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AUGUST 20, 1985

PROJECT EMN

PHASE I

- A. CONCEPT
- NOT MARKETING ORIENTED
  - NO FINANCIAL RESTRICTIONS

B. THEIR DEFINITION OF THE PROBLEMS

SURGEON GENERAL

ROYAL COLLEGE OF PHYSICIANS

C. DEFINITION TO INCLUDE RELATIVE VALUES OF SPECIFIC TOXIC COMPONENTS IN DIFFERENT SOURCES

I.E. SOIL, AIR, WATER AND FOOD

P.J. DUNN

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**D. TOXIC AGENTS - GAS PHASE AND PARTICULATE MATTER**

**IDENTIFICATION BY CATEGORY  
AND  
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**S.R. MASSEY**

**E. EVOLUTION OF THE SMOKING AND HEALTH ISSUE**

**MECHANISM OF MEDICAL METHODOLOGY  
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**6. WHAT WOULD BE ACCEPTABLE AS A SAFER CIGARETTE**

**LITERATURE REVIEW**

**C. WARREN**

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REVIEW

1 9 6 2

REPRESENTATION OF

AMERICAN CANCER SOCIETY  
AMERICAN COLLEGE OF CHEST PHYSICIANS  
AMERICAN HEART ASSOCIATION  
AMERICAN MEDICAL ASSOCIATION  
TOBACCO INSTITUTE INC.  
FOOD AND DRUG ADMINISTRATION  
NATIONAL TUBERCULOSIS ASSOCIATION  
FEDERAL TRADE COMMISSION  
PRESIDENTS OFFICE OF SCIENCE & TECHNOLOGY

MET WITH THE SURGEON GENERAL TO ESTABLISH THE WORK OF AN EXPERT COMMITTEE AND TO AGREE ON A LIST OF SOME 150 SCIENTISTS AND PHYSICIANS QUALIFIED TO EVALUATE DATA ON THE RELATIONSHIP BETWEEN TOBACCO USE AND HEALTH.

THE SURGEON GENERAL SELECTED 10 FROM THE LIST AND, THUS, THE SURGEON GENERAL'S ADVISORY COMMITTEE ON SMOKING AND HEALTH WAS LAUNCHED AT ITS FIRST MEETING OF NOVEMBER 9, 1962.

THE JUDGMENTS OF THE ADVISORY COMMITTEE LED TO A SERIES OF CONCLUSIONS RELEASED IN 1964 IN THE 'REPORT OF THE ADVISORY COMMITTEE TO THE SURGEON GENERAL OF THE PUBLIC HEALTH SERVICE ON SMOKING AND HEALTH.'

THE COMMITTEE CONCLUDED:

"CIGARETTE SMOKING IS A HEALTH HAZARD OF SUFFICIENT IMPORTANCE IN THE UNITED STATES TO WARRANT APPROPRIATE REMEDIAL ACTION."

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FIFTEEN YEARS AFTER THE INITIAL 'SURGEON GENERAL'S REPORT' THE U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE PUBLISHED

**"SMOKING AND HEALTH A REPORT OF THE SURGEON GENERAL"**

THIS REPORT IS A COMPENDIUM OF NEW DATA FROM MANY SOURCES INCLUDING THE OFFICE ON SMOKING & HEALTH AND THEIR REPORT ON THE EXPERT PANEL CLASSIFICATION OF COMPOUNDS IN CIGARETTE SMOKE.

**Toxic and Carcinogenic Agents**

Compounds in cigarette smoke have been classified by an expert panel into:

1. Those judged most likely to contribute to the health hazards of smoking.

- (a) Carbon monoxide (gas phase).
- (b) Nicotine and "tar" (particulate phase).

2. Those judged as probable contributors to the health hazards of smoking.

- (a) Gas phase: acrolein, hydrocyanic acid, nitric oxide and nitrogen dioxide.
- (b) Particulate phase: cresols and phenol.

