Review Article

Toxicology of PPOM

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In June, 1961, my late colleague, Dr. Horace W. Cerarde, presented a paper on the natural occurrence of hydrocarbons in living matter and in the tissues of plants and animals which contribute to our daily diet. This paper was given before the Association of Food and Drug Officials of the U.S. and was titled, "The Ubiquitous Hydrocarbons".' Ubiquitous was defined in part as that which is present or turns up unexpectedly in many places. After working his way through the aliphatic hydrocarbons in rose wax, brussel sprouts and fish oils; the linear and cyclic olefins in flavor oils; and the terpene theory underlying the Biblical burning bush (Dictamnus fraxinella), he noted that "pyrolysis of organic matter results in the production of polycyclic aromatic hydrocarbons." "The organic matter may be slices of bacon, a piece of bread in a toaster, a **log** in a fireplace, tobacco . . . gasoline . . . ."

We might take this as a basis for a working definition of PPOM — particulate polycyclic organic material. These are condensed ring aromatic hydrocarbons normally arising from combustion of organic matter. Frequently included in this group are compounds containing a nitrogen heteroatom, the acridines and carbazoles. In community and workplace air, this polycyclic organic material is largely associated with particulate matter. It is uncertain whether the polynuclear aromatic hydrocarbons (PNAs) condense out as discrete particles after cooling or condense on the surface of existing particles after formation during combustion. In recognition of this association, the term PPOM (particulate polycyclic organic matter) is used. However, occupational exposure to PNAs can result from substances besides PPOM. These alternates-can include coal tar and heavy petroleum fractions. PPOM (and PNA) refer, therefore, to a class of materials regardless of source. The thrust of this conference, however, is a special subclass, Coal Tar Pitch Volatiles (CTPV). These PPOM are thus further characterized by the organic substrate from which they are derived. PPOM may also be classified by the particular pyrolytic or combustion process by which they are made. Three come to mind immediately (since they are the subjects of the epidemiology studies to be reviewed this afternoon) — coke oven emissions, roofing operations and electrode manufacture in the aluminum industry.

It is important not to use PPOM, CTPV and coke oven emissions interchangeably. There is enough confusion in the field without adding a semantic burden.

PPOM — Particulate Polycyclic Organic Matter
CTPV — Coal Tar Pitch Volatiles
Coke Oven Emissions
Not Interchangeable

Is PPOM toxic? The answer is yes and no. All chemicals are toxic (the credo by which most of us earn our bread), yet there

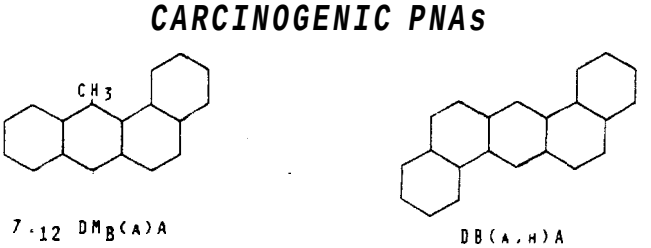

Fig 1

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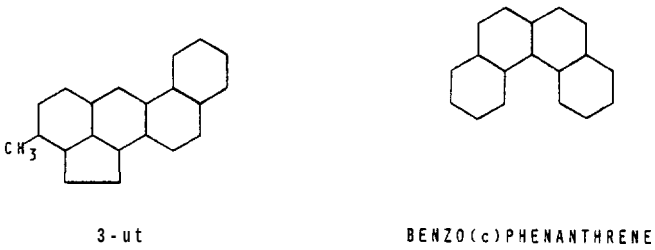

Fig 2

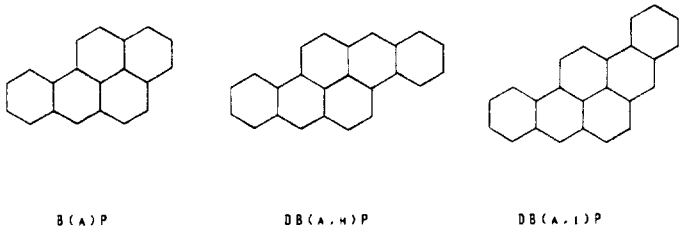

Fig 3

is a dose for any material below which no toxic response is manifest. This dose-response concept is a key element in safety evaluation. Is PPOM carcinogenic? The answer again is yes and no. PPOM refers, as noted before, to a class of condensed ring aromatic compounds. In the Shubik and Hartwell[2] compilations of compounds which have been tested for carcinogenicity, there are over 3300 listings (including some duplications), about 20 to 25% of which were found to produce tumors in experimental animals. There are over 400 4- and 5-ring compounds described and without checking every entry, it might be assumed that the same percentage holds. Thus, some are carcinogenic and some are not. Some carcinogenic PNAs are shown in Figures 1, 2 and 3.

