Fifty years of benzo(*a*)pyrene

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It is fifty years since the publication of the report on the isolation, from coal tar, and identification of the potent chemical carcinogen benzo(a)pyrene, the culmination of over 10 years of research instigated and directed by E.L. Kennaway. The events leading to that discovery are of interest in themselves. Subsequent progress in unravelling the metabolic fate of polycyclic aromatic hydrocarbons has contributed to our understanding of the mechanism of chemical carcinogenesis.

In the nineteenth century, high incidences of skin cancer were reported among workers in the paraffin refining[1], shale oil[2] and coal tar industries[3]. Early attempts to produce cancer in experimental animals with the raw materials of these industries were unsuccessful and it was not until 1915 that the pathologist Yamagiwa and his assistant Ichikawa, at the Imperial University of Tokyo, succeeded in inducing tumours by repeatedly painting the ears of rabbits with coal tar[4]. Soon afterwards Tsutsui[5] obtained malignant skin tumours in mice by painting them with coal tar. In both cases application of the tar every 2–3 days for several months was required.

E.L. Kennaway joined the Research Institute of the Cancer Hospital (Free) (subsequently the Chester Beatty Research Institute, now the Institute of Cancer Research) in London in 1922 and began his attempts to characterize the carcinogen in coal tar. All that was known then was that the carcinogenic factor was concentrated in the high-boiling fractions and was free of arsenic, nitrogen and sulphur, as had been shown by Bloch and Dreyfuss[6] in Zurich in 1921. Kennaway, with his assistant F. Goulden, attempted to make tars that were carcinogenic when painted on mouse skin, by heating a variety of materials to high temperature under hydrogen. Positive results were obtained from experiments with isoprene, acetylene, cholesterol, yeast, human hair, muscle and skin[7]. He knew from the classical paper of Berthelot[8] that acetylene condenses to polycyclic aromatic compounds in such conditions and he had noted from the literature that carcinogenic coal tars contained more aromatic compounds and less paraffins than non-carcinogenic ones[9]. He concluded, therefore, that the carcinogenic agent was some complex polycyclic aromatic hydrocarbon (PAH). He was also able to obtain carcinogenic mixtures by treating tetralin with aluminium chloride at 30–40°C, a process that Schroeter[10] had shown to yield complex aromatic compounds.

In 1924, I.Hieger joined Kennaway and collaborated on studying the Schroeter reaction. They were joined in 1926 by the physicist W.V. Mayneord who began to study the intense fluorescence noted in the Schroeter fractions. Mayneord made the important observation that the same distinct bands were present in the fluorescence spectra of both the carcinogenic Schroeter fractions and Kennaway's synthetic tars, but attempts to match the fluorescence spectrum with any of the known hydrocarbons in coal tar were unsuccessful.

In 1928, having obtained some samples of PAHs from J.W. Cook, an organic chemist at Sir John Cass College (now the City of London Polytechnic), Hieger and Mayneord found that the fluorescence spectrum of one of them, benz(*a*)anthracene (Fig.1), was very similar to those of the carcinogenic tars, although shifted to longer wavelengths[11], suggesting that the carcinogen contained the benz(*a*)anthracene nucleus with some additional substituents. Kennaway and Goulden in 1929 then made dibenz(*a*,*h*)anthracene, the synthesis of which had been published by Clar[12] in Dresden, and its 3-methyl derivative, as described by Fieser and Dietz[13] from Bryn Mawr, Pennsylvania. The fluorescence spectra of the two hydrocarbons showed the same characteristic bands as benz(*a*)anthracene and the tars, this time at intermediate wavelengths. When, in 1930, they were tested by painting on the skin of mice, the compounds were found to produce tumours[14]. This was the first demonstration of the carcinogenic activity of pure chemical compounds.

