PLAINTIFF'S EXHIBIT SA-155

Conference on Environmental Carcinogens

During the May 7 - 8, 1955 meeting of the Cancer Control Committee, a special conference on Environmental Carcinogens was authorized to be financed from the Chairman's Grant at a cost not to exceed $3,000. It was proposed that a limited number of individuals interested in this field, including grantees, past and present, other investigators and staff members of the National Cancer Institute be assembled:

> "to outline the present knowledge of environmental carcinogens and to indicate the need and direction of additional research in this field for the guidance of the National Cancer Institute and the Cancer Control Committee."

A preliminary discussion with staff members of the National Cancer Institute was held May 10 and it was decided to call the first meeting of the subcommittee during the annual American Medical Association convention in Atlantic City. Notices of the impending conference also were sent out to the grantees, past and present, to insure their participation.

The meeting in Atlantic City on June 6, 1955 was attended by Drs. Moore, Arnold, Williams, Kaiser, Hon and Phair. It was decided immediately that additional members of the Cancer Control Committee should join in this enterprise, giving particular attention to the number of years of membership remaining in order that whatever conclusions were reached would serve to guide the Committee for as long as possible. Accordingly, Drs. Gowen, Griswold, McGavran and Spellman were invited to participate.

Other participants were reviewed and it was decided to limit the total number to 25 exclusive of National Cancer Institute staff workers. The final list of participants is appended to this report. Dr. Hon again took the responsibility of issuing invitations immediately to the other investigators.

It was planned that the conference discussions follow this general pattern:

(a) The discussion of each individual or category of carcinogens would be opened by a discussion leader with a ten to 15 minute prepared statement. Selected discussants would be prepared to follow this presentation and then the subject would be opened to all participants.

(b) The objectives of the discussions were to seek agreement upon the evidence required - clinical, epidemiological, statistical or experimental before a material or compound can be considered hazardous to man. One secondary goal was to describe the obstacles and pitfalls likely to be encountered in such investigations and another was to describe areas where studies should be initiated or extended.

The final agenda listing the topics covered and the discussion leaders is attached as Appendix 2. Due to lack of time, it was found necessary to limit the consideration of certain materials and to omit all reference to ultra-violet radiation. At the conference, each participant was given a crude

score sheet to record his impression as to the validity of the evidence, human or experimental, available at the moment. Sixteen turned in the sheets and these have been summarized, roughly and hurriedly, in Appendix 3.

No final or definitive recommendations were formulated by the Conference. All participants seemed to appreciate the opportunity to discuss generally these problems afforded by this meeting. All believed that similar talks should be arranged periodically in the future. It was evident, also, that the experimental group should be assembled to standardize terminology and experimental methods. Part of the confusion in this field is due to minor variations in their approaches and these differences could be readily resolved if they agree on the same terminology and definitions.

Respectfully submitted,

John J. Phair, M.D.

Conference on Environmental
Carcinogens
Stone House Conference Room A and
Study Room
September 12, 13, 1955

Invited Guests

Dr. Donald J. Birmingham
Occupational Health Field Headquarters
Public Health Service
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Dr. Willard Machle
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Boca Rotan, Florida

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Medicine and Hygiene
College of Medicine
Wayne University
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Detroit 7, Michigan

Dr. William E. Smith
Institute of Industrial Medicine
New York University - Bellevue
Medical Center
New York 16, New York

Dr. Paul Kotin
Assistant Professor of Pathology
University of Southern California
1200 North State Street
Los Angeles 33, California

Dr. Wesley Horton
Kettering Laboratory
University of Cincinnati
College of Medicine
Eden and Bethesda Avenues
Cincinnati 19, Ohio

Dr. Robert E. Eckardt
Director, Medical Research Division
Esso Research and Engineering Co.
Post Office Box 51
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Dr. William E. Poel
University of Pennsylvania
School of Medicine
36th and Pine Streets
Philadelphia 4, Pennsylvania

Dr. Harvey W. Maguigan
P. O. Box 831
Hopewell, Virginia

Dr. Jean S. Felton
Associate Professor
Department of Preventive Medicine
and Public Health
University of Oklahoma
School of Medicine
801 North East 13th Street
Oklahoma City 4, Oklahoma

Dr. Charles L. Dunham
Deputy Director
Division of Biology and Medicine
U. S. Atomic Energy Commission
Washington 25, D. C.