In 1975, it is inappropriate to discuss the carcinogenicity of PPOM without giving proper recognition to that "other" bicentennial — the clinical observations in 1775 of scrotal cancers in chimney sweeps by an English surgeon, Sir Percival Pott. I am indebted to my chief and mentor, Dr. R. E. Eckardt, for the following quotation from Pott's 1775 treatise on surgery in the chapter titled "Cancer Scroti" as well as the other historical material which is included here.[3] Pott noted "Ramazzini has written a book de morbis artificum; the Colic of Poictou is a well known distemper; and everybody is acquainted with the disorders to which painters, plummers (sic), glaziers and the workers in white lead are liable: but there is a disease as peculiar to a certain set of people which has not, at least to my knowledge, been publicly noticed; I mean the chimney-sweepers' cancer." "It is a disease which always makes its first attack on, and its first appearance in, the inferior part of the scrotum where it produces a superficial, painful, ragged, ill-looking sore with hard and rising edges: the trade call it the soot-wart." Pott went on to associate the disease with the occupation but his suggested means of "putting a stop to, or preventing this mischief" was by "the immediate removal of the part affected."

Eckardt has noted that in Pott's three and one-half pages of observations one may infer many of the basic concepts of occupational cancer and an industrial control program. They are: (1) "Exposure must be severe. (2) Exposure must be prolonged. (3) The latent period is of the order of 10 years. (4) Personal hygiene leaves much to be desire& (5) Once developed, the disease runs the same course as cancers of similar sites of non-occupational origin. *(6)* Qnce developed, early detection and surgical extirpation offer the only hope. (7) The disease may aeverop even after exposure has ceased. *(8)* The disease may recur in another adjacent site even after removal of the first lesion and cessation of exposure."

It is typical of the work of early investigators in medical science that they provided a brilliant insight into the problem and that no one did anything for a hundred years more afterwards. It was 1875 before the next occupational cancer was described — that of scrotal cancer in workmen separating paraffin from distillates of German brown coal. The next 50 years saw descriptions of skin cancer from certain coal tars, lung cancer in Schneeburg and Joachimsthal miners, skin cancer in sailors, bladder cancer in dye industry workers, the first creosote and chrome cancers, mule skinners cancer and the like.

It was only 140 years after Pott's observations that the experimentalists first produced cancers in animals with materials comparable to what was suspected as the causative agent in man. In 1915 Yamagiwa and Ichikawa produced skin cancer in rabbits from repeated applications of coal tar. A few years later one of their pupils duplicated this feat using the skin of mice and in 1922 Passey confirmed the clinical observations of Pott by producing malignant growths on the skin of mice with an ether extract of soot. Eight years later Kennaway and Hieger produced the first tumor with a known chemical compound, dibenzanthracene. From that time to now there has been a cascade of studies on the carcinogenic activity of various PNAs followed closely by chemical, biochemical, electron density and other theories to explain the activity or lack thereof. One may, therefore, read that only 4-, 5-, and 6-ring PNAs are car-

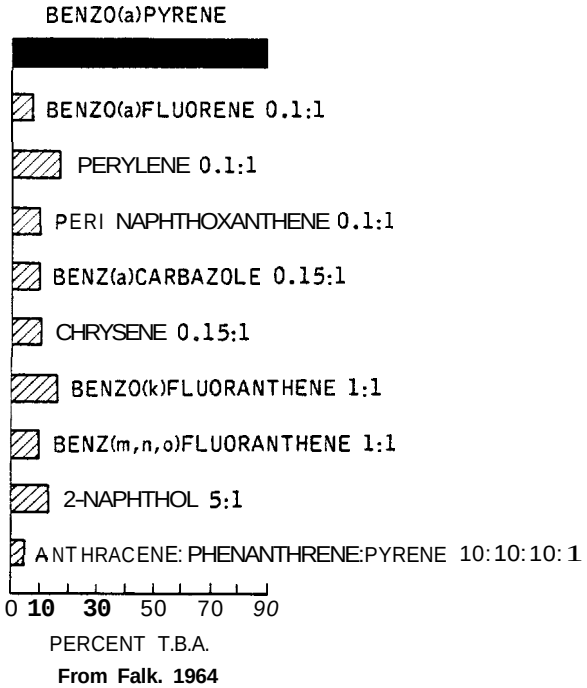

Fig 4. — Tumor production from benzo(a)pyrene and mixtures of PNAs with B(a)P. Data are given as percent of animals which are tumor-bearing.