Cook had joined Kennaway's group in 1929 to synthesize PAHs. In a year he had made 60 new compounds and the group had 146 different mouse skin-painting experiments in progress[15]. Early in 1930, work was begun on the isolation of the coal tar carcinogen. Two tons of pitch were distilled at the Becton works of the Gas Light and Coke Company, and the distillate extracted with alcohol. Hieger then successively purified the waxy extract by fractional distillation, differential extraction and crystallization. Fractions were analysed for carcinogenic activity on mouse skin and for their fluorescence spectra; the latter test was "the single thread that led all through the labyrinth"[15] as it greatly simplified the task of identifying likely carcinogenic fractions. In the autumn of 1931 about 7 g of a yellow crystalline material of melting point 116°C had been isolated that was highly carcinogenic and exhibited the correct fluorescence.

C.L. Hewett then joined the group and purified another batch of this material further, obtaining crystals which melted at 160°C, from which Cook isolated two pure products (melting points 176°Cand 187°C) and found them to be isomeric with the pentacyclic aromatic hydrocarbon, perylene ($C_{20}H_{12}$). Cook and Hewett synthesized for comparison the then unknown compounds benzo(*a*)pyrene (BP) (melting point 177°C) and benzo(e)pyrene (melting point 187°C) and found them to be identical with the major and minor components, respectively, of the mixed crystals. Moreover, both the synthetic and the isolated samples of BP were highly carcinogenic. The results of these experiments were published in April 1933 by Cook, Hewett and Hieger[16], and although Kennaway was not an author of this paper, it is clear that the initiative behind the work was entirely his, despite his having suffered from the debilitating symptoms of Parkinson's disease since 1929 (ref.17).

Kennaway's contribution and that of Mayneord were acknowledged by the award in 1939 of the first Anna Fuller Memorial Prize jointly to Cook, Hewett, Hieger, Kennaway and Mayneord, "in recognition of their notable accomplishments in the fields of cancer research, specifically for the isolation and synthesis of cancer-producing hydrocarbons from

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coal tar, their identification by fluorescence spectroscopy, and for the study of the biological effects of these substances".

Structure and activity

In the decade after the isolation of BP, several hundred PAHs were synthesized and tested for carcinogenicity in mice by topical application or by subcutaneous injection. The work of Kennaway's group during this period is summarized in six papers[18–23]. While benz(*a*)anthracene itself had only very weak activity, substitution by methyl groups at some positions produced potent carcinogens, a phenomenon for which there is still no satisfactory explanation. Thus, Bachmann (University of Michigan) synthesized 7,12-dimethylbenz(*a*)anthracene and 7,8,12-trimethylbenz(*a*)anthracene[24]; both were highly active in inducing tumours in mouse skin[25] and have since been used widely for the induction of mammary tumours in rats using a single oral dose[26]. Another potent carcinogen, 3-methylcholanthrene, was obtained by a series of reactions from a bile acid, deoxycholic acid[20,27]; this aroused interest in the possible endogenous formation of carcinogens of this class and a still unsubstantiated explanation for the occurrence of 'spontaneous' tumours.

The fervour for investigating the properties of PAHs even led Cottini and Mazzone[28] to paint the skin of human subjects with BP. The justification for this dubious experiment was the observation made by Haddow[29] in 1935 that injections of BP into experimental animals caused a decrease in the growth rate or an actual regression of transplanted tumours. Accordingly, 26 patients with various skin complaints were given daily treatments of BP for up to 4 months. BP caused pigmentation and veruccae in normal skin, which regressed after cessation of treatment, but it was concluded that BP would be carcinogenic if applied to human skin for more protracted periods. There was little therapeutic effect and in some cases the symptoms were aggravated. It is unlikely that such a trial would be sanctioned now.

Several attempts were made to correlate chemical structure with biological activity.