3. Those judged as suspected contributors to the health hazards of smoking.

- (a) Gas phase: acetaldehyde, acetone, acetonitrile, acrylonitrile, ammonia, benzene, 2-3 butadione, carbon dioxide, crotononitrile, ethylamine, formaldehyde, hydrogen sulfide, methacrolein, methyl alcohol, and methylamine.
- (b) Particulate phase: butylamine, dimethylamine, DDT, endrin, furfural, hydroquinone, nickel compounds, pyridine.

These compounds have been so designated not only because of their harmful actions but also because of their concentrations in tobacco smoke. Although other constituents are considered toxic, they are not present in concentrations deemed a health hazard.

A number of tumor initiators, co-carcinogens, and organ-specific carcinogens have been isolated and identified. The majority of co-carcinogens remain to be identified. The increased risk cigarette smokers have for cancer of the esophagus, kidney, and urinary bladder suggests the possibility that cigarette smoke contains unidentified organ-specific carcinogens besides the known trace amounts of carcinogenic aromatic and N-nitrosamines.

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SMOKING & HEALTH A REPORT OF THE SURGEON GENERAL  
INTRODUCTION & SUMMARY

OFFICE ON SMOKING & HEALTH 1-30

IN THE PREFACE TO THE 1979 "SURGEON GENERAL'S" REPORT, THE SURGEON GENERAL REFERS TO A 1966 PUBLIC HEALTH SERVICE REPORT THAT STATED:

THE PREPONDERANCE OF SCIENTIFIC EVIDENCE STRONGLY SUGGESTS THAT THE LOWER THE 'TAR' AND NICOTINE CONTENT OF CIGARETTE SMOKE, THE LESS HARMFUL WOULD BE THE EFFECT"

PREFACE XII

THIS WAS FOLLOWED BY THE DECISION OF THE FEDERAL TRADE COMMISSION TO BEGIN MEASURING THE "TAR" AND NICOTINE YIELDS OF CIGARETTES AND TO PERMIT MANUFACTURERS TO BEGIN USING THIS INFORMATION IN THEIR ADVERTISING.

THIS IN TURN TRIGGERED:

CHANGES IN CIGARETTE PRODUCTION TECHNOLOGY  
DEVELOPMENT OF RECONSTITUTED TOBACCO  
REFINEMENT OF CIGARETTE FILTERS AND PAPER  
NEW TOBACCO STRAINS

TO MENTION A FEW.

THE OBJECTIVE WAS TO REDUCE THE "TAR" AND NICOTINE OF CIGARETTE SMOKE.

THE IMPACT OF THESE CHANGES IS NOTED IN THE FOREWORD OF THE 1982 REPORT.

**'THE HEALTH CONSEQUENCES OF SMOKING'**  
A REPORT OF THE SURGEON GENERAL

**Lower Tar Cigarettes**

This report also notes that smokers who use filtered or lower tar cigarettes have statistically lower death rates from lung cancer than do cigarette smokers who use nonfiltered or higher tar brands. This reduced risk was also noted for laryngeal cancer. However, cancer death rates for smokers of lower tar cigarettes were still significantly higher than those noted for nonsmokers.

Edward N. Brandt, Jr., M.D.  
Assistant Secretary for Health

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IN THE 1979 'SMOKING AND HEALTH A REPORT OF THE SURGEON GENERAL', JULIUS B. RICHMOND, M.D. STATES

Adhering to this spirit of inquiry and recognizing the magnitude of the public health problem, we must ask: What is our current knowledge about "appropriate remedial action?" What scientific, economic, and behavioral facts are important for the design of public policy toward cigarette smoking? What have we learned so far, and where do we go from here? To answer these questions, we must confront three central facts: Individuals vary in their health risks associated with cigarette smoking. Individuals vary in their cigarette-smoking behavior. The cigarette product itself is changing.