Dr. Norton Nelson
Director, New York University-
Bellevue Medical Center
Institute of Industrial Medicine
550 First Avenue
New York 16, New York

* Dr. Thomas F. Mancuso
Chief, Division of Industrial
Hygiene
State of Ohio Department of Health
306 Ohio Departments Buildings
Columbus 15, Ohio

Dr. Lemuel C. McGee
Delaware Trust Building
Wilmington, Delaware

Guests invited to attend Conference on Environmental Carcinogens (Cont'd.)

Dr. James H. Sterner
Medical Director, Eastman Kodak Co.
Kodak Park
Rochester 4, New York

* Dr. Irving Tabershaw
115 West 55th Street
New York 19, New York

Dr. Kenneth W. Smith
Medical Director, Johns-Manville Corp.
22 East 40th Street
New York 16, New York

Dr. Anna M. Baetjer
Johns Hopkins School of Hygiene and Public Health
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Baltimore 5, Maryland

Dr. John H. Foulger
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Dr. Gilbert Thiessen
Manager, Laboratory Section
Research Department
Koppers Company, Inc.
Pittsburgh 19, Pennsylvania

Dr. J. Wister Meigs
Associate Professor of Occupational Medicine
Yale University School of Medicine
Department of Public Health
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* Dr. Paul E. Steiner
Associate Professor of Pathology
University of Chicago
School of Medicine
Chicago 37, Illinois

* Dr. Herman Lisco
Post Office Box 299

Dr. Lester Breslow
Chief, Bureau of Chronic Diseases
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2151 Berkeley Way
Berkeley, California

* Dr. Morton L. Levin
Assistant Commissioner for Medical Services
State of New York Department of Health
Division of Medical Services
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Albany 7, New York

* Dr. Matthew H. Griswold
Chief, Division of Cancer and Chronic Diseases
Connecticut State Department of Health
Hartford 6, Connecticut

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Tufts-College Medical School
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Brookline 46, Massachusetts

Dr. Murray M. Copeland
Professor of Oncology
Georgetown University Medical Center
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Dr. John J. Phair
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Eden and Bethesda Avenue
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Dr. Philippe Shubik
Assistant Professor of Surgery
Director, Department of Oncology
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710 South Wolcott Avenue
Chicago 11, Illinois

Dr. Roy Albert
Division of Biology and Medicine

Guests invited to attend Conference on Environmental Carcinogens (Cont'd.)

* Dr. John R. Heller
Director, National Cancer Institute
Bethesda 14, Maryland

Dr. G. B. Mider
Assoc. Director in Charge Research
National Cancer Institute
Bethesda 14, Maryland

Dr. Michael B. Shimkin
Chief, Biometry and Epidemiology Branch
National Cancer Institute
Bethesda 14, Maryland

* Dr. Harold F. Dorn
Chief, Office of Biometry
Office of the Director
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* Mr. William N. Haenszel
Chief, Biometry Section
National Cancer Institute
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Dr. A. G. Gilliam
Chief, Epidemiology Section
National Cancer Institute
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Dr. Harold L. Stewart
Chief, Pathologic Anatomy Branch
National Cancer Institute
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Dr. Samuel C. Ingraham
Head, Field Studies Section
Field Investigations and Demonstrations
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Mr. Pope Lawrence
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Dr. Richard A. Malmgren
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Dr. John E. Dunn, Jr.
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Dr. Maurice L. Sievers
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Field Investigations and Demon-
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Guests invited to attend Conference on Environmental Carcinogens (Cont'd.)