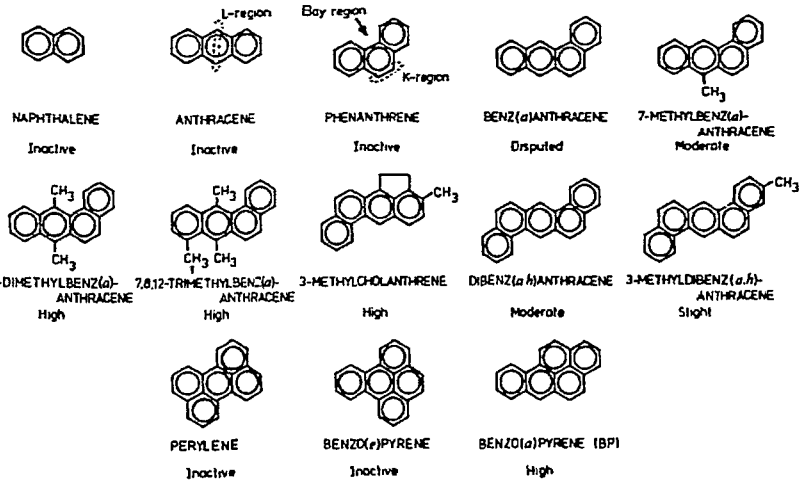

Fig. 1 Structural formulae and carcinogenic activity of PAHs mentioned in the text. Most of the compounds were tested in mice by subcutaneous injection, giving rise to sarcomas, and by topical application to the skin, giving rise to papillomas and epitheliomas. Classification of activity is that of Dipple[139] and is based on the percentage of treated animals that developed tumours: up to 33%, slight; 33–66%, moderate; >66%, high. Although inactive as complete carcinogens, phenanthrene, benz(*a*)anthracene and benzo(*e*)pyrene have tumour-initiating activity[140].

It was noted early on that most carcinogenic PAHs contain the angular three-ringed phenanthrene unit. The bond equivalent to the 9,10 bond in phenanthrene, called the K-region (Fig. 1) by Pullman[30], was identified as possessing greater "double-bond character" and chemical reactivity than other parts of such molecules[31]. Schmidt[32] proposed an early qualitative model to explain the significance of this region, that PAH structures contained units of special stability and that, in general, the K-region could not be included in any such unit, but this theory took no account of the delocalized π-electrons which characterize aromatic systems. It was Svartholm[33] in 1941 who first used quantum mechanical methods to infer the electronic properties of the molecules. The French theoretical chemists A. and B. Pullman and R. and P. Daudel, developed Svartholm's model and made it quantitative (reviewed by Coulson[34] and the Pullmans[35]). Although the calculations appeared at one stage to correlate carcinogenic activity with high electron density at the K-region, as anomalies emerged it became necessary to incorporate the concept of an unreactive L-region (equivalent to the meso 9- and 10-positions of anthracene, Fig. 1) which, in combination with a reactive K-region, would result in carcinogenic activity[35]. But as time went on, more and more compounds were tested that did not display their predicted carcinogenicity and the theory became untenable. It is now clear that it was based on the false premise that the parent PAHs themselves were biologically active and that their metabolism was a purely detoxifying process.

As early as 1877, it had been found that the urine of naphthalene-fed animals liberated naphthalene on boiling with acid[36]. By the mid-1930s several metabolites had been identified as specific derivatives of PAHs[37–39]. Further studies revealed that the main metabolites were *trans*-dihydrodiols and phenols, their glucuronic acid and sulphuric acid conjugates, and mercapturic acids (later shown to be derived enzymatically from glutathione conjugates); metabolism was found to affect many parts of the hydrocarbon ring structures and not just the chemically reactive K-region. In 1950, Boyland[40] (of the Chester Beatty Research Institute) proposed that all the metabolites could theoretically be formed from epoxides and that such intermediates might be responsible for the biological activity of the hydrocarbons. In the absence of direct evidence for the formation of hydrocarbon epoxides, however, Boyland and others continued to subscribe to the theory that carcinogenesis by PAHs was due to their physical intercalation into DNA[41], an idea that persisted at least until 1968[42], partly because it was almost impossible to either prove or disprove it. But this mechanism could not account for the carcinogenicity of the many other classes of chemical car-

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cinogens that had then been discovered[43] and which lacked the properties characteristic of intercalating agents.