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PREFACE VII

THE LAST SENTENCE "THE CIGARETTE PRODUCT ITSELF IS CHANGING" LEADS TO THE THEME OF THIS PROJECT I.E. HOW DO WE DESIGN AND MANAGE FUTURE PRODUCT CHANGES?

THE NATIONAL CANCER INSTITUTE PORTION OF THE "SMOKING AND HEALTH A REPORT OF THE SURGEON GENERAL" CONTAINS THEIR THOUGHTS RELATIVE TO PRODUCT CHANGE.

In this chapter we will consider the tobacco as a raw material, how it is made into cigarettes, the cigarette smoke generation process, the composition of cigarette smoke, physiological responses to cigarette smoke, the pharmacology of nicotine as a component of cigarette smoke, and efforts to define less hazardous cigarettes through cigarette smoke modification. Also, consideration will be given to the effects of smoke characteristics on smoking behavior and, therefore, on the dose inhaled by man and experimental animals.

14-9

THESE THOUGHTS WILL BE AMPLIFIED IN THE FOLLOWING PARTS OF THIS REORT.

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A PARALLEL ACTIVITY IN THE FIELD OF SMOKING AND HEALTH  
WAS TAKING PLACE IN GREAT BRITAIN.

1959

THE ROYAL COLLEGE OF PHYSICIANS OF LONDON SET UP A  
COMMITTEE TO:

"REPORT ON THE QUESTION OF SMOKING  
AND ATMOSPHERIC POLLUTION IN RELATION  
TO CARCINOMA OF THE LUNG AND OTHER  
ILLNESSES"

AND HAD DIFFICULTY IN WORKING WITH TWO VARIABLES SO THAT  
IN:

1962

THE FIRST REPORT 'SMOKING AND HEALTH' WAS PUBLISHED.

1971

THE SECOND REPORT BY THE ROYAL COLLEGE OF PHYSICIANS  
OF LONDON 'SMOKING AND HEALTH NOW' WAS PUBLISHED.

CHAPTER 3 OF THAT REPORT 'THE CHEMISTRY AND PHARMACOLOGY  
OF TOBACCO SMOKE' IDENTIFIES THE SUBSTANCES OF MEDICAL  
IMPORTANCE AND GROUPS THEM INTO FOUR MAIN GROUPS.

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- a *Known cancer-producing substances.* These are of two kinds: carcinogens or cancer initiators, which have been shown by themselves to induce cancer in experimental animals, and co-carcinogens or cancer promoters, which do not themselves produce cancer but accelerate its production by cancer initiators.
- b *Irritant substances.* These may stimulate secretion of mucus in the bronchial tubes and inhibit the action of the cilia<sup>a</sup> lining them. Some of these irritants are also co-carcinogens.
- c *Nicotine.* This has a wide range of pharmacological actions on tissues throughout the body, especially on the nervous system.
- d *Carbon monoxide and other gases.* Carbon monoxide interferes with the blood's capacity to carry oxygen or with the use of oxygen in the tissues. There are other chemically active gases, including oxides of nitrogen and hydrogen cyanide, the effects of which in the low concentrations occurring in tobacco smoke are uncertain.

1 9 7 7

THE THIRD REPORT BY THE ROYAL COLLEGE OF PHYSICIANS  
OF LONDON 'SMOKING OR HEALTH WAS PUBLISHED.

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PAGES 25 AND 26 OF THIS REPORT CONTAIN THE FOLLOWING:

#### Less Harmful Smoking Habits

The tobacco manufacturers have been steadily reducing the tar and nicotine delivery of their cigarettes in recent years by changing the tobacco leaf used, and by increasing the efficiency of filters. Forty years ago, one of the most popular cigarettes had tar and nicotine yields of 36 and 3.3 mg respectively (30). If these figures were typical for that period, average yields were already considered lower in 1965 when regular analyses were started (Table 1.2). Since then, owing especially to the large switch from plain to filter-tipped brands of cigarettes, there has been a further striking fall in the average amount of tar and nicotine to which British smokers expose themselves (Table 1.2).