cinogenic (but an anthracene derivative, a phenanthrene derivative and at least one seven-ring compound have demonstrated activity). Methyl substitution may increase activity (9,10DMB(a)A) or it may decrease it (1',10-DMB(a)A).

From the many studies on pure chemicals or mixtures, some observations have been critical in the development of an understanding of the action of PNAs first on the skin, then in the lungs: (1) The work of Rous in which rabbit ears were painted with tar until tumors began to appear. Painting stopped and the tumors disappeared. If a hole were then punched in the ear, tumors appeared at the edges but generally nowhere else. (2) A single application of a carcinogen may produce no tumors; however, if followed by repeated applications of certain non-carcinogenic materials, tumors appear. (3) Use of different solvents for the active carcinogen has the same effect as an increased dose of carcinogen itself.

From these and related studies has emerged the two-step theory of carcinogenic action on the skin.4 The steps are initiation, an irreversible change in a cell (DNA binding according to the current wisdom) and promotion, the facilitation of the manifestatidn of tumor growth. Typical data are shown in Table 1. The theory is further encumbered by the concept of an accelerator, a material which appears to involve the promotion phase but not initiation and is inactive without the promotor itself. Inhibitors are also known.

The following quasi mathematical form might be used to express these relationships: Ca = f (I x Pr x Ac over Inh). Carcinogenic action is a function of initiator, promotor and accelerator and is reduced by the presence of inhibitors. PNAs can be complete carcinogens (initiator and promotor), promotors, possibly accelerators, suggestions have been made of inhibitory action or they may be inactive. The role of any given PNA may depend upon the matrix in which it acts. For example, pyrene is generally considered to be non-carcinogenic. Yet when applied with B(a)P in a 3:1 molar ratio, the B(a)P response was enhanced significantly.[5]

One form of inhibition study in mice has involved the effect of washing on tumor induction. The carcinogenic potency (measured by potency number on a scale where 10 = non-carcinogenic) was significantly reduced when the animals were washed as much as six hours after painting with a carcinogenic oil.[3] The data are shown in Table 2.

Experimental evidence for anti-carcinogenic effects from PPOM is limited but does include studies by Falk[6] cited in the NAS PPOM review.' Falk showed that the weakly carcinogenic PPOM present in polluted air and cigarette smoke inhibited the production of subcutaneous sarcomas by B(a)P. The significance of this finding is that a given mixture of PPOM in any system may have a lower net carcinogenic effect than would be expected from the individual known carcinogenic

Table 1. — Two-Stage Tumor Induction — Mouse Skin.

Primary	Secondary	Results
DMBA, B(a)P	3 to 380 Days Later	First Papillomas 30-70 D. After Promotor
Single Subcarcinogenic Dose	Phorbol Ester 3x Weekly	50-100% TBA in 220-250 D. 40-60% Animals with Squamous Carcinoma after 1 Year

From Van Duuren, 1969

Table 2. — Effect of Washing on Tumor Induction.

Treatment	Potency Number
Back Painted - Belly Washed	63
Back Painted and Washed, 5 Min. Delay	21
Back Painted and Washed, 1 Hour Delay	22
Back Painted and Washed, 6 Hour Delay	31
No Painting, Back Washed	No Tumors

From Eckardt. 1959

PNAs present in the mixture. Reference will be made to this observation in assessing the value of analytical studies.