It was at about this time that the Millers[44,45] proposed what has become a central tenet of present thinking on the mechanism of cancer induction by chemicals: that chemical carcinogens are, or are converted by metabolism into, electrophilic reactants that exert their biological effects by covalent interaction with cellular macromolecules, the critical target most probably being DNA. The Millers had shown that aromatic amines were activated via *N*-hydroxy metabolites (proximate carcinogens) to reactive esters (ultimate carcinogens). A proximate carcinogen might therefore be expected, when metabolized, to exhibit biological activity greater than that of its parent compound, and an ultimate carcinogen to be an electrophile and biologically active as such.

Covalent interactions

In the case of BP (and of PAHs in general), it was some time before the link between metabolism, covalent binding and biological activity was firmly established and the ultimate carcinogen identified.

In 1951, E.C. Miller[46] (University of Wisconsin) reported that BP, detected by its intense fluorescence, became covalently bound to protein in the skin of mice treated with the hydrocarbon. The observation followed on from her earlier work with J.A. Miller[47] in which they demonstrated the persistent binding of carcinogenic azo dyes to rat liver protein *in vivo*. In 1961, Heidelberger and Davenport[48] (University of Wisconsin) demonstrated the covalent binding of dibenz(*a*,*h*)anthracene to DNA in mouse skin and in 1964 Brookes and Lawley[49] at the Chester Beatty Research Institute demonstrated a correlation between the carcinogenic potency of six hydrocarbons and the extent to which they became covalently bound in mouse skin to DNA, but not to RNA or protein. That provided important evidence to support the growing conviction that DNA is the critical target for carcinogenesis.

Metabolism studies had progressed, meanwhile, from the use of whole animals to using hepatic microsomal fractions, rich in the mixed-function monooxygenases that metabolize PAHs and other xenobiotics[50], and Conney *et al.*[51] had shown that treatment of rats with PAHs markedly increases the levels of the enzymes that metabolize them. It was clear by now that the chemical reactivity of the PAHs themselves could not account for the covalent binding observed in animal tissues, but it was not until the late 1960s that direct evidence of the importance of metabolic activation was obtained when Grover and Sims[52] (Chester Beatty Research Institute) and Gelboin[53] (US National Institutes of Health) showed that BP and other PAHs became bound to DNA *in vitro* only in the presence of active metabolizing systems, in these cases provided by the inclusion of induced rat liver microsomal fractions in the incubation mixture.

Although the metabolic activation of PAHs to DNA-binding products was firmly established, the biological significance of this covalent binding was not. What probably finally convinced the sceptics was the discovery of metabolites having biological activity and the demonstration, in 1973, that many chemical carcinogens are mutagenic for bacteria in the presence of the same metabolizing systems that can catalyse covalent binding to cellular macromolecules. B.N. Ames at Berkeley had developed several histidine-requiring (His^-) strains of *Salmonella typhimurium* which, when treated with a series of chemical carcinogens, including BP and other PAHs, in the presence of rat or human liver homogenates, underwent back-mutation to a His^+ wild type[54]: this is the basis of the Ames test, now widely used to screen chemicals for potential carcinogenic activity. The evident link between metabolism of PAHs and biological activity thus led to the concentration of efforts to identify the metabolites responsible.

K-region epoxides

Although the formation of epoxide intermediates had been proposed in 1950[40] and the results of the metabolism studies of Boyland, Sims and others were wholly consistent with this hypothesis[55], conclusive evidence of epoxide formation was not obtained until 1968 when Jerina *et al.*[56] (NIH) detected the formation of naphthalene 1,2-oxide from naphthalene in a microsomal system by using a radiotracer trapping technique. This was followed by reports[57–60] of the formation of epoxides from carcinogenic PAHs, including BP. All the hydrocarbons examined formed epoxides at the K-region of the molecules which, in view of the now obsolete electronic structure correlations[35], naturally focused attention on the possibility that K-region epoxides are the ultimately reactive forms *in vivo*.