Table 1.2  
Sales-weighted Average Tar and Nicotine Yields of  
Cigarettes Sold in the UK 1965 to 1975

| Year           | Mean Tar Yield (mg) | Mean Nicotine Yield (mg) |
|----------------|---------------------|--------------------------|
| 1965           | 31.4                | 2.08                     |
| 1967           | 26.0                | 1.82                     |
| 1969           | 23.9                | 1.67                     |
| 1971           | 21.3                | 1.51                     |
| 1973           | 18.7                | 1.44                     |
| 1975           | 17.9                | 1.35                     |
| Change 1965-75 | -13.5               | -0.73                    |
| % Change       | -43                 | -35                      |

Figures supplied by the TRC

PAGE 121, UNDER THE HEADING OF "LESS HARMFUL SMOKING," CONTAINS THE FOLLOWING:

Reducing the harmful constituents of cigarette smoke. Since we do not know precisely which of the many hundreds of chemical compounds in the smoke of cigarettes are responsible for cancers, bronchitis, emphysema, or damage to the heart and blood vessels, we cannot specify exactly what constituents in the smoke should be reduced to lessen the risk. But most smoking-related cancers are probably caused by carcinogenic substances in the 'tar' fraction of the smoke, and it has been shown that American smokers who for at least ten years have smoked only filter-tipped cigarettes (which have a lower tar delivery than plain cigarettes) have their risk of getting lung cancer almost halved (46). A more recent, larger study indicates that the risk is reduced by only some 20 per cent (15a).

100505079

1983

"HEALTH OR SMOKING." FOLLOW-UP REPORT OF THE ROYAL COLLEGE OF PHYSICIANS

CHAPTER THREE PAGE 23

TABLE 3.1. Changes in England and Wales male lung cancer death rates in early middle age since tar deliveries have been reduced

| Age at time of observation | Death rates per million men from cancers of the respiratory tract, excluding larynx |   | Ratio |
|----------------------------|---|---|-------|
|                            | Men born in about 1910, and observed in 1940-1960                                   | Men born in about 1930-1950, and observed in 1980 |       |
| 30-34                      | 39**  | 13  | 0.3   |
| 35-39                      | 98**  | 45  | 0.5   |
| 40-44                      | 253**   | 134   | 0.5   |
| 45-49                      | 597**   | 378*  | 0.6   |

\* High mean tar intake only in first decade or so of smoking history  
 \*\* High mean tar intake throughout smoking history

CHAPTER NINE PAGE 87

*Less dangerous forms of smoking?*

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*Changes in national lung cancer deaths*

As pointed out earlier (Figure 3.1) there has been an important downward trend in lung cancer mortality in men of all ages in the United Kingdom. In women this trend has been seen only in the youngest age groups. In seeking an explanation for these trends the influence of smoking habits 20-30 years earlier has been shown to be of paramount importance (the 'generation effect').

There is no obvious explanation for these falls in national lung cancer death rates other than the changes in the tar delivery of cigarettes. Cigarette consumption per head did not begin to fall in men until very recently (see Figure 11.2). If the fall in lung cancer deaths is due to smoking lower tar/nicotine cigarettes, complete compensation for the lower nicotine by increasing total smoke intake cannot have been widespread. Declining air pollution is unlikely to have contributed much to this effect since air pollution appears to have little if any effect on lung cancer incidence [13], and moreover similar decreases have been observed in unpolluted Finland [13].

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CHAPTER FIVE OF "HEALTH OR SMOKING" IS ENTITLED 'SUSCEPTIBILITY TO SMOKING HAZARD' AND SOME OTHER CONSIDERATIONS ARE BROUGHT INTO THE PICTURE.