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Field Investigator
Field Investigations and Demonstrations Branch
National Cancer Institute
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Dr. George Z. Williams
Chief, Clinical Pathology Department
Clinical Center, Nat. Inst. of Health
Bethesda 14, Maryland

Dr. Wilhelm C. Hueper
Head, Environmental Cancer Section
National Cancer Institute
Bethesda 14, Maryland

Dr. Raymond F. Kaiser
Chief, Field Investigations and Demonstrations Branch
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Dr. William Baum
Assistant Chief, Field Investigations and Demonstrations Branch
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Dr. N. B. Hon
Head, Grants Section
Field Investigations and Demonstrations Branch
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Dr. Benno K. Milmore
Biometrics and Epidemiology Branch
National Cancer Institute
Bethesda 14, Maryland

Dr. William A. Walters
Biometrics and Epidemiology Branch
National Cancer Institute
Bethesda 14, Maryland

Miss Rosalie I. Peterson
Head, Nursing Section
Field Investigations and Demonstrations Branch
National Cancer Institute
Bethesda 14, Maryland

Miss Ruth Kahl
Nursing Section
Field Investigations and Demonstrations Branch
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Miss Mary-M. Bouser
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Bethesda 14, Maryland

Conference on Environmental
Carcinogens
Stone House Conference Room A and
Study Room
September 12, 13, 1955

AGENDA

I. Opening Remarks:

Purpose of the Conference—— Chairman, Dr. John J. Phair

II. Discussion Leaders - Discussants

1. Inorganic Compounds

a. Arsenic — Dr. Donald J. Birmingham, Dr. Norton Nelson, Dr. Thomas F. Mancuso

b. Chromates — Dr. Willard Machle, Dr. Anna M. Baetjer, Dr. Thomas F. Mancuso, Dr. Norton Nelson

c. Nickel — Dr. Wilhelm C. Hueper, Dr. Lemuel C. McGee, Dr. James H. Sterner, Dr. Robert E. Eckardt

d. Beryllium — Dr. Arthur J. Vorwald, Dr. Willard Machle, Dr. Irving Tabershaw

e. Asbestos — Dr. William E. Smith, Dr. Kenneth W. Smith, Dr. Arthur J. Vorwald

2. Organic Compounds

a. Aliphatic — Dr. Paul Kotin, Dr. Norton Nelson, Dr. A. Wesley Horton, Dr. Robert E. Eckardt

b. Polycyclic

(1) Petroleum Products - Catalytic and Thermal Cracked
Dr. A. Wesley Horton, Dr. Robert E. Eckardt, Dr. Philippe Shubik, Dr. Paul Kotin

(2) Petroleum Cutting Oils (Additives)
Dr. Robert E. Eckardt, Dr. A. Wesley Horton, Dr. Norton Nelson, Dr. John H. Foulger

(3) Coal Tar
Dr. William E. Poel, Dr. Philippe Shubik, Dr. Gilbert Thiessen

II. 2. Organic Compounds (cont.)

c. Dyes and Intermediates
Dr. Harvey W. Maguigan, Dr. J. Wister Meigs, Dr. James H. Sterner, Dr. John H. Foulger

3. Physical Agents

a. Ultra Violet Radiation
Dr. Joan S. Felton, Dr. Paul Steiner

b. Radioactive Materials
Dr. Charles Dunham, Dr. Hermann Lisco

PROGRAM - ORDER OF DISCUSSION

September 12	9:00 - 12:30 AM	Working Session
	12:30 - 2:00 PM	Lunch
	2:00 - 5:00 PM	Working Session
	5:30 - 6:30 PM	Dutch Hospitality Hour
	6:30 - 8:00 PM	Subscription Dinner
September 13	9:00 - 12:30 AM	Working Session
	12:30 - 2:00 PM	Lunch
	2:00 - 5:00 PM	Working Session

Appendix 3

Summation of Score Sheets

	Epidemiological			Experimental				
INORGANIC	Skin	Lung	Other Organs	Mice	Rabbits	Rats	Others	Site
Arsenic	+	0	0	0	?	-	-	Skin papilloma
Chromates	0	+	0	0	0	0	0	0
Nickel	0	+	Nasal cancer	?	-	-	-	Lung sarcoma
Beryllium	0	0	0	-	-	+	-	Adeno and squamous cancer
Asbestos	0	?	0	0	-	0	-	0
ORGANIC								
Aliphatic	0	0	0	?	-	-	-	Lung adenoma
Polycyclic Petroleum Products	+	0	0	+	+	+	-	Squamous cancer
Cutting Oils	+	0	0	+	+	-	-	Papillomas
Coal Tar	+	0	0	+	+	-	-	Squamous cancer
Dyes and Intermediates	0	0	Bladder carcinoma	-	-	-	Dog	Bladder tumor
PHYSICAL AGENTS								
Ultra Violet	Not Discussed							
Radioactive	+	+	Bone, Thymus, Blood	+	-	-	-	Leukemia