Syntheses of K-region epoxides had first been achieved in 1964 by Newman and Blum[61] at the Ohio State University. Epoxides were found to react with nucleic acids and protein in the absence of any metabolizing systems[62], to cause malignant transformation of rodent cells in culture[63] and to be mutagens for mammalian cells[64] and bacteria[65]. These were all properties to be expected of candidate ultimate carcinogens, but tests for carcinogenicity revealed that the K-region epoxides were weaker carcinogens than their parent hydrocarbons[66–68]. Subsequently, Baird *et al.* found that the chromatographic profiles of hydrocarbon–nucleoside adducts in hydrolysates of DNA from cells treated with PAHs differed from those of hydrolysates of DNA that had been reacted *in vitro* with the K-region epoxide of the hydrocarbon, first for 7-methylbenz(*a*)anthracene[69] and then for BP[70]. Thus, the major metabolites responsible for the covalent modification of DNA and, by inference, for the biological activities of the parent PAHs, were not K-region epoxides. This path of research appeared to have reached a dead end.

Activation via diol-epoxides

Although K-region epoxides seemed not to be responsible for the covalent binding of PAHs to DNA, the involvement of other, as yet unidentified, epoxides was not ruled out. As oxidative metabolism occurs at many sites in PAH, the transient formation of non-K-region epoxides was indeed likely. However, Baird's adduct profiles[69,70] did not suggest a simple non-K-region epoxide because the hydrocarbon–nucleoside adducts present in digests of DNA from treated cells were more polar than would be expected for those derived from the reaction of a simple epoxide with DNA.

The paper which gave the vital clue to the problem appeared in 1973 from Crocker's laboratory[71] in San Francisco. When BP or various metabolities were incubated with DNA in the presence of hamster liver microsomal fractions, one metabolite, *trans*-BP-7,8-dihydrodiol (Fig.2), became covalently bound to DNA to a 10-fold greater extent than BP, a clear indication that this metabolite is an intermediate in the pathway leading to binding of BP to DNA.

At about the same time, Booth *et al.*[72] showed that non-K-region dihydrodiols of benz(*a*)anthracene and 7,12-dimethylbenz(*a*)anthracene undergo further metabolism to more polar products, possibly via epoxide intermediates. The oxidation of a hydrocarbon to a non-K-region dihydrodiol can create in the substituted ring an olefinic double bond that might be expected to be a prime site for further metabolism; indeed, Booth and Sims[73] obtained a vicinal diol-epoxide, the 8,9-diol-10,11-epoxide of benz(*a*)anthracene, by incubating the *trans*-8,9-dihydrodiol with rat liver microsomal fractions. Sims and his group then prepared the 7,8-diol-9,10-epoxide of BP and showed that the chromatographic profiles of DNA digests obtained from cells treated with BP matched

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those of digests of DNA reacted with the diol-epoxide. This result, which suggested that *trans*-BP-7,8 dihydrodiol was the proximate carcinogen, and that a 7,8-diol-9,10-epoxide was the ultimate carcinogen of BP, was presented by Sims[74] at the XIth International Cancer Congress in 1974, and published in *Nature* in the same year[75].

The next five years saw an explosion of activity in many laboratories aimed at confirming this pathway and elucidating its finer details (Fig.2). The absolute stereochemistry of each active intermediate has been determined and biological activity confirmed in carcinogenicity and mutagenicity (both bacterial and mammalian) tests. Physicochemical studies of the interaction of BP metabolites with DNA *in vivo* and *in vitro* have provided further supportive evidence.