GENETIC PREDISPOSITION

GENETIC FACTORS THAT MIGHT INFLUENCE SUSCEPTIBILITY TO SMOKING.

DIET

"FOR CANCER OF THE LUNG, THE EVIDENCE SO FAR AVAILABLE SUGGESTS THAT LOW INTAKE OF VITAMIN A INCREASES THE CHANCE THAT SMOKING WILL CAUSE THIS CANCER. STUDIES TO SEE WHETHER INCREASING THE DIETARY INTAKE OF VITAMIN A CAN DECREASE THE CARCINOGENIC EFFECTS OF CIGARETTE SMOKING ARE NOW UNDER WAY."

THESE TWO POINTS ARE INDICATIVE OF THE INCREASING AWARENESS OF THE INTER-RELATIONSHIP OF LIFESTYLE, DIET, ENVIRONMENT, AND HEALTH.

CIGARETTE SMOKING IS ONE FACTOR AND MUCH HAS BEEN DONE TO IDENTIFY TOXIC SMOKE COMPONENTS. INDUSTRY HAS REDUCED THE QUANTITY PER CIGARETTE THROUGH A "TAR" REDUCTION PROGRAM. THE VALUE OF THIS CHANGE WAS IDENTIFIED EARLIER.

CONTINUED GROSS REDUCTION OF "TAR" TO BRING ABOUT REDUCTION OF TOXIC COMPONENTS MAY LEAD TO AN APPRECIABLE ALTERATION OF THE ORGANOLEPTIC PROFILE AND CONSEQUENTLY TO CONSUMER REJECTION.

WHAT APPEARS TO BE A REASONABLE COURSE OF ACTION IS THE SELECTIVE REDUCTION OF SPECIFIC SMOKE COMPONENTS TO REDUCE THE SPECIFIC TOXICITY OF CIGARETTE SMOKE.

C. WARREN

SEPTEMBER 9, 1985

100505081

THERE HAVE BEEN EXPRESSIONS OF CONCERN BY LAWYERS THAT IF WE OVERTLY STATE THAT WE ARE ATTEMPTING TO REMOVE TOXIC AGENTS IN THE GAS PHASE AND PARTICULATE MATTER OF CIGARETTE SMOKE THAT WE ARE ADMITTING GUILT IN THE SMOKING AND HEALTH CONTROVERSY.

THIS IS NOT NECESSARILY SO. THE PROGRESSION FROM TOXIC AGENT TO BIOLOGIC ACTIVITY IS DONE BY THE SURGEON GENERAL, WITH VARYING DEGREES OF CERTAINTY. FOR EXAMPLE, IN THE 1981 PUBLICATION

'THE HEALTH CONSEQUENCES OF SMOKING  
THE CHANGING CIGARETTE  
A REPORT OF THE SURGEON GENERAL'

ON PAGE 24, "RESEARCH NEEDS ON LOW-YIELD CIGARETTES," THERE IS A LIST OF RESEARCH RECOMMENDATIONS AMONG WHICH IS

- Another research need is routine, frequent surveillance of current and future lower "tar" and nicotine cigarettes for specific chemical constituents and biological activity. In addition to "tar," nicotine, and carbon monoxide yield, new types of cigarettes should be monitored regularly for delivery of other potentially harmful constituents, such as benzo[a]pyrene, phenols, catechols, nitrosamines, nitrogen oxides, volatile aldehydes, and radionuclides. More frequently updated ratings of "tar," nicotine, and carbon monoxide content would permit more accurate studies on the potential impact of cigarette components on health.

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IT WOULD BE REASONABLE FOR US TO SAY THAT WE DO NOT DEBATE THE BIOLOGICAL AND HENCE MEDICAL INTERPRETATION OF THE SPECIFIC CHEMICAL CONSTITUENTS, BUT THAT WE ARE WORKING TOWARD REDUCING OR REMOVING THE TOXIC AGENTS, AND LET THE SURGEON GENERAL OR THE ROYAL COLLEGE OF PHYSICIANS DETERMINE WHAT, IF ANY, ARE THE MEDICAL IMPLICATIONS. THIS, THEY HAVE ALREADY DONE, E.G. WHEN THEY LINK REDUCED 'TAR' CONTENT OF CIGARETTE SMOKE AND DECLINING INCIDENCE OF LUNG CANCER.