With respect to mixtures, as compared with pure compounds, there is ample evidence of production of skin cancers in experimental animals and man from prolonged and repeated contact. Occupationally, these effects have resulted from shale oil, coal tar pitch, mineral oils, and creosote oil.[3]

Does the two-step hypothesis apply to the action of PPOM on the lung? The limited evidence does not provide an unambiguous conclusion. The work of Kuschner, Laskin and colleagues[8] has shown that even at very high concentrations (10 mg/m³), DBA, B(a)P and Me Cholanthrene do not produce cancer in the lung of experimental animals. Direct instillation of solutions of the material into the lung was likewise without effect. However, if a thread impregnated with the chemical was fixed in the lung or if a carcinogen impregnated wire mesh is lodged in the lung, then there is a good yield of benign and malignant tumors. Most recently, combination exposure of SO_2 and B(a)P have produced lung cancer where none were seen following B(a)P alone. These data are shown in Tables 3 and 4. In still other studies conducted by Saffiotti, Shubik and coworkers cited in the NAS review7 the adsorption of B(a)P on hematite (Fe_2O_3) particles and subsequent instillation into the lung of Syrian golden hamsters produced a large number of cancers of the tracheobronchial tree and lung parenchyma. These lesions mimic those seen in man. The test system was able to generate dosage effects and was quite free of inflammation and spontaneous lung tumors. (This model has been extended to primates as well.)

The successful induction of tumors by the intratracheal instillation of a carcinogen appears to require some additional physical factor which appears to prolong the residence time of the active molecules at some target site, Such retention agents include besides hematite, carbon particles such as India ink and asbestos. No great insight is required to postulate that the PNA is reversibly adsorbed on the surface of the particle and is slowly released at the sensitive tissue, providing prolonged, constant contact. Disappearance studies, including those with tritiated B(a)P demonstrate reduced clearance (i.e., increased retention) of PNA as a function of the amount of inert material present. This explanation may also apply to the earlier studies in which implantation of impregnated pellets or threads was employed. (In the latter case the effects of trauma cannot be eliminated.) The lung irritant SO_2 may act in a comparable fashion by slowing ciliary action thereby prolonging the presence of PNA at the target site. Other studies suggest that irritant gases may function through some form of chronic injury and regenerating tissue (cells in mitosis) may be more susceptible to carcinogenic agents. This section of the discussion can be closed by making reference again to the unpublished work in progress at Wright-Patterson in which there has been no success to date in producing lung tumors in three

species of animals following massive exposures to coal tar aerosols. Skin tumors, however, were readily produced in mice.

Other inhalation studies of mixtures have yielded mixed results. Purified asphalt did not produce lung tumors in guinea pigs or mice. Pulmonary adenomas have been produced by road sweepings, chimney soot, dust, etc. The relationship of mouse lung adenoma to human lung cancer is tenuous.

The evidence for human lung cancers associated with exposure to certain mixtures containing PPOM is substantial but without adequate indication of the precise causative agents. Work in England has described an increased frequency of lung cancer among gas company workers exposed to coal gas and tar. Certain jobs seemed to carry a higher risk. Similar findings have been reported from Japan.[9] Most of this audience is familiar with the studies of the Pittsburgh group[10 11] on coke plant employees and the latest installment is expected later today. There is certainly a convincing weight of evidence which points to certain job classifications as carrying a level of risk of lung cancer up to 10x that of a comparable population without the same work assignment. This risk can also be related to age and duration of employment. Unmistakeably, this is an occupational cancer problem and such problems are frequently amenable to control without knowing precisely what the causative agents are. As an example, cancers of the sinus and larynx were reported over 20 years ago in one company and confirmed shortly thereafter in a second: despite extensive animal testing the causative agent is still not known. Continuous employee surveillance in both plants has developed the fact that no cancers have appeared in workers who began employment after a certain date. Certain process changes were instituted about that time and the causative agents appear to have been vitiated or eliminated.,

In the quest for identification of the causative agent in the coke oven workers studies, measurements of the emissions have been made in the vicinity of these plants. Correlations between these measurements and the extent of occupational disease have been attempted in order to determine meaningful occupational exposure limits. The data of Fannick et al[12] have been used to relate an analytically convenient measure of emissions to the age and cause specific mortality data for the workers. It is vital to remember that the measurements of the work environment — B(a) P, CTPV are analytically convenient; they can be conducted almost routinely and somewhat reproducibly. The correlation of these measurements with health effects in workmen does not by itself establish the things measured as the causative agents. This primitive logic, though self-evident, has certainly led good investigators astray before and may be doing so now. It is possible to accept Redmond's reasoning in supporting the present TLV of 0.2 mg/m³ CTPV (benzene soluble) since her data show that 200 mg/m³/ months of exposure (equivalent to — 0.56 mg/m³ for 30 years) is without increased risk of lung cancer[10] and yet not state that CTPV are the causative agents.