Spectrophotofluorimetry of DNA isolated from tissues or cells treated with BP has shown that the covalently bound BP retains an intact pyrene aromatic nucleic and has thus undergone metabolism in the 7,8,9,10-ring[76,77]. When radiolabelled samples of *trans*-BP-7,8- and *trans*-BP-9,10-dihydrodiol were applied to mouse skin, only the former gave rise to hydrocarbon–nucleoside adducts, and these were chromatographically indistinguishable from adducts obtained from mice treated with BP[78]. *Trans*-BP-7,8-dihydrodiol is more carcinogenic than BP in mouse skin[79–81], and more potent in inducing malignant transformation in cultured mammalian cells[82,83] and mutations in *S. typhimurium* in the presence of a microsomal activating system[84]. The stereoselectivity of the activation pathway is demonstrated by the fact that BP is metabolically converted preferentially to (–)-*trans*-BP,7,8-dihydrodiol[85,86] via (+)-BP-7,8-oxide[87], each of which is more active than its enantiomer[87–89].

Trans-BP-7,8-dihydrodiol can give rise to two diastereoisomeric vicinal diol-epoxides which differ in the displacement of the epoxide function from the plane of the molecule to the same side as the 7-hydroxyl group (the *syn* configuration) or to the opposite side (the *anti* configuration, Fig.2). The chemical reactivity of

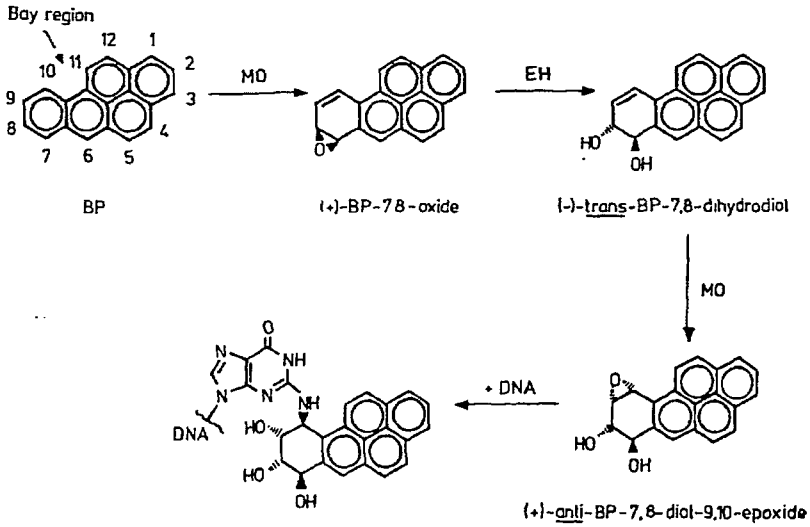

Fig.2 Major pathway of metabolic activation of benzo(*a*)pyrene. The biotransformations are catalysed by: MO, monooxygenase; and EH, epoxide hydrolase. The structure of the major BP–guanine adduct in DNA is also shown.

these compounds stems from the relative ease with which the strained three-membered epoxy ring will open to generate an electrophilic carbonium ion, and the prediction[90] that a *syn*-diol-epoxide would form such a carbonium ion more easily than would an *anti*-diol-epoxide because of anchimeric assistance from the favourably positioned 7-hydroxyl group has been confirmed experimentally[91].

Mutagenicity studies on racemic mixtures of the diol-epoxides indicate that the *syn*-isomers are the more potent mutagens to strains of *S. typhimurium*[92,93], while the *anti*-isomers are the more active in the mammalian V79 cell system[92,94–96]. This difference is probably due to the much shorter half life of the *syn*-isomers in aqueous solution[97], and to their consequent lower concentrations in the mammalian cell nucleus.

There are also significant differences in the mutagenicities and carcinogenicities of the enantiomers of the *anti*- and *syn*-diol-epoxides. Thus, the (+)-*anti*-isomer, the predominant isomer formed metabolically[85], and the (–)-*syn*-isomer are more mutagenic than their respective enantiomers[98]. Only the (+)-*anti*-diol-epoxide produced significantly more pulmonary tumours than BP in newborn mice when administered intraperitoneally[99]. Perhaps because of their high chemical reactivity, all the isomers show less activity than BP when applied topically to mouse skin, but again the (+)-*anti*-isomer is the most active[100,101].