THE APPROACH THAT WE REMOVE THE TOXIC AGENTS IDENTIFIED BY OTHERS IS COMMON PRACTICE E.G. WHEN THE F.D.A. MAKES A JUDGMENT IN THE AREAS OF

FOOD  
PHARMACEUTICAL  
BEVERAGE

I.E. REMOVES SOME COMPONENT FROM THE G.R.A.S. LIST, THE RESPONSE IN INDUSTRY IS AUTOMATIC.

WE COULD ASSUME THE SAME IMPLIED DIRECTIVE BY TAKING TABLE I AND TABLE II FROM THE 1981 SURGEON GENERAL'S REPORT

'THE CHANGING CIGARETTE.'

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**TABLE 1.—Major toxic agents in the gas phase of cigarette smoke (unaged)\***

| Agent   | Biologic activity <sup>a</sup> | Concentration/cigarette |                              |
|---|--------------------------------|-------------------------|------------------------------|
|   |                                | Range reported          | U.S. cigarettes <sup>b</sup> |
| Dimethylnitrosamine                             | C                              | 1-200 ng                | 18 ng                        |
| Ethylmethylnitrosamine                          | C                              | 0.1-10 ng               | 1.8 ng                       |
| Diethylnitrosamine                              | C                              | 0-10 ng                 | 1.5 ng                       |
| Nitrosopyrrolidine                              | C                              | 2-42 ng                 | 11 ng                        |
| Other nitrosamines<br>(4 compounds)             | C                              | 0-20 ng                 | ?                            |
| Hydrazine                                       | C                              | 24-43 ng                | 32 ng                        |
| Vinyl chloride                                  | C                              | 1-16 ng                 | 12 ng                        |
| Urethane  | TI                             | 10-86 ng                | 30 ng                        |
| Formaldehyde                                    | CT, CoC                        | 20-90 µg                | 30 µg                        |
| Hydrogen cyanide                                | CT, T                          | 80-200 µg               | 110 µg                       |
| Acrolein  | CT                             | 25-140 µg               | 70 µg                        |
| Acetaldehyde                                    | CT                             | 18-1,400 µg             | 800 µg                       |
| Nitrogen oxides (NO <sub>x</sub> ) <sup>c</sup> | T                              | 10-600 µg               | 350 µg                       |
| Ammonia   | TM                             | 10-150 µg               | 80 µg                        |
| Pyridine  | TM                             | 9-93 µg                 | 10 µg                        |
| Carbon monoxide                                 | T                              | 2-20 mg                 | 17 mg                        |

\*Cigarettes may also contain such carcinogens as arsenic, nickel carbonyl, and possibly volatile chlorinated olefins and nitro-olefins.

<sup>a</sup>C denotes carcinogen; TI, tumor initiator; CoC, cocarcinogen; CT, class toxic agent; and T, toxic agent.

<sup>b</sup>85 mm cigarettes without filter tips bought on the open market 1978-1979.

<sup>c</sup>NO<sub>x</sub> > 85% NO; rest NO<sub>2</sub>.

<sup>d</sup>Not toxic in smoke of bleached U.S. cigarettes because pH < 5.5, and therefore ammonia and pyridine are present only in protonated form.

SOURCE: Wynder and Hoffmann (1967).