The evidence to date from animal and human experience points to multiple causative factors. Inability to identify or measure the critical one(s) is inadequate reason not to initiate appropriate medical, industrial hygiene and operational controls to minimize risk.

This overview of some of the factors involved in carcinogenic action on the skin or in the lung following exposure to PNAs highlights the importance of the experimental animal

Table 3. — Mixed SO_2/B(a)P Exposures of Rats — (1).

Type	Irritant 6 HR/D	Pattern 5 D/WK Ca - IRR 1 HR/D	Exposure, Days I	CT
A				
A + CT		10 mg/m³ B(a)P + 3.5 ppm SO_2		494
I	10 ppm SO_2		534	
I + CT	10 ppm SO_2	10 mg/m³ B(a)P + 3.5 ppm SO_2	534	494

as an integrator of chemical exposures. In terms of skin painting studies, unpublished work from Exxon Corporation suggests that the mouse is indifferent to the specific PNAs present in mixtures, but rather sums the total effect and responds by producing (or not producing) skin growths. This is best illustrated by the data on three industrial oils. PNA analyses for pyrene, B(a) A and B(a) P were made on each oil as well as the percent carbon in any aromatic ring. Which oil is carcinogenic?

Oil	A	B	C
B(a)A, ppm	8.6	18.3	8.7
B(a)A, ppm	6.6	7.9	2.7
B(a)P, ppm	4.5	1.2	0.2
% CA	15.4	15.2	12.3
Activity (cancer)	+	—	+

The analytical chemist is now able to identify with some ease and precision up to 20 or so individual PNAs in petroleum hydrocarbon fractions at the ppm level. Diligent, although not computerized, efforts to correlate the concentration of any one of these with carcinogenic activity is futile at such low levels. Increase the concentration to the order of fractions of a percent such as Wallcave, et al[13] found in coal tar pitch and the distinctions no longer matter.

A review of the toxicity of PPOM would not be complete without some mention of the non-tumor diseases associated with occupational or other exposures to PPOM. A small portion of the NAS PPOM document7 deals with this subject and the comments which follow as well as the summary given below have been drawn from that source.

Other occupational effects of PPOM: (1) Chronic bronchitis; (2) Nonallergic dermatitis; (3) Allergic contact dermatitis; (4) Cutaneous photosensitization; (5) Pilosebaceous reactions.

- Chronic bronchitis. A series of observations have linked occupational exposures to PPOM and the increased incidence of this disease. Gas company workers in England with very high PPOM exposures had much higher incidence of chronic bronchitis than the general population. (Animal studies have shown B(a) P to be of low irritancy except at very high doses.)
- Nonallergic dermatitis. Those materials containing PNAs which produce skin cancer are also reported to be associated

Table 4. — Mixed SO_2/B(a)P Exposures of Rats — (2).

Type	No. Animals	Adv. Sq. Metaplasia	Sq. Cell Ca
A	3	0/3	0/3
A + CT	21	1/21	2/21
I	3	0/3	0/3
I + CT	21	2/21	5/21

From Laskin, 1970

with contact dermatitis. These include coal tar, pitch, shale oil, high-boiling petroleum oils, cutting oils, etc. Animal studies have shown B(a)P and DMB(a)A are primary skin irritants at low concentrations.

- Allergic contact dermatitis. Although apparently easily induced to guinea pigs, allergic contact dermatitis is only rarely reported in man from contact with PNAs. These have largely come about from use of therapeutic coal tar preparations.
- Cutaneous photosensitization. Exposure to PPOM in the presence of solar or other UV sources can produce phototoxic and photoallergic reactions. Components of pitch, coal tar and creosote to which roadbuilders, roofers, gas workers, coke oven workers, etc. may be exposed have produced phototoxic responses.
- Pilosebaceous reactions. Some oils containing PNAs have been associated with follicular and sebaceous gland changes in workers. This commonly takes the form of oil acne. The extent to which PNAs contribute as compared with other components of the oil is unknown.

A brief review of the toxicity of PPOM has been presented. Evidence from historical, epidemiological, animal experiments and analytical studies has been examined. It is hoped that simplistic explanations of complex phenomena will be avoided.

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