Physicochemical studies on the interaction of the BP diol-epoxides with DNA and polyribonucleotides have established that they react principally with guanine residues[102,103], the C-10 position of BP becoming linked to the exocyclic 2-amino group of the base[104–108] (Fig.2). Adducts formed in tissues or cells treated with BP are derived predominantly from the (+)-*anti*-diol-epoxide, with minor involvement of the (+)-*syn*-diol-epoxide in some cases[104,109–112].

The exact nature of the major BP–DNA interaction and how it may cause a mutagenic event, or initiate a carcinogenic one, is still a matter for speculation. It is even possible that a minor product of the reaction between BP diol-epoxides and DNA[102,112–116] is responsible — assuming that DNA is the critical target. Electrical linear dichroism studies[117] suggest that the angle between the long axis of DNA and the plane of the bound diol-epoxide is 35° and that the bound carcinogen therefore lies in the minor groove of DNA. Theoretical studies suggest that such a conformation would cause minimal distortion of the DNA double helix[118].

Another model proposes that the guanine–deoxyribose bond is rotated through 180°, placing the BP moiety in the major groove, again with little distortion of the DNA structure[119]. Inversion of the guanine base could conceivably lead to a transversion mutation by mispairing with

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another guanine. However, it should be remembered that BP diol-epoxides are also frameshift mutagens and that their modification of superhelical simian virus 40 (SV40) DNA results in conformational changes similar to those seen with intercalating agents[120], although the expected binding angle for intercalation (close to 90°) has not been observed. It is possible that several binding conformations occur but only some initiate events that result in a permanently altered phenotype.

Predictions of the sites of metabolic activation of other carcinogenic PAHs have been made by Jerina and colleagues[121,122]. The C-10 position of BP, at which carbonium ion formation occurs, can be envisaged as being adjacent to the 'bay-region' of the molecule, that is, the angle formed between benzo rings fused in a nonlinear arrangement. The simplest molecule with a 'bay region' is phenanthrene, in which it lies between the 4- and 5-positions (Fig.1); in BP it is bordered by the 10- and 11-positions (Fig.2). Quantum mechanical calculations predict that a carbonium ion is more readily formed at benzylic positions of saturated benzo rings that are adjacent to 'bay regions' than at non-bay regions for a given hydrocarbon. Since, as we have seen, ring-saturation and carbonium ion formation are both achieved by diol-epoxide formation, the theory predicts greater reactivity for 'bay region' diol-epoxides than non-bay region diol-epoxides, and this has been found to be the case[91]. The theory does not, however, predict the carcinogenic potency of a hydrocarbon, which will depend both on the reactivity of the ultimate carcinogen and how much of it is formed metabolically. Nevertheless, 'bay region' diol-epoxides do seem to have an important role in the metabolic activation of the 20 or more PAHs whose metabolites have been examined for biological activity and DNA binding capability so far[123, 124].

The metabolic activation of chemical carcinogens can be viewed as an error in the process by which organisms detoxify and excrete foreign compounds. The enzymes responsible efficiently metabolize most compounds to less harmful and more readily excretable derivatives even though the organism and its evolutionary precursors may never have been exposed to them. This very versatility occasionally results in the production of an electrophilic metabolite that is not readily detoxified by further metabolism and that may therefore be able to express its genotoxic potential. Thus, what probably distinguishes the BP-7,8-diol-9,10-epoxides from other electrophilic metabolites of BP, such as BP-4,5-oxide, is that the former are poor substrates for epoxide hydrolase and thus are not as readily detoxified[125]. Other mechanisms of detoxification, such as conjugation with glutathione[126] and non-enzymatic hydrolysis to tetrols[97,127], may still have some influence on the balance between activation and deactivation.