1. Arsenic

A. Epidemiological Evidence

Skin - squamous cell carcinoma and hyperkeratotic lesions. All sixteen reporting believed that the association particularly with inorganic arsenic, such as As_2O_3 was valid. Some expressed doubt about the relationship with contact or industrial exposures. Ingestion was generally conceded as proved.

Lungs - Bronchogenic Carcinoma

All expressed doubt about the data to-date in regard to the hazard of lung cancer following either industrial or community exposures. The strongest affirmative opinion given was that the observations were suggestive.

Other Organs

No one felt that any evidence, clinical or epidemiological, was available to show a relationship to cancer of other organs.

B. Experimental Evidence

Rabbits

Topical application of arsenical compounds on the skin of rabbits has produced papillomas. About half of the reporting participants felt that these observations at the best were only suggestive. The others accepted without question the results as reported.

C. General Aspects.

a. We have no knowledge of the action of A_s in the skin or other tissues. In the light of the discussion this would seem to be a useful avenue to explore.

b. There is no real understanding of the dosage and kind of exposure required. This is true also as to the importance of various arsenic compounds.

2. Chromates

A. Epidemiological Evidence

Skin

Have a marked association between exposure to chromium and skin and nasal ulcers. However, no skin cancers have been reported. All of the participants reporting accepted this observation without question.

Lung

All sixteen score sheets recorded that the evidence of relationship between industrial exposures (chrome production) and bronchogenic carcinoma seemed good. Community exposure is a different question and there is no acceptable evidence available at this time.

Other Organs

No evidence.

Other Occupations

Suggestive evidence in occupations using chromates, i.e., painting and welding. Will require an enormous amount of work due to need to determine the precise exposure, both in kind and degree, and the particular compound.

B. Experimental Evidence

C57 Mice, rabbits, guinea pigs and rats have been exposed, by inhalation, intravenous and subcutaneous injections and by skin applications. All results have been essentially negative. The participants uniformly recorded that no experimental evidence has been produced to support the epidemiological findings.

C. General Aspects

a. It was brought out that we may be dealing with a carcinogenic industrial operation rather than exposure to a single element or compound.

b. The variation in tissue uptake, both in degree and kind of compound, offers an interesting avenue of study. Retention also differs.

c. Here we have reasonably good epidemiological evidence but no experimental studies to support the observations. Can control be based on such results, particularly, if only certain compounds may be involved?

3. Nickel

A. Epidemiological Evidence

Skin

No evidence presented.

Lung (Including nasal passages)

Carcinoma of the nasal passages and lungs has been related to plant exposures and a causal relationship suggested particularly with metallic nickel and follows inhalation. Exactly half of the participants considered the evidence available as suggestive but not entirely convincing. The others felt that the hazard had been demonstrated.

Other Organs

No evidence.

B. Experimental Evidence

Mice

Inhalation experiments with metallic nickel dust was followed by a higher incidence of lung carcinoma than in the controls. (Significance?). Sarcomas were found only in the test animals. It was reported that nickel dust in embryonic lung tissue transplants was followed by an adenoma in one animal.

Other Animals

No evidence presented.

C. General Aspects

a. May be dealing with an "operation exposure" rather than exposure to a single compound and similar to the chromium experience.

b. Nickel carbonyl has been considered but apparently the hazard is more closely related to metallic nickel.

c. A very long latent period is present, 8-30 years, if the epidemiological evidence is accepted.

4. Beryllium

A. Epidemiological Evidence

Skin

No evidence of human hazard presented.

Lung

Acute pneumonitis and chronic berylliosis have been shown to follow various kinds of beryllium exposures. Three or four cases of lung carcinoma have been seen in individuals with Be exposure histones but evidence at the moment cannot be considered acceptable. There is no relationship between the amount of Be in the tissues and the pathologic reaction.

