars into phenolic (P-tar) and nonphenolic (N-tar) fractions and exposed mice by inhalation to various blends of the coal tar fractions and to one of the original tars. The same coal tar (T-1) (specific gravity 1.17; 4.5% tar acid, 0.7% benzo[a]pyrene, and 67% Diels-Adler compounds*) that was used in the experiments by Horton, Tye, and Stemmer (1963) and a second, somewhat different tar (T-2) (specific gravity 1.24; 1.4% tar acid, 1.1% benzo[a]pyrene, and 2% Diels-Adler compounds*), were the two tars from which the phenolic (P-tar) and nonphenolic (N-tar) fractions were separated.

Fifty male C3H/HeJ mice, 3 to 5 months old, were in each test group. The tests groups consisted of untreated, Tar-1, N-Tar-1, N-Tar-1 plus P-TAR-1, N-Tar-1 plus P-Tar-2, and N-Tar-2 plus P-TAR-1. Mice were exposed for 2 hours

*As indicative of anthracene and polycyclic aromatic hydrocarbons with three linear aromatic rings with a free meso position.

every 3 weeks. During the first 8 weeks, the exposure was at a concentration of 0.20 mg/liter, but this was reduced to 0.12 mg/liter because so many mice died.

Three mice from each group were killed after 4 weeks, and five mice were killed after 31 weeks. Surviving mice were killed at the end of 55 weeks. Mortality from exposure was high in all groups of treated mice. At the end ofthe experiment, there were 31/50 (62%), 11/50 (22%), 11/50 (22%), 10/50 (20%), 21/50 (42%), and 21/50 (42%) mice alive in the control, Tar-1, N-Tar-1, N-Tar-1 plus P-Tar-1, N-Tar-1 plus P-Tar-2, and N-Tar-2 plus P-Tar-1 groups, respectively. Tumor response is recorded in Table VI-21.

The most prominent lesions were intrabronchial adenomas and adenocarcinomas, occurring anywhere in the bronchial tree. Multiple tumors were frequently seen. The intrabronchial adenomas were papillary. There also were alveolar adenomas which were peripheral. Tumors of the lung were diagnosed as adenocarcinomas only if there was invasion or if metastases were observed.

Adenomas and adenocarcinomas of the lung were observed in 60% to 100% of the mice inhaling aerosols of coal tars, whereas tumors were not seen in any of the control mice. Incidences of squamous metaplasia varied from 10% to 38% in treated mice and were absent in control mice. "Alveolar epithelization" was also observed, but less often than squamous metaplasia. Areas of squamous and alveolar metaplasia were not considered as tumors, even when they occupied relatively large spaces.

MacEwen and Vernot (1972-1974), Kinkead (1973), and McConnell and Specht (1973) reported on a study in which mice, rats, hamsters, and rabbits were exposed to a coal tar aerosol from which the light oil and solid fraction was

TABLE VI-21. INCIDENCE OF LUNG TUMORS IN MICE INHALING AEROSOLS OF COAL TARS* (adapted from Tye and Stemmer 1967)

Treatment	Metaplasia	Adenomas†	Adenocarcinomas	Adenomas and Carcinomas
Untreated Controls	0/32 (0%)	0/32 (0%)	0/32 (0%)	0/32 (0%)
Tar-1	5/13 (38%)	12/13 (92%)	3/13 (23%)	13/13 (100%)
N-Tar-1	2/20 (10%)	16/20 (80%)	0/20 (0%)	16/20 (80%)
N-Tar-1† P-Tar-1	5/19 (26%)	14/19 (74%)	1/19 (5%)	15/19 (79%)
N-Tar-1† P-Tar-2	7/25 (28%)	14/25 (56%)	1/25 (4%)	15/25 (60%)
N-Tar-2† P-Tar-1	4/23 (17%)	14/23 (61%)	0/23 (0%)	14/23 (61%)

*Mice surviving for 46 weeks or longer.

†Includes intrabronchial and alveolar adenomas.

removed. Gross skin pathology for the mice was reported; any other tumor response in the mice and in the other animals was not reported.*

Groups of 64 female yearling and 64 weanling (32 of each sex) Sprague-Dawley rats, 50 male JAX-CAF1 mice, and 50 male ICR-CF1 mice were exposed continuously for 90 days (except for 15 minutes a day to allow for animal maintenance) to concentrations of 0.2, 2.0, and 10.0 mg/m^3 of coal tar aerosol. Ninety-two female yearling Sprague-Dawley rats, 82 weanling Sprague-Dawley rats (73 female and 9 male), 75 male JAX-CAF1 mice, 75 male ICR-CF1 mice, 100 male golden Syrian hamsters, and 24 New Zealand white rabbits were exposed continuously, as above, for the same 90-day period to a concentration of 20 mg/m^3. The control animals consisted of 41 female and 41 male Sprague-Dawley weanling rats, 82 female Sprague-Dawley yearling rats, 75 male JAX-CAF1 mice, 75 male ICR-CF1 mice, 24 female New Zealand white rabbits, and 100 male golden Syrian hamsters (MacEwen and Vernot 1972). Many of the mice contracted a streptococcus infection and died before 93 days postexposure. Skin tumor response for the mice is found in Table VI-22.

Tumor responses of 28% (10 of 36), 38% (3 of 8), and 8% (2 of 25) were seen in the three highest dose groups of the ICR-CF1 mice; no tumors (0 of 62) were found in the controls. A tumor response of 37% (10 of 27) was found in the highest dose group JAX-CAF1 mice; no tumors (0 of 74) were found in the JAX-CAF1 controls. McConnell and Specht (1973) examined some of the skin tumors histologically and concluded that a whole spectrum of epithelial tumors, from squamous cell papilloma to keratoacanthoma to "frankly aggressive" appearing squamous cell carcinoma are stimulated by the coal tar aerosol, although the majority of these tumors fall in the squamous cell

*Per contractual agreement, Sasmore performed internal and skin histopathology for the study and reported his results (Sasmore 1976), but because information in the Sasmore report is incomplete, no conclusions can be made about the report.

TABLE VI-22. TUMOR RESPONSE IN MALE ICR-CF1 AND JAX-CAF1 MICE FOLLOWING EXPOSURE TO COAL TAR AEROSOL
(adapted from McConnell and Specht 1973)

Dose (mg/m^3)	ICR-CF1*		JAX-CAF1*	
20.0	10/36	(28%)†	10/27	(37%)†
10.0	3/8	(38%)§	0/12	(0%)§
2.0	2/25	(8%)§	0/47	(0%)§
0.2	0/2	(0%)§	0/47	(0%)§
0.0	0/62	(0%)†	0/74	(0%)†

*The numerator is the number of animals with tumors at 415 days postexposure. The denominator is the number of animals that were alive at 93 days postexposure.

†This dose group began with 75 animals.

§This dose group began with 50 animals.

category. McConnell and Specht also found a time-to-tumor dose-response for the coal tar aerosol. This dose-response is shown in Table VI-23. As stated above, tumor response was not reported for the rats, hamsters, or rabbits.