The risk to humans

The nature of research is such that BP will continue to be an important research tool for many disciplines. The vast amount of data that has accumulated on the cellular processing of BP[128-130] makes it a valuable standard with which new systems can be characterized and evaluated. Much current research simply uses BP in this capacity: tissues and cells can be rapidly assayed for their ability to metabolize BP; originally by means of the strong fluorescence of one metabolite, 3-hydroxybenzo(*a*)pyrene[131], more recently by the use of sensitive HPLC techniques to separate and assay complex mixtures of metabolites[132,133].

Equally, however, BP is deserving of study because PAHs are now recognized as major environmental pollutants[134]. They are released into the atmosphere during the combustion of fossil fuels and vegetation and are present in tobacco smoke. Exposure to PAHs is virtually unavoidable, and they are strongly suspected of being a causative factor in several human cancers of epithelial origin (for example, skin, lung, bronchus and colon). The metabolism of PAHs, especially BP, in cell and organ cultures of many human tissues[124, 135] gives no evidence to suggest that human tissues would not be susceptible to PAH carcinogenesis: metabolism is qualitatively similar in animal tissues known to be susceptible to the carcinogens and in the corresponding human tissues, although there are significant quantitative differences between human tissue samples from different people. Whether or not such differences reflect differences in individual human susceptibility to cancer is not yet clear. Some animal studies do not support this concept, however, because inbred strains of mice with different susceptibilities to PAH carcinogenesis nevertheless metabolize PAHs to DNA-binding products to similar extents[136]. Estimating the risk from human exposure to these compounds will probably require more direct methods than tissue culture studies. The production of antibodies to BP-diol-epoxide–DNA adducts[137] which has made possible the assay of human biopsy material for prior exposure to BP[138] may — together with prospective epidemiological studies — be a step towards determining the hazard that PAHs present to humans.

Addendum: PAHs have been investigated to a limited extent in the treatment of human cancer. Beginning in 1934, Bauer[141,142] treated 22 patients with advanced skin cancer with BP and the tumours regressed in seven cases. Also Huggins and McCarthy[143] treated six cases of metastatic breast cancer with intramuscular injections of 3-methylcholanthrene and observed inhibition of malignancy in five of the patients. □

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More Drug Addicts in Britain But Fewer Cigarette Smokers

LONDON, July 6 (AP)—There are more heroin addicts but fewer cigarette smokers in Britain these days, according to two new government reports.

The Home Office, in a report issued today, said there were about 2,800 new registered addicts of heroin, cocaine and other hard drugs in 1982, compared with the 1981 increase of 2,250.

The Advisory Council on the Misuse of Drugs has estimated there are about 9,000 registered addicts and a total of 40,000 serious drug abusers.

On Tuesday, a government report said cigarette smoking in Britain has fallen sharply in the past two years, with the number of smokers down from 42 percent in 1980 to 38 percent last year—a drop of more than 1 million in this nation of 56 million persons.

THE NEW YORK TIMES, THURSDAY, JULY 7, 1983

Nonsmoker Protection

To the Editor:

Norman Adler, whose letter ["Airliners Devoid of Unpolluted Air"] you published on July 1, as well as your other readers may be interested to know that the U.S. Court of Appeals has just ordered the Civil Aeronautics Board to protect nonsmoking passengers from drifting tobacco smoke, and to promulgate a rule providing that "carriers shall ensure that nonsmoking passengers are not unreasonably burdened by breathing smoke."

This order came in response to a motion filed by Action on Smoking and Health (ASH), which cited numerous examples of nonsmokers suffering serious medical and other problems as a result of drifting tobacco smoke.

Airlines may be fined up to $1,000 for every violation of the smoking regulations, and ASH has successfully brought action regarding many such violations or obtained financial reimbursement for nonsmokers. (ASH also distributes a free wallet-sized card telling nonsmoking airline passengers about their rights and how to enforce them.)

JOHN F. BANZHAF
Executive Director
Action on Smoking and Health
Washington, July 1, 1983

San Francisco Examiner
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