Other Tissues

No evidence presented.

B. Experimental Evidence

Rats

Inhalation exposures (intratracheal) with beryllium oxide dusts have been followed by squamous and adenocarcinoma of the lungs. Also scirrhous types and metastasis have been demonstrated. Be SO_4 has not given such results.

Rabbits

Intravenous injections have produced bone lesions, both adenocarcinoma and osteosarcoma.

C. General Aspects

a. All of the participants concluded that the evidence for a human hazard was insufficient.

b. All accepted the rat studies but one or two questioned the work with rabbits.

c. One or two had definite reservations about the desirability of extrapolating the results of these experimental studies to man.

d. Attention was called to the extent of the hazard if a causal relationship is established due to the presence of Be in the soil of a large part of Virginia and the Carolinas.

5. Asbestos

A. Epidemiological Evidence

Skin

No evidence.

Lung

English reports are very suggestive - 13% of asbestosis deaths had carcinoma compared to 1.3% of silicotics. Canadian workers - 6 cases of lung cancer in 52 autopsies (11%). All of the participants were impressed but on the whole felt that more studies in greater detail were needed. The tumors generally found were adenocarcinoma, squamous and oat cell anaplastic.

Other Organs.

No evidence.

B. Experimental Evidence

Rats and Mice

Intratracheal exposures have given negative results but the studies are obviously inadequate. The general consensus of the conference group reporting was that the evidence was inconclusive and much more work was needed in this area.

C. General Aspects

a. Worker studies have been very suggestive but no great reliance can be placed on the data assembled to date. Additional studies are needed.

b. The laboratory investigations reported do not confirm the human experience although only scanty observations are available.

c. Widespread hazard if a causal relationship is established due to many uses of this material under various conditions.

6. Aliphatic Organic Compounds

A. Epidemiological Evidence

No evidence was presented for any kind of exposures. Widespread exposure exists in all walks of life but no data establishing a human hazard has ever been collected.

B. Experimental Evidence

Mice

Inhalation exposures to synthetic smogs and epoxides alone and adsorbed on "soot" have been followed by adenomas of the lung.

Painting experiments with epoxides have given a few epithelial cancers but this work is only preliminary and cannot be used with qualifications at the moment.

C. General Aspects

a. No human hazard has been established.

b. Animal experiments are interesting but not conclusive and cannot be extrapolated to man.

7. Petroleum Products (Polycyclic Organic Compounds)

A. Epidemiological Evidence

Skin

The relationship between human skin carcinoma and exposures to certain petroleum oils - particularly paraffin oils in America and shale oils in England - was accepted by all participants. The relative importance of accelerators and cocarcinogens (initiators and promoters) found in petroleum has not been completely established, although it is generally accepted today that they play a major role. The tumors produced are squamous or basal cell carcinoma. Scrotal cancers are a very prominent group.

Lung

No evidence to date that the incidence of lung cancer is increased by exposure.

Other Organs

No evidence to date.

B. Experimental Evidence

Animal

A wide variety of animals has been used experimentally, but mice and rabbits have been found most satisfactory. Some doubt was expressed as to the ability to quantitate the relative potency of different fractions by animal tests. The tumors produced are papillomas and squamous carcinoma.

Chemical Testing

A considerable amount of time was spent on a discussion of the value of precise chemical analyses of petroleum products in the appraisal of potency. The participants did not reach any definite conclusion but this is one area where agreement among the various investigators should be sought.

C. General Aspects -

(a) With these materials, the epidemiological observations have been substantiated by experimental studies.

(b) The differences found when the English and American studies are compared may be due in part to personal hygiene habits and working conditions.

(c) Additional studies, both in the field and laboratory are still needed.

3. Cutting Oils (Polycyclic Organic Compounds)

A. Epidemiological Studies

Skin

Carcinoma of the skin, particularly of the forearms, although scrotal lesions are found, has been associated with exposure to cutting oils both in America and England. The occurrence of hyperkeratosis and neoplasms is part of the over-all picture of skin irritation which is also marked by folliculitis. The participants as a group felt that the invidence was good.