**TABLE 2.—Major toxic agents in the particulate matter of cigarette smoke (unaged)\***

| Agent   | Biologic activity <sup>a</sup> | Concentration/cigarette |                              |
|---|--------------------------------|-------------------------|------------------------------|
|   |                                | Range reported          | U.S. cigarettes <sup>b</sup> |
| Benzo(a)pyrene  | TI                             | 8-50 ng                 | 20 ng                        |
| 8-Methylchrysenes                                       | TI                             | 0.5-2 ng                | 0.8 ng                       |
| Benzo(j)fluoranthene                                    | TI                             | 5-40 ng                 | 10 ng                        |
| Benzo(a)anthracene                                      | TI                             | 8-80 ng                 | 40 ng                        |
| Other polynuclear aromatic hydrocarbons (>20 compounds) | TI                             | ?                       | ?                            |
| Dibenz(a,j)acridine                                     | TI                             | 3-10 ng                 | 8 ng                         |
| Dibenz(a,h)acridine                                     | TI                             | ?                       | ?                            |
| Dibenz(e,g)carbazole                                    | TI                             | 0.7 ng                  | 0.7 ng                       |
| Pyrene  | CoC                            | 50-200 ng               | 150 ng                       |
| Fluoranthene  | CoC                            | 50-250 ng               | 170 ng                       |
| Benzo(g,h,i)perylene                                    | CoC                            | 10-60 ng                | 30 ng                        |
| Other polynuclear aromatic hydrocarbons (>10 compounds) | CoC                            | ?                       | ?                            |
| Naphthalenes  | CoC                            | 1-10 µg                 | 6 µg                         |
| 1-Methylindoles   | CoC                            | 0.3-0.9 µg              | 0.8 µg                       |
| 8-Methylcarbazoles                                      | CoC                            | 0.005-0.2 µg            | 0.1 µg                       |
| Other neutral compounds                                 | CoC                            | ?                       | ?                            |
| Catechol  | CoC                            | 40-460 µg               | 270 µg                       |
| 3- & 4-Methylcatechols                                  | CoC                            | 30-40 µg                | 32 µg                        |
| Other catechols (>4 compounds)                          | CoC                            | ?                       | ?                            |
| Unknown phenols and acids                               | CoC                            | ?                       | ?                            |
| N'-Nitrosornicotine                                     | C                              | 100-250 ng              | 250 ng                       |
| Other nonvolatile nitrosamines                          | C                              | ?                       | ?                            |
| β-Naphthylamine   | BC                             | 0-25 ng                 | 20 ng                        |
| Other aromatic amines                                   | BC                             | ?                       | ?                            |
| Unknown nitro compounds                                 | BC                             | ?                       | ?                            |
| Polonium-210  | C                              | 0.03-1.3 pCi            | ?                            |
| Nickel compounds  | C                              | 10-600 ng               | ?                            |
| Cadmium compounds                                       | C                              | 9-70 ng                 | ?                            |
| Arsenic   | C                              | 1-25 µg                 | ?                            |
| Nicotine  | T                              | 0.1-2.0 mg              | 1.5 mg                       |
| Minor tobacco alkaloids                                 | T                              | 0.01-0.2 mg             | 0.1 mg                       |
| Phenol  | CT                             | 10-200 µg               | 85 µg                        |
| Cresols (3 compounds)                                   | CT                             | 10-150 µg               | 70 µg                        |

\*Incomplete list.

<sup>a</sup>C denotes carcinogen; BC, bladder carcinogen; TI, tumor initiator; CoC, cocarcinogen; CT, class toxic agent; and T, toxic agent.

<sup>b</sup>85 mm cigarettes without filter tips bought on the open market 1978-1979.

SOURCE: Wynder and Hoffmann (1967).

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-3-

IN THIS CASE, WE WOULD USE ONLY THE 'AGENT' COLUMN  
SINCE THE 'BIOLOGIC ACTIVITY' BELONGS TO THE SURGEON GENERAL.

THE STATED OBJECTIVE COULD BE:

CIGARETTE AND SMOKE, CHEMISTRY MODIFICATION

C. WARREN

SEPTEMBER 12, 1985

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