MacEwen and Vernot (1975 and 1976) and MacEwen et al. (1976) reported on two studies of the tumor response of mice, rats, rabbits, and monkeys following exposure to coal tar aerosol. In the first study, 80 female Sprague-Dawley yearling rats, 80 Sprague-Dawley weanling rats (40 males and 40females), 75 JAX-CAF1 male mice, 75 ICR-CF1 male mice, and 100 male Syrian golden hamsters were exposed continuously for 90 days (except for 15 minutes a day to allow for animal maintenance) to concentrations of 0.2, 2.0, and 10.0 mg/m^3 of coal tar aerosol. An equal number of each species were used for controls. The coal tar used to generate the aerosol in this study was:

> a composite mixture collected from multiple coking ovens around the greater Pittsburgh area. The coking ovens were of several different types and used different coal sources for their starting materials. The coke oven effluents were collected in air collection devices using a chilled water spray to condense the higher boiling distillate fractions. After settling and separation of the liquid phase, the various coal tar samples were blended together with a 20% by volume amount of the BTA (benzene, toluene, xylene) fraction of the coke oven distillate.

An aerosol particle size determination in the exposure chambers was performed, and it was found that a minimum of 97% of all droplets were in a respirable range of 5 microns or less in diameter. Only skin tumor response for the mice was reported (Table VI-24). Tumor response was not reported for the hamsters or rats.

In the second study, 75 female and 100 male ICR-CF1 mice (described as tumor susceptible), 50 female JAX-CAF1 mice (described as a tumor-resistant hybrid strain), 40 male and 40 female CFN strain Sprague-Dawley weanling rats, 18 New Zealand albino rabbits, and 5 male and 9 female Macaca mulatta monkeys

TABLE VI-23. LATENT PERIOD OF FIRST TUMOR INDUCTION IN CTV-I EXPOSED ICR-CF1 MICE
(McConnell and Specht 1973)

Dose (mg/m^3)	Time of Tumor Appearance (Days)
20	< 93
10	128
2	142

TABLE VI-24. SKIN TUMOR RESPONSE IN ICR-CF1 AND JAX-CAF1 MICE FOLLOWING EXPOSURE TO COAL TAR AEROSOL
(MacEwen and Vernot 1976)

		Cumulative Number of Tumors*			
Dose (mg/m^3)	Week of Observation†	ICR-CF1 Exposed	ICR-CF1 Control	JAX-CAF1 Exposed	JAX-CAF1 Control
10	100	44/75 (59%)	3/75 (4%)	18/75 (24%)	1/75 (1%)
2	103	14/75 (19%)	0/75 (0%)	3/75 (4%)	0/75 (0%)
0.2	101	1/75 (1%)	0/75 (0%)	1/75 (1%)	1/75 (1%)

*The numerator is the number of animals with tumors; the denominator is the number of animals exposed.

†Includes the 90-day exposure period.

were exposed to 10 mg/m^3 of coal tar aerosol for 6 hours each day, 5 days per week, for 18 months. The coal tar used to generate the aerosols in this study was the same as that of the first study. Aerosol particle size was determined monthly in the exposure chambers. A minimum of 99% of the total droplets in both chambers were 5 microns or less in diameter and were thus within a respirable size range for rodents.

Exposure to the coal tar at 10 mg/m^3 significantly reduced the body weight of rabbits and rats compared with the controls, whereas monkeys showed no significant change in body weight. Sixteen of 18 rabbits and 6 control mice died during the test period. These deaths were attributed to a chronic respiratory infection which caused debilitation and dehydration. At the conclusion of the exposure period, the test monkeys and the surviving test rabbits along with the unexposed controls were delivered to the National Institute for Occupational Safety and Health (NIOSH) Laboratories in Cincinnati, Ohio. Since the number of surviving rabbits (2 of 18) was too few for statistical comparison, and those animals were sacrificed (Gibb 1978a), no tumor response was found in the sacrificed rabbits (Gibb 1978b). The monkeys were kept for observation at the NIOSH Laboratories until 1979 when they were moved to Gulf South Research in New Iberia, Louisiana, where they are currently being maintained. One of the dosed monkeys died in 1981; results of the autopsy are not yet available (Gibb 1981).

Alveolargenic [sic] carcinomas were produced in 26 of 61 (43%) ICR-CF1 mice and in 27 of 50 (54%) JAX-CAF1 mice. The number of tumors in the ICR-CF1 and the JAX-CAF1 control mice were 3 of 68 (4%) and 8 of 48 (17%), respectively. The exposed and control groups did not differ in the incidence of other types of tumors including squamous cell carcinomas, lymphosarcomas,

subcutaneous sarcomas, alveolargenic adenomas, bronchiogenic carcinomas, reticulum cell sarcomas, hemangiosarcomas, and hemopoietic tumors.

Skin tumors were produced in 5 of 75 (7%) of the ICR-CF1 mice and 2 of 50 (4%) of the JAX-CAF1 mice as compared to 3 of 75 (3%) and 1 of 50 (2%) in the ICR-CF1 and JAX-CAF1 controls, respectively. The criterion for counting a lesion as a skin tumor was a growth greater than 1 mm in diameter and in height. Each tumor was ultimately confirmed by histologic examination. MacEwen et al. compared the lack of skin tumor response in the second study to the tumor response of the 10 mg/m^3 dose group of the first study. As stated previously, the first study found a skin tumor incidence of 14 of 75 (59%) in the treated ICR-CF1 controls and 18 of 75 (24%) in the treated JAX-CAF1 mice as opposed to only 3 of 75 (4%) in the ICR-CF1 controls and 1 of 75 (1.3%) in the JAX-CAF1 controls, respectively. A calculation of total exposure time (MacEwen et al. 1976) revealed that the same amount of coal tar aerosol reached the skin of mice in the second study as in the first study. MacEwen et al. suggested that the 18-month intermittent exposure of the animals in their study allowed the animals enough time each day to permit normal cleaning of the fur.

The incidence of coal tar tumorigenesis in rats is reported in Table VI-25. The incidence of squamous cell carcinomas in the lungs was 100% (38/38) in exposed males and 82% (31/38) in exposed females as opposed to 0% (0/36) in male controls and 0% (0/37) in female controls.

A dose-related tumor response was observed for both the ICR-CF1 and the JAX-CF1 mice.

TABLE VI-25. COAL TAR TUMORIGENESIS IN RATS
(MacEwen et al. 1976)

	Controls		Exposed	
	Males	Females	Males	Females
Number Examined Histologically*	30	37	38	38
Number of Rats with Tumors:				
Squamous Cell Carcinoma, Lung	0	0	38	31
Squamous Cell Carcinoma	0	1	0	0
Intra-abdominal Carcinoma	0	1	0	0
Mammary Fibroadenoma	0	1	0	3
Mammary Adenocarcinoma	0	1	0	0
Other Tumors	0	1	8	2
Overall Tumor Incidence (%)	0	13	100	82

*The original number of rats per group was 40. However, because of autolysis and/or cannibalization, a few animals were unsuited for histopathological examinations.

Topical Application Studies--

Bonser and Manch (1932) studied the tumor response from application to mouse skin of three samples of Scottish blast-furnace tar, one sample of English crude tar, and an ether extract of the latter. The three samples of Scottish tar (I, II, III) were made from coke oven charges which contained in addition to the coal, 15 to 17%, 25%, and 10% coke, respectively; the English crude tar was made from a charge containing 75% coal and 25% coke. Sixty mice were used for testing each sample of tar. There were no negative and positive control groups. The hair was clipped away from a small area of skin in the region between the shoulder blades. The tar was applied biweekly for the first 14 weeks, and thereafter once weekly because of marked ulceration of the skin of many mice. Tar samples were used without indication of further preparation in solvent. The study was continued for 56 weeks, by which time all the mice had died. Fifty-seven tumors were grossly identified. Thirty-one of the total 57 tumors that had developed were confirmed histologically.

Tumor findings are described in Table VI-26. In mice treated with the three Scottish samples, the first tumors appeared at the 18th week. The Scottish I, II, and III tar samples produced a tumor incidence of 7/60 (12%), 10/60 (17%), and 8/60 (13%), respectively. The tumors were malignant in three mice. The first tumor appeared at the 21st week when an English crude tar was used. Eight mice (13%) treated with the English crude tar developed tumors as did 24 mice (40%) treated with an ether extract of the English crude tar. Nine tumors in mice given the ether extract were malignant.

The tumors were papillomas or squamous cell carcinomas of the skin. The carcinomas invaded the muscle. One malignant tumor, seen after 47 weeks of application of ether extract of English tar, consisted of a mass of "mononuclear round cells" invading the adjacent muscle and fat and metastasizing to the lymph nodes.

TABLE VI-26. INCIDENCE OF SKIN TUMORS IN MICE TREATED WITH BLAST FURNACE TARS (adapted from Bonser and Manch 1932)

Tar Sample	Number of Animals with Tumors/ Number of Animals		Appearance of First Tumor (weeks)	Malignant Tumors	
Scottish I	7/60	(12%)	16	0/60	(0%)
Scottish II	10/60	(17%)	16	2/60	(3%)
Scottish III	8/60	(13%)	16	1/60	(2%)
English Crude	8/60	(13%)	21	0/60	(0%)
Ether Extract of English Crude	24/60	(40%)	12	9/60	(15%)

Hueper and Payne (1960) found that skin tumors were produced in mice following the application of coal tar. Coal tar, four petroleum road asphalts (Venezuelan, Mississippian, Oklahoman, and Californian), one petroleum roofing tar, and paraffin oil were applied to the napes of the necks of groups of 50 black C57 mice (25 of each sex) for 2 years. An untreated control group consisted of 200 mice. A positive control group was not used in this study. So that the materials could be applied as droplets, the coal tar and roofing asphalt were heated to make them liquid, and the road asphalts were diluted with a sufficient amount of acetone. The paraffin oil was painted on the skin. Post-mortem examinations were performed on all mice, and histological examinations were made of all tissues which exhibited gross abnormalities. The results are found in Table VI-27.

Carcinomas of the skin were found in 22 of 50 (44%) and papillomas in four of 50 (8%) mice receiving dermal applications of coal tar, whereas control mice did not develop tumors of the skin.

Hueper and Payne also administered some of the substances via inhalation and intramuscular injection. Daily volatilization of 10 to 30 g of coal tar did not produce lung tumors in female Bethesda black rats or strain 13 guinea pigs inhaling the fumes 5 hours daily, 4 days per week, for periods up to 2 years. However, coal tar distillate produced muscle sarcomas in 50 of 100 mice given 6 biweekly intramuscular injections and observed for a duration of 2 years.

Horton (1961), in several experiments, tested a number of crude coal tars, coal tar distillates, and fractions of coal tar for skin tumor response in C3M mice. In the first part of the study, five coal tars (four from the coking of bituminous coal and one from the coking of lignite coal), a mixture of one

TABLE VI-27. SKIN TUMORS IN MICE GIVEN DERMAL APPLICATIONS OF COAL TAR, PETROLEUM ROOFING TAR, PARRAFIN OIL, OR PETROLEUM ROAD ASPHALTS (adapted from Heuper and Payne 1960)

Treatment	Skin Carcinomas		Skin Papillomas		Total	
Control	0/200	(0%)	0/200	(0%)	0/200	(0%)
Coal Tar	22/50	(44%)	4/50	(8%)	23/50	(46%)
Petroleum Roofing Tar	1/50	(2%)	0/50	(0%)	1/50	(2%)
Paraffin Oil	1/50	(2%)	1/50	(2%)	2/50	(4%)
Petroleum Road Asphalt						
Venezuelan	0/50	(0%)	0/50	(0%)	0/50	(0%)
Mississippian	1/50	(2%)	1/50	(2%)	2/50	(4%)
Oklahoman	0/50	(0%)	1/50	(2%)	1/50	(2%)
Californian	1/50	(2%)	0/50	(0%)	1/50	(2%)

of the bituminous coal tars in 50% benzene, and a benzo[a]pyrene mixture were tested. The authors did not report using a control group. No data were provided on the number of mice tested nor on the length of time the animals were treated; however, the time-to-tumor for each group was reported. The incidence of tumors was reported to be greater than 75% (only a percentage was reported) for each test group. Horton developed a numerical index designed to grade the various tars and tar fractions for relative carcinogenic potency. This index was referred to as the potency for a minimum concentration of material (PMC). A high PMC value was meant to indicate a greater carcinogenic potency. For tars D-1 and D-613, for which multiple doses were applied, a dose-response was evident. The mean time-to-tumor (in weeks), the schedule of application, and the PMC values for each of the tars, the tar solution, and the benzo[a]pyrene solution are reported in Table VI-28.

Two tars from the previous group (D-1 and D-8) were chosen to test the effect of skin washing with a detergent in water 5 to 60 minutes after tar application. Tars D-1 and D-8 had the highest (0.8) and lowest (0.1) benzene-insoluble content, respectively. Washing delayed tumor development, but the final tumor incidence was not significantly changed. The delay was greater in the animals washed 5 minutes after dermal application.

Horton also determined the relationship between the amount of benzo[a]pyrene in distillates of coal tar and the carcinogenic potency of those distillates. Tar D-1, a distillate oil of D-1 (the first 9 to 13.5% of the distillation), a proportionate reblend of nine distillate fractions of D-1 and two distillate fractions (a carbolic oil and a light creosote oil) of a coal tar (D-9) not previously used in the experiments, were tested for BaP content and carcinogenic potency (PMC) to the skin of mice. With the exception of Tar D-1, all test materials were applied to mice (strain

TABLE VI-28. MEAN TIME-TO-TUMOR AND PMC VALUES FOR FOUR BITUMINOUS TARS, ONE LIGNITE TAR, AND ONE SOLUTION OF BENZO[A]PYRENE (adapted from Horton 1961)

Treatment	Schedule of Application (Doses/week - mg/Dose)	Mean Time-to-Tumor (weeks)	PMC*
D-1 - bituminous tar	2-10	15.6†	0.27†
	2-50	12.6†	0.37†
	3-100	7.0†	0.63†
D-4 - bituminous tar	2-10	24.8	0.13
D-5 - bituminous tar	2-10	23.6	0.14
D-5A - 50% dilution by weight of D-5 tar	2-10	25.1	0.13
D-8 - bituminous tar	3-50	21.9	0.11
D-12 - lignite tar	3-50	17.1	0.16
D-613 - benzo[a]pyrene in 85% beta-methylnaphthalene and 15% benzene solution	2-15	33.0†	0.08†
	2-50	30.6†	0.10†

*PMC: Potency for minimum dose of test sample, i.e., the PMC increases as carcinogenic potency increases.

†The multiple doses for Tars D-1 and D-613 demonstrated a mean time-to-tumor and a PMC dose-response.

unspecified) in 10 mg doses. Tar D-1 was applied in 20 mg doses. The number of applications was described as "repeated," but neither the frequency nor the duration was specified. The PMC values and benzo[a]pyrene content of the test substances are reported in Table VI-29.

Comparison of the benzo[a]pyrene content with the carcinogenic potencies of various fractions showed that no tumors were produced by those fractions in which no benzo[a]pyrene could be detected, while the carcinogenic potency of the test materials that contained benzo[a]pyrene was correlated with their content by weight of this carcinogen. Despite this observation, the authors did caution that these results do not imply that benzo[a]pyrene is the only carcinogen in these substances.

TABLE VI-29. PMC VALUES AND BENZO[A]PYRENE CONTENT FOR TWO COAL TARS, SEVERAL DISTILLATES OF THOSE COAL TARS, AND A PROPORTIONATE REBLEND OF THE DISTILLATES FROM ONE OF THE TARS
(adapted from Horton 1961)

Test Material	Doses (mg)	Content of Benzo[a]pyrene (%)	Relative Carcinogenic Potency (PMC)
Tar D-1	20	0.74	0.27
Distillate Oil of Tar D-1	10	0.01	0.01
Proportionate Reblend the Nine Cuts of Tar D-1	10	0.08	0.11
Carbolic Oil of Tar D-9	10	0.00	0.00
Light Creosote Oil of Tar D-9	10	0.00	0.00

Wallcave et al. (1971) prepared benzene extracts of coal tar pitches obtained from coke ovens and tested them for carcinogenic activity on mouse skin. Equal numbers of male and female Swiss albino mice received twice weekly applications of 1.7 mg of coal tar pitch in 25 ul of benzene. Exposed animals survived for an average of 31 weeks. Among 58 treated mice, 53 developed skin tumors, of which 31 were carcinomas. Although tumors at other sites were present, the incidence in the control and experimental groups were similar. No carcinomas and only one papilloma on the skin were found in 26 control mice painted with benzene alone. Wallcave et al. (1971) identified several polycyclic hydrocarbons, including benzo[a]pyrene (0.84 and 1.25% of undiluted coal tar pitch in 2 samples), in the pitch samples and concluded that they were responsible for the tumorigenic effects observed.

CARCINOGENICITY OF COKE OVEN EMISSION COMPONENTS

Polycyclic Organic Matter (POM)

Numerous polycyclic aromatic compounds are distinctive in their ability to produce tumors in skin and most epithelial tissues of practically all species tested. Malignancies are often induced by acute exposures to microgram quantities of POM (for a review, see U.S. EPA 1979). Latency periods can be short (4 to 8 weeks) and the tumors produced may resemble human carcinomas. Carcinogenesis studies involving POM have historically involved primarily effects on the skin or lungs. In addition, subcutaneous or intramuscular injections are frequently employed to produce sarcomas at the injection site. Ingestion has not been a preferred route of administration for the bioassay of POM. A listing of POM found in coke oven emissions is presented in Table VI-30 along with an indication of carcinogenic activity.

Other Carcinogens Identified in Coke Oven Emissions

The contribution of compounds other than POM to the carcinogenic activity of coal combustion products has received little attention. Other constituents of coke oven emissions that have been found to be carcinogenic include arsenic, lead, beryllium, chromium, nickel, 2-naphthylamine, and benzene (U.S. EPA 1977a; 1978b, c; 1980n; IARC 1973b; 1974; 1976; 1979).

Cocarcinogens

Numerous compounds, which by themselves display no carcinogenic activity, are known to enhance the tumorigenic activity of B[a]P when applied together to the skin of mice (Hoffman et al. 1978, Van Duuren and Goldschmidt 1976). These so-called cocarcinogens include certain PAH-containing fractions of tobacco tar, and several structurally diverse compounds (catechol, pyrogallol,

TABLE VI-30. POLYCYCLIC ORGANIC MATTER (POM) IDENTIFIED IN COKE OVEN EMISSIONS*

Compound	Animal Carcinogenicity†	
	IARC	CAG
Anthracene	-	+
Benz[a]anthracene	+	
Dibenz[a,c]anthracene	+	
Methylphenanthrene	-	
Phenanthrene	-	
Benzo[c]phenanthrene	+	
Benzo[a]fluorene	-	
Benzo[b]fluorene	-	
Dihydrobenzo[a]fluorene	?	
Dihydrobenzo[b]fluorene	?	
Dihydrobenzo[c]fluorene §	?	
Fluoranthene	-	
Benzo[c]fluorene	-	
Benzo[b]fluoranthene	+	+
Benzo[j]fluoranthene	+	+
Benzo[k]fluoranthene	-	
Benzo[ghi]fluoranthene	-	
Pyrene	-	
Methylpyrene	-	
Benzo[a]pyrene	+	+
Benzo[e]pyrene	+	
Dibenzopyrenes	+	+
Chrysene §	+	+
Triphenylene §	-	
Perylene	-	
Benzo[ghi]perylene §	-	
Anthanthrene §	+	
Coronene	-	
Acridine	-	
Benzoquinoline	-	
Octahydrophenanthrene	?	
Octahydroanthracene	?	
Dihydrofluorene	?	
Benzindene	?	
Fluorene	-	
Dihydrophenanthrene	?	
Dihydroanthracene	-	
Methylfluorenes	?	
Fluorene Carbonitrile	?	
Methylanthracene	-	
Ethylphenanthrene	?	
Ethylanthracene	-	

(continued on the following page)

TABLE VI-30. (continued)

Compound	Animal Carcinogenicity† IARC	CAG
Octahydrofluoranthene §	?	
Octahydropyrene §	?	
Indeno[1,2,3-cd]pyrene	+	+
Dibenz[a]anthracene	+	
Benz[c]acridine	+	+
Dibenz[a,h]acridine	+	+
Dibenz[a,j]acridine	+	+
Dihydrofluoranthene	?	
Dihydropyrene	?	
Methylfluoranthene	+	
Dihydrobenz[a]anthracene §	?	
Dihydrochrysene §	?	
Dihydrotriphenylene §	?	
Dihydromethylbenz[a]anthracene §	?	
Dihydromethylchrysene §	?	
Dihydromethyltriphenylene §	?	
Methylbenz[a]anthracene	±	
Methyltriphenylene	±	
Methylchrysene	±	
Dihydromethylbenzo[k and b]-fluoranthenes§	?	
Dihydromethylbenzo[a and e]pyrenes §	?	
Dimethylbenz[a]anthracene §	+	+
Dimethyltriphenylene §	-	
Dimethylchrysene §	+	
Methylbenzo[k]fluoranthene §	?	
Methylbenzo[b]fluoranthene §	?	
Methylbenzo[a]pyrene	+	
Dimethylbenzo[k and b]-fluoranthenes	?	
Dimethylbenzo[a]pyrene	+	
o-Phenylenepyrene	?	
Methyldibenzanthracene	+	
Methylbenzo[ghi]perylene	?	

*The POM's were identified in coke oven emissions by Lao et al. 1975 or Bjorseth et al. 1978. The data on carcinogenicity is taken from CAG (1980b) and IARC (U.S. EPA 1979).

†Symbols: + complete carcinogen or tumor initiator
- negative
? activity not known
± may be positive or negative depending on the isomer tested

§Confirmation of chemical structure questionable in Lao et al. (1975).

anthralin, decane, undecane, tetradecane). Since many of these compounds may occur in coke oven emissions, the possibility arises that they may contribute to carcinogenic risk. However, the mechanism of cocarcinogenesis is not understood, and its relevance to tumor formation in tissues other than mouse skin is not known. Thus, we can only conclude that the presence of cocarcinogens in complex mixtures such as coke oven effluents may pose an additional risk for humans beyond that attributable to recognized carcinogens such as benzo[a]pyrene.

VII. UNIT RISK ESTIMATE

The shortest possible period of time from the initiation of an event due to an exposure to a carcinogen to death or diagnosis of cancer caused by the event is defined here as the "minimum initiation time." The "minimum initiation time" is an important factor that should be taken into consideration whenever an attempt is made to determine the relationship between the level of exposure and subsequent cancer incidence or mortality. This is particularly true when human epidemiological or animal data based upon an exposure and/or follow-up of less than a full lifespan is utilized to establish the dose-response relationship.

Mazumdar et al. (1975) generated an extensive data base concerning the exposure to coke oven emissions and the respiratory cancer death rates of black steelworkers. A cancer mortality model is developed in this report and is fitted to the Mazumdar et al. (1975) data to estimate the "minimum initiation time" and respiratory cancer potency associated with coke oven emissions. The derived "minimum initiation time" and potency estimates are then used to estimate the "unit risk" of coke oven emissions, where the unit risk is the lifetime probability of respiratory cancer death due to a continuous lifetime exposure of 1 ugm/m^3 of coal tar pitch volatiles.

MATHEMATICAL MODEL RELATING EXPOSURE TO AN ENVIRONMENTAL HAZARD TO PROBABILITY OF DEATH DUE TO A SPECIFIED CAUSE

The estimation of the probability of occurrence of a disease in the presence of competing causes of death is a problem that has received considerable attention. Chiang (1968, pp. 242-268) has given a general solution to the problem using standard methods in competing risk analysis. Gail (1975), using these methods, gives a simple and detailed derivation of the probability of a

disease being caused by an environmental hazard by time t, that may be expressed as:

$$P(t,x) = \int_0^t h_2[X(v),v]\, S(v)dv$$

where

$$S(v) = e^{-\int_0^v \{h_1(s) + h_2[X(s),s]\}ds}$$

is the probability of survival until age v,

$h_1(s)$ = the total age-specific death rate at age s in the absence of the environmental hazard of concern, and

$h_2[X(s),s]$ = the age-specific death rate at age s due to X(s), the prior exposure pattern of the environmental hazard.

Knowledge of the exact form for $h_2[X(s),s]$ would depend upon a detailed understanding of the mechanism by which the environmental hazard causes the disease. For the case of cancer, such an understanding does not presently exist. As a result, it is necessary to postulate a form for $h_2[X(s),s]$ that is based upon as few and as simple a set of assumptions as is possible that still gives predictions which are consistent with observed results.

Taking this approach we define the following terms:

$g_2[x(v),v]$ = the instantaneous probability of the initiation of an event at time v caused by an exposure to an environmental agent at level x(v), that ultimately will lead to death in the absence of competing mortality, and

$w(t-v)$ = the probability distribution of the time from the initiation of the event until death in the absence of competing mortality.

Using these definitions, it follows that the age-specific or instantaneous

death rate due to the environmental hazard at time t is

$$h_2[X(t),t] = \int_0^t g_2[x(v),v]w(t-v)dv \quad .$$

Assuming events are initiated linearly proportional to exposure at that time, the instantaneous initiation probability may be written as

$$g_2[x(v),v] = \Delta x(v) \quad .$$

If we assume that a fixed initiation time "I" must pass before death can occur from an initiated event, but beyond that time the probability of death occurring is equal for all times for a duration of length R after which it again becomes zero, then it follows that:

$$w(t-v) = w^*(v) = \begin{cases} 0 & v \leq t-I-R \\ 1/R & t-I-R < v \leq t-I \\ 0 & t-I < v \end{cases}$$

Thus, given the exposure pattern $x(v)$, $0 \leq v \leq t$, the instantaneous death rate at time t due to that exposure is

$$h_2[X(t),t] = \int_0^t \Delta x(v)w^*(v)dv \quad .$$

The utility of this model will depend upon its ability to predict observed results within normal statistical variability. Its utility in predicting the occurrence of respiratory cancer in a population exposed to coke oven emissions is explored in the next section.

MODEL APPLIED TO EFFECTS OF COKE OVEN EMISSIONS ON RESPIRATORY CANCER RATES OF NONWHITE MALE STEELWORKERS

In a series of papers, Lloyd et al. (1970), Lloyd (1971), Redmond et al. (1972), and Redmond et al. (1976) presented their findings concerning respiratory cancer death in a cohort of nonwhite steelworkers followed over a 15-year period. Mazumdar et al. (1975) calculated the total mg/m^3 months of exposure to coal tar pitch volatiles for each worker. This was done by taking the sum over all job classifications of the products of the estimated exposure in a specified job classification by the number of months worked in that classification.

Land (1976) grouped these data into age intervals at the start of the observation period and obtained average ages and exposures for the grouped data. To obtain more stable estimates of the respiratory cancer rates, the data were grouped into larger age intervals and the average exposures and ages recalculated for use in the subsequent analysis. The results of this recalculation and the basic observed epidemiological data are presented in Table VII-1, along with the definitions of the symbols used to represent the types of epidemiological data.

Estimation of Exposure Pattern

The actual timing of the exposure is unknown to us; we are given only the totals. However, as a first approximation we assume that exposure was uniform over time and occurred over the maximum possible time frame. This time frame is considered to be from age 18, the earliest possible age at first employment, to the age at the end of the observation period or retirement at age 65, if that came first.

TABLE VII-1. SUMMARIZATION OF GIVEN DATA ON NONWHITE STEELWORKERS
(adapted from Land 1976)

Nonwhite Male Steelworkers Exposed to Coke Oven Emissions					Controls Nonwhite Male Steelworkers Not Exposed to Coke Oven Emissions	
s	X	N	W	O	W*	O*
Average Age in Interval	Average Cumulated Exposure in mg^3 Months ÷ 12	Number of Individuals in Cohort	Man-Years of Observation	Observed Number of Respiratory Cancer Deaths	Man-Years of Observation	Observed Number of Respiratory Cancer Deaths
24.24	11.82	912	12,695	3	28,047	1
34.51	20.66	795	11,251	10	18,505	3
44.25	30.44	561	7,615	17	13,927	11
53.54	43.66	344	4,342	17	8,770	12
63.04	40.62	70	727	5	2,062	1

Under these assumptions it follows that the exposure at age v may be expressed as

$$x(v) = \begin{cases} X/(t^* - 18) & 18 \leq v < t^* \\ 0 & \text{elsewhere} \end{cases}$$

where X is mg/m^3 - years and t^* is the smaller of 65 and the age at the end of the observation period.

Derivation of Form of Age-Specific Respiratory Cancer Death Rates Due to Coke Oven Emissions

Using the previous definition for x(v) and the additional simplifying assumption that R > t-I, it follows that

$$h_2[X(t),t] = \int_0^t \Delta x(v)w^*(v) = \begin{cases} 0 & t \leq 18+I \\ \dfrac{\Delta X(t-I-18)}{R(t^* - 18)} & 18+I < t \leq t^* + I \\ \Delta X/R & t^*+I < t \end{cases}$$

In other words, this says simply that: 1) the age-specific cancer rate increase due to coke oven emission is not affected until a waiting period of length I after first exposure at age 18, 2) after this time the age-specific rate increases in a linear manner for a length of time equal to the assumed maximum exposure time reaching a maximum at a time that is length I after the last exposure, and 3) from this point on the rate remains constant at this maximum level.

The unknowns in this derived relationship are Δ, R, and I; however, under the assumption R > t-I, only the ratio, $\delta = \Delta/R$, and I can be estimated.

Derivation of the Expression for the Expected Number of Respiratory Cancer Deaths in Each Cohort

Consider a cohort of our coke oven exposed population whose average age at the start of the observation period is s. Under our risk model and the assumptions:

(1) each individual in the cohort is identical in regards to age and exposure pattern, and

(2) the background respiratory cancer rate $h_2(v)$ is independent of the coke oven-caused respiratory cancer rate.

The expected number of total respiratory cancer deaths in the m years of the observation period is

$$E(x,m) = \int_s^{s+m} \{h_2(v) + h_2[x(v),v]\}\, N(v)dv$$

where N(v) is the number of individuals under observation in the cohort at time or "age" v.

The values for N(v) are not known. All that is given is the total man-years of observation W and N(s), the number of individuals in the cohort at the time of the start of the observation period. However, under the approximate assumption that the fraction r of individuals lost from the cohort for all reasons is constant over time, it follows directly that

$$W = \int_s^{s+m} N(t) = N(s) \int_s^{s+m} e^{-r(t-s)}\, dt = \frac{N(s)}{r} [1-e^{-rm}] \quad .$$

Since for each cohort, W, N(s), and m are given, the unknown r can be estimated from the non-linear equation

$$\frac{W}{N(s)} - (1-e^{-15r})/r = 0 \quad .$$

Solving this equation for each cohort gives the values shown below:

Cohort Age	$\hat{r}$
$\leq$ 29	0.010091
30-39	0.007834
40-49	0.013549
50-59	0.023716
> 60	0.052435

Thus for each cohort

$$N(t) = N(s)e^{-r(t-s)} \quad .$$

In addition, we assume that for a given cohort the background age-specific respiratory cancer death rate is constant throughout the entire observation period and equal to the observed control rate. In terms of our notation, this assumption is equivalent to assuming

$$h_2(v) = 0^*/W^* \qquad s \leq v \leq s + m \quad .$$

Substituting these approximations for $h_2(v)$ and $N(v)$ into the expected value equation, along with $h_2[x(v), v]$ which was previously derived, gives the

result:

$$E(x,m) = WO^*/W^* + \delta G(I)$$

where

$$G(I) = \begin{cases} 0 & s \leq I+3 \\ \frac{XN(s)}{(t^*-18)r^2}\{e^{-r(18+I-s)} - e^{-rm}[r(s+m-I-18)+1]\} & I+3 < s \leq I+18 \\ \frac{XN(s)}{(t^*-18)r}\{\frac{W}{N(s)}[1+r(s-I-18)]-me^{-rm}\} & I+18 < s \leq I+50 \\ \frac{XN(s)}{(t^*-18)r^2}[(s-I-18)r+1-(1+47r)e^{-r(65+I-s)}] + \frac{XN(s)}{r}[e^{-(65+I-s)r}-e^{-mr}] & I+50 < s \leq I+65 \\ XW & I+65 < s \end{cases}$$

The expected number of deaths so defined can be used in conjunction with the observed number of deaths in order to estimate the unknown parameters δ, I, in the manner indicated in the next section.

ESTIMATION OF THE UNKNOWN PARAMETERS I, δ

To estimate the unknown parameters I, δ , the assumption that to a close approximation the number of respiratory cancer deaths in an age-cohort is a Poisson random variable with mean E(x,m) is made. Using this assumption the maximum-likelihood solution to the unknown parameters is found in the following manner.

The likelihood of the observed values may be written as

$$L \propto \prod_{\text{all cohorts}} e^{-[O^*W/W^* + \delta G(I)]} [O^*W/W^* + \delta G(I)]^O$$

and

$$\ln L \propto \sum_{\text{all cohorts}} -[O^*W/W^* + \delta G(I)] + O \ln [O^*W/W^* + \delta G(I)] \quad .$$

For an assumed value of I the maximum likelihood estimator of δ is obtained by solving the equation

$$\frac{d \ln L}{d\delta} = \sum_{\text{all cohorts}} - G(I) + \frac{OW^*G(I)}{WO^*+W^* \delta G(I)} = 0$$

To find the joint maximum likelihood estimator for δ, I, the maximum likelihood estimates for δ were found for a series of I values 0.1 units apart. The fixed value of I and its corresponding maximum likelihood estimate $\delta(I)$ were then substituted into the likelihood equation to obtain the numerical estimates L(I). These estimates L(I) were next plotted against I. The values of this plot are shown in Figure VII-1. The point I_0 where $L(I_0)$ is a maximum along with its corresponding value $\delta(I_0)$ are the joint maximum likelihood estimates for I and δ.

Proceeding in this manner, it was found that $I_0 = 11.4$ and $\delta(I_0) = 9.7646 \times 10^{-5}$. These values are then substituted into the equation E(x,m) to obtain numerical estimates of the expected number of cases in each of the cohorts under the assumed model.


FIGURE VII-1- PLOT OF LIKELIHOOD EVALUATED AT I AND BEST ESTIMATION $\hat{S}$ AGAINST I
L(I) 10^{-5}
MAXIMUM AT
$I_0 = 11.4$, $\hat{S}(11.4) = 9.76 \times 10^{-5}$
2.0
1.8
1.6
1.4
1.2
1.0
.8
.6
.4
.2
.0
0
2
4
6
8
10
12
14
16
18
20
I

EVALUATION OF THE GOODNESS OF FIT OF THE MODEL

Of obvious interest is how well the developed model fits the observed data. We calculate the expected number of respiratory cancer deaths in each cohort from the relationship

$$E(x,m) = O^*W/W^* + 9.7646 \times G(11.4) \times 10^{-5} \quad .$$

The numerical results obtained from this equation, as well as all the information needed to perform the calculations that cannot be found in Table VII-1 can be found in Table VII-2.

A standard chi-square goodness of fit test is next used to compare the observed and expected number of respiratory cancer deaths in the five cohorts. Since two parameters I, δ were estimated, the test had 5 - 2 = 3 degrees of freedom associated with it. A chi-square value of 1.98 was obtained which has a corresponding $P \simeq 0.58$ associated with it indicating an excellent fit. We can say that no other possible model could give a statistically significantly better fit to the observed data than the one used here. Thus, until additional information is obtained that is inconsistent with this model, the model will be utilized to predict the respiratory cancer effects of coke oven emissions.

ESTIMATION OF THE UNIT RISK FOR COAL TAR PITCH VOLATILES

As part of the U.S. Environmental Protection Agency's Office of Air Quality Planning and Standards program of regulating airborne carcinogens, a "unit risk" is calculated for each suspect human carcinogen. The unit risk is defined as the lifetime probability of cancer death due to a continuous exposure of 1 ugm/m^3 of the agent for the entire lifespan.

To obtain a unit risk for coal tar pitch volatiles we note that the potency

TABLE VII-2. COMPARISON OF OBSERVED AND EXPECTED NUMBER OF RESPIRATORY CANCER DEATHS FOR RISK MODEL WHERE MAXIMUM LIKELIHOOD ESTIMATES OF PARAMETERS ARE, I = 11.4, $\delta = 9.7646 \times 10^{-5}$

Age Interval	O^*/W^*	$G(11.4) \times 10^{-5}$	Expected $E(x,m) = WO^*/W^* + \delta G(11.4)$	Observed O
18 - 29	3.5654×10^{-5}	0.2184	2.586	3
30 - 39	1.6212×10^{-4}	0.9194	10.802	10
40 - 49	7.8983×10^{-4}	1.2417	18.140	17
50 - 59	1.3683×10^{-3}	1.2583	18.228	17
$\geq$ 60	4.8947×10^{-4}	0.2520	2.84	5

$$X^2_3 = \sum_{\text{all cohorts}} [O - E(x,m)]^2/E(x,m) = 1.98$$

$P \simeq 0.58$

parameter for δ was in units of mg/m^3 per working day. To convert this to lifetime ugm/m^3, we assume that a person works 240 days per year, 8 hours per day, so that exposure would be $10^3 \times (240/365) \times (8/24) = 220$ times as large expressed in the new units. Thus, the potency parameters estimate is $\delta\ (I_0)/220 = 4.438 \times 10^{-7}$.

To obtain a unit risk estimate under the same model as was fitted to the coke oven workers, we assume that

$$x(v) = 1 \qquad v \geq 0$$

and

$$w(t-v) = \begin{cases} 0 & t-v < 11.4 \\ 1/R & t-v \geq 11.4 \end{cases}$$

so that

$$h_2[X(t),t] = 4.438 \times 10^{-7} \times (t-11.4) \qquad t \geq 11.4 \ .$$

The risk we wish to calculate is to a "typical" U.S. inhabitant given a specified exposure level. Thus, we set $h_1(t)$ equal to the death rates for all causes for the total population for 5-year age groups found in the Vital Statistics of the United States (U.S. Dept. of Health, Education, and Welfare 1977) and evaluate the integral of the function found by substituting the required terms into the lifetime risk equation. This results in the relationship

$$P(\infty,1) = \int_{11.4}^{\infty} \delta\, 4.438 \times 10^{-7} \times (t-11.4) e^{-[2.219\times10^{-7} \times (t-11.4)^2 + \int_0^t h_1(v)dv]} dt$$

$$= 9.25 \times 10^{-4} \ .$$

For small exposures when $x(v) = x$, $v \geq 0$, it follows that the lifetime risk is

$$P(\infty,x) \simeq P(\infty,1)x \quad .$$

Thus, for example, if the average increase in coal tar pitch volatiles in the air due to coke oven emissions is 0.45 ug/m^3, then an estimate of the increase in the lifetime risk associated with such a lifetime exposure is

$$P(\infty, 0.45) \simeq 9.250 \times 10^{-4} \times 0.45 = 4.163 \times 10^{-4} \quad .$$

Estimation of Confidence Limits for the Unit Risk

The unit risk, as it is defined, is a function of two known parameters I, δ. Under maximum likelihood theory, it is possible to obtain a joint confidence region for the unknown parameters assuming that the underlying assumptions utilized to obtain the likelihood are correct.

Once this confidence region is obtained, a confidence bound for the unit risk is found by finding the maximum and minimum of all possible unit risks computed from pairs of points contained within the joint confidence region.

The joint confidence region was generated in the following manner. First, a fixed value I was selected and the unknown values δ^*_I found from the relationship

$$-2\ln \{ L[\delta(I_0),I_0]/L(\delta^*_I, I)\} = \chi^2_{2,1-\alpha} \quad .$$

The term $L[\delta(I_0),I_0]$ is the likelihood evaluated assuming that the likelihood estimates are the true parameters and $L(\delta^*_I, I)$ is the likelihood evaluated at I and the two values δ^*_{Iu}, δ^*_{Il} that give a numerical solution to the above relationship. The same procedure is repeated for a series of I values of 0.1 units apart for all possible values for which a solution is possible. Next, on a graph the upper and lower values of δ^*_I are plotted against I forming the envelope depicted in Figure VII-2 where $\alpha = 0.05$. All possible pairs of values of δ,I, with a confidence of 95%, fall within this generated region. It should be noted that only points in the positive quadrant are biologically possible. Thus, the region is restricted to this quadrant.

It is obvious that the maximum and the minimum calculated unit risk estimates obtained from all possible points within the confidence region would be from points that lie on the boundary of the confidence region. As a result, the unit risk was calculated for each point on the boundary and plotted against I as is shown in Figure VII-3. From this graph the absolute maximum unit risk was found to be $Pu(\infty,1) = 1.535 \times 10^{-3}$ and the absolute minimum $P_l(\infty,1) = 4.98 \times 10^{-4}$. Thus, the true unit risk $P(\infty,1)$ lies within this interval with a probability of 0.95 or more, or this statement may be written in the form

$$P\{0.498 \times 10^{-3} \leq P(\infty,1) \leq 1.535 \times 10^{-3}\} \geq 0.95 \quad .$$

It must be recognized that this confidence statement assumes that the underlying cancer hypothesis is correct and only accounts for the statistical imprecision in the estimation of the unknown parameters. The true value may, with a probability that is unknown, be far beyond the region given above if some of the underlying assumptions deviate considerably from reality.

Other potential sources of error are discussed in the next section.

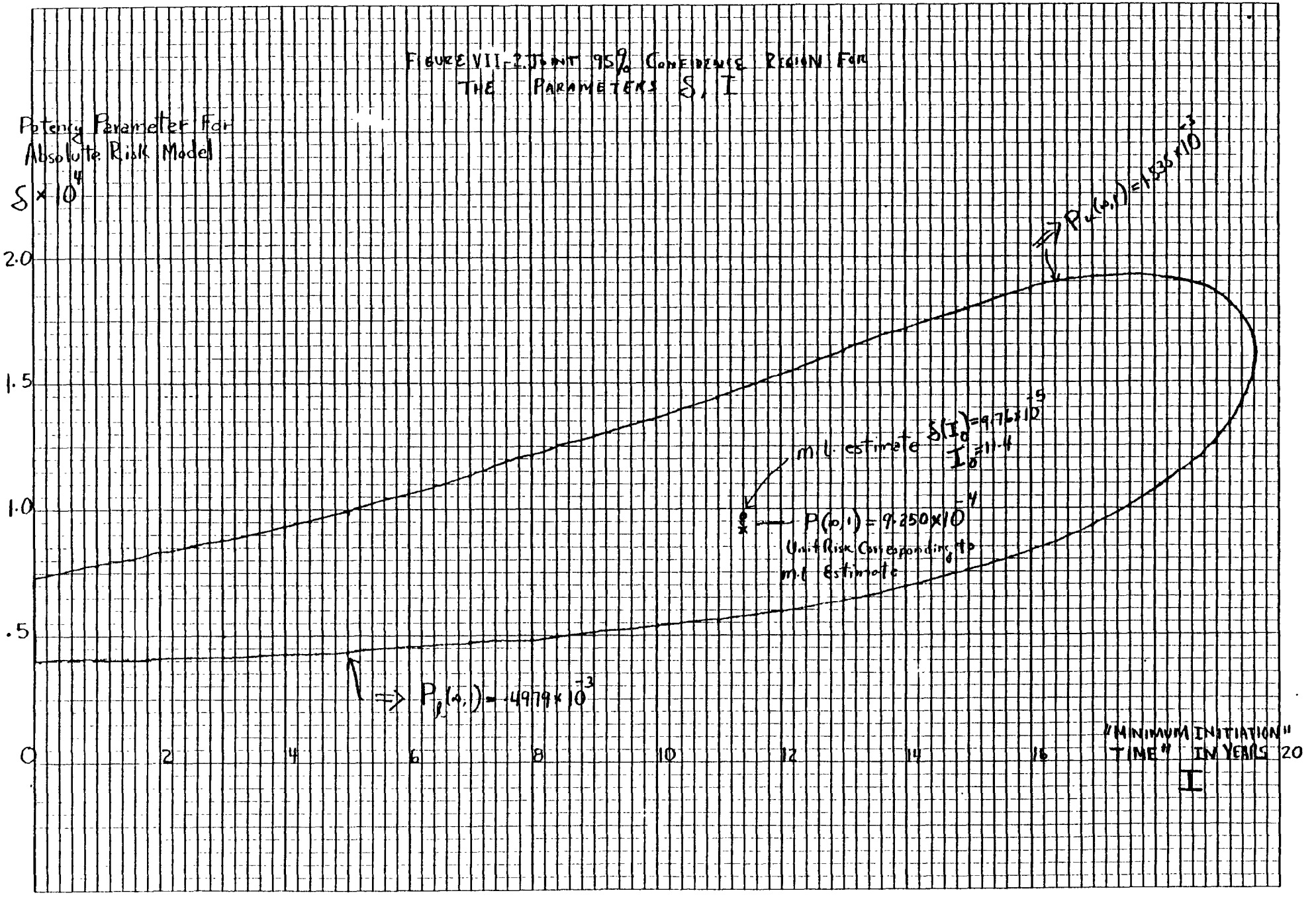


FIGURE VII-2. JOINT 95% CONFIDENCE REGION FOR THE PARAMETERS S, I
Potency Parameter for Absolute Risk Model
$S \times 10^{4}$
2.0
1.5
1.0
.5
0
2
4
6
8
10
12
14
16
20
"MINIMUM INITIATION" TIME" IN YEARS
I
$P_4(4,1) = 1.633 \times 10^{-3}$
m.l. estimate $\delta(I_0) = 9.763 \times 10^{-5}$
$I_0 = 11.4$
$P(0,1) = 9.250 \times 10^{-4}$
Unit Risk Corresponding to m.l. Estimate
$\Rightarrow P_5(4,1) = .4979 \times 10^{-3}$

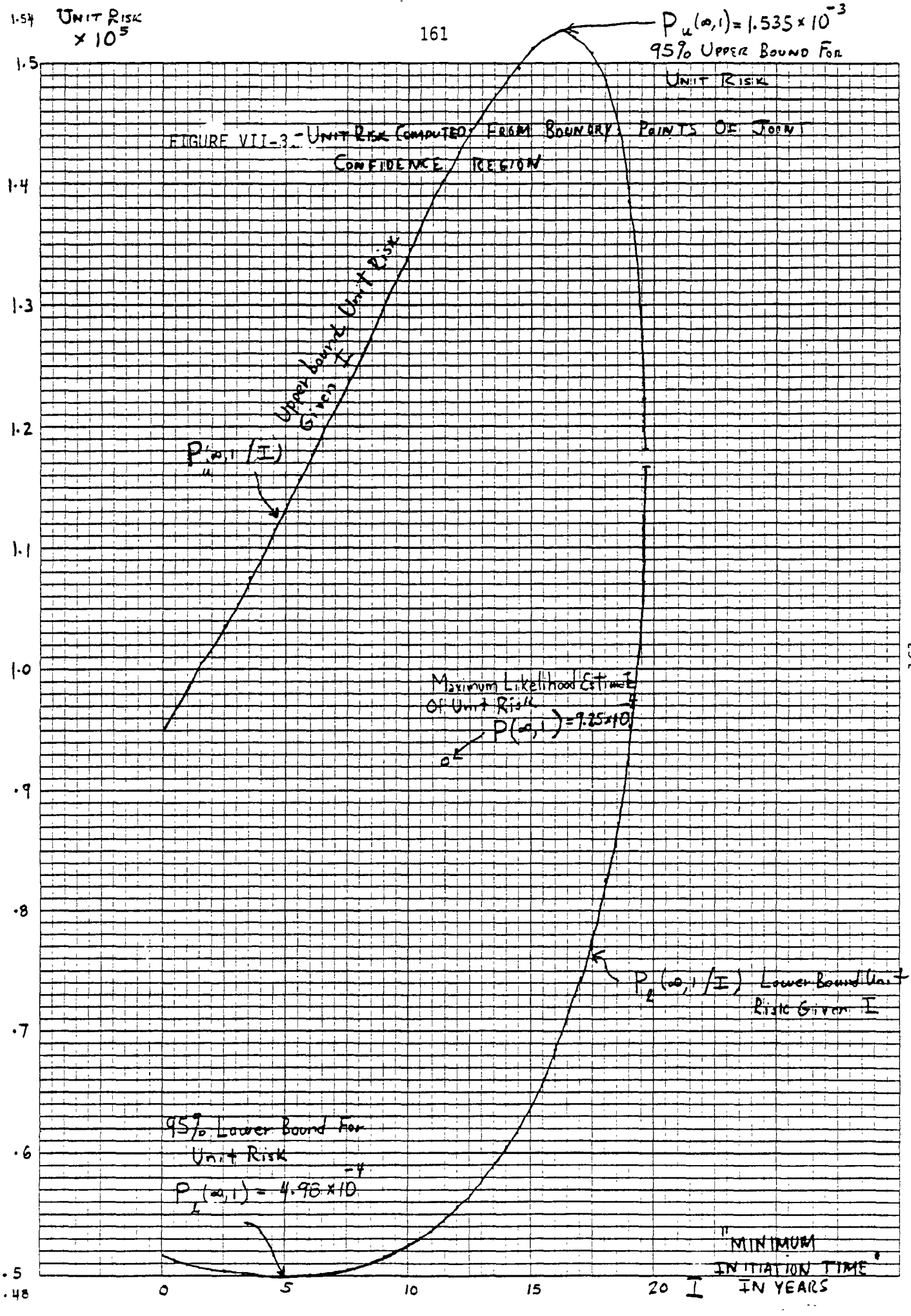


FIGURE VII-3 - UNIT RISK COMPUTED FROM BOUNDARY POINTS OF JOINT CONFIDENCE REGION

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ADDITIONAL POTENTIAL PROBLEMS AND SOURCES OF ERROR ASSOCIATED WITH THE UNIT RISK ESTIMATE

As noted, the confidence interval that was generated for the unit risk estimate is conditional upon: 1) the accuracy of the exposure estimates used in the epidemiological study, and, 2) the mathematical model used describing the true biological dose-response.

A number of factors could make the estimated exposure inaccurate. First, the samples taken around a single coke oven battery within a relatively short time period are extrapolated into other locations and times in order to estimate all of the workers total lifetime exposures. Also, there are several factors in the sampling procedure that could seriously bias the results: Samples were collected for as long a period as possible, i.e., until the personal-type portable air pump's battery became exhausted or until the filter became so clogged that the resistance was too great for the pump to overcome; average sampling rates varied from 2.0 to 2.8 liters/min with total air volumes ranging from 103 to 1200 liters; the moisture content of the air has a great effect on the clogging of filters; improper seating of filter pads caused leakage around the edges. All of these factors would tend to underestimate exposure which would result in an overestimate of risk.

Some of the problems associated with the dose-response model are:

(1) Exposures were not uniform and over the maximum possible time frame as was assumed.
(2) Cancer at sites other than the respiratory system was not considered.
(3) The response in nonwhite males was used to predict the response expected in the population as a whole. If a synergistic effect existed between some factor that is more common in the nonwhite lifestyle and coke oven emissions, then an overestimate of risk would occur.

The extent and or plausibility of these factors being important is unknown so that their influence on the precision of our estimate is pure conjecture at this stage of knowledge.

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