Lung

No evidence of a causal relationship to tumors has been presented to date. It was brought out that there is a real hazard of oil pneumonitis in such occupational exposures.

Other Organs

No evidence.

B. Experimental Evidence

Animal Studies

Mice and rabbits have been used and papillomas produced. It was brought out that possibly not enough attention has been given to papillomas. The consensus of the conference, based on the score sheets, was that the evidence was essentially good and more than suggestive.

Chemical Studies

It was brought out that cutting fluids vary widely in formula and that it is impossible to determine what material is at fault. The problem is magnified because the material is expensive and is usually recirculated and periodically recharged. As a result, the formula changes from day to day and the fluid likewise can become contaminated with many other materials.

C. General Aspects

a. Epidemiological observations are well established under certain circumstances.

b. The laboratory investigations will be hampered by the wide variety of compounds in formulas and possible contaminants.

c. The role of chronic skin irritation is very important.

9. Coal Tar (Polycyclic Organic Compounds)

A. Epidemiological Evidence

Skin

The participants accepted the association between exposure to coal tar and certain products. It was brought out that chronic skin irritation has an important role and personal hygiene and plant housekeeping were also important factors. Attention was directed also to the fact that there are many compounds in various fractions and that pure materials do not exist. It was also noted that the number of workers in the industry itself is rather small.

Lung

No evidence to date to indicate such a hazard.

Other Organs

No evidence.

B. Experimental Evidence

Animals

Mice and rabbits have been used and carcinomas produced. Tests for "promoting" substances have been negative so the materials are considered essentially primary carcinogens.

Chemical

The complexity of the various fractions hampers chemical studies and for the most part they have been confined to the determination of the benzpyrene concentration. Industry does not believe that extensive chemical fractionation would be fruitful. Environmental factors probably have a large role.

C. General Aspects

(a) Epidemiological evidence is apparently good for skin tumors.

(b) Animal and chemical experimentation hampered by the complexity of the materials.

(c) Personal hygiene and plant housekeeping are very important.

10. Dyes and Intermediates (Polycyclic Organic Compounds)

A. Epidemiological Evidence

Skin

No evidence presented.

Lung

No evidence presented.

Other Organs

Bladder tumors have been definitely associated with Beta-naphthylamine and benzidine. The participants accepted the evidence for these two compounds but considered the data demonstrating a hazard from other materials in this field as doubtful or not present. It was pointed out that Beta-naphthylamine should be classified as one of our most potent carcinogens.

B. Experimental Evidence

Animal

Dogs have been used principally and tumors have been induced by feeding. No one questioned these observations.

Chemical

Research in this area is very important. The question of contamination with Beta-naphthylamine is very important and may be the reason why other compounds are considered hazardous. There is the possibility that workers may have such exposures without actually working with this compound.

C. General Aspects

a. Epidemiological studies seem conclusive for at least two compounds.

b. Animal experiments have substantiated the field observations.

c. Much additional work is needed to determine if additional hazards exist.

11. Ultra-Violet Radiation (Physical Agents)

This area was not discussed due to limitation in time.

12. Radioactive Materials (Physical Agents)

A. Epidemiological Evidence

Radium, X-Ray, and fission products have all been associated definitely and clearly with carcinomas, sarcomas and leukemias and involving bones, skin, blood and mucous membranes. Radon still remains dubious because there is no direct evidence except with German experience.

All of the participants accepted the causal relationships which have been demonstrated for actual tumor productions. Attention was called to the need to define the degree and kind of exposure in more detail. Consideration should be given also to question of cumulative effect and the latent period. The problem of intra-uterine exposure was also brought up as an example of the need for controls.

B. Experimental Evidence

"Operation Greenhouse" demonstrated 100% leukemic response in mice above certain dosages. Many other animals have also been used successfully in similar studies with various radioactive materials.

C. General Aspects

A. There is no question of the hazard to man of this particular group of physical agents.

B. Co-carcinogenis needs further investigation.

C. There is a great need for extension and application of controls due to the increasing use and exposures to radioactive materials, both in industry and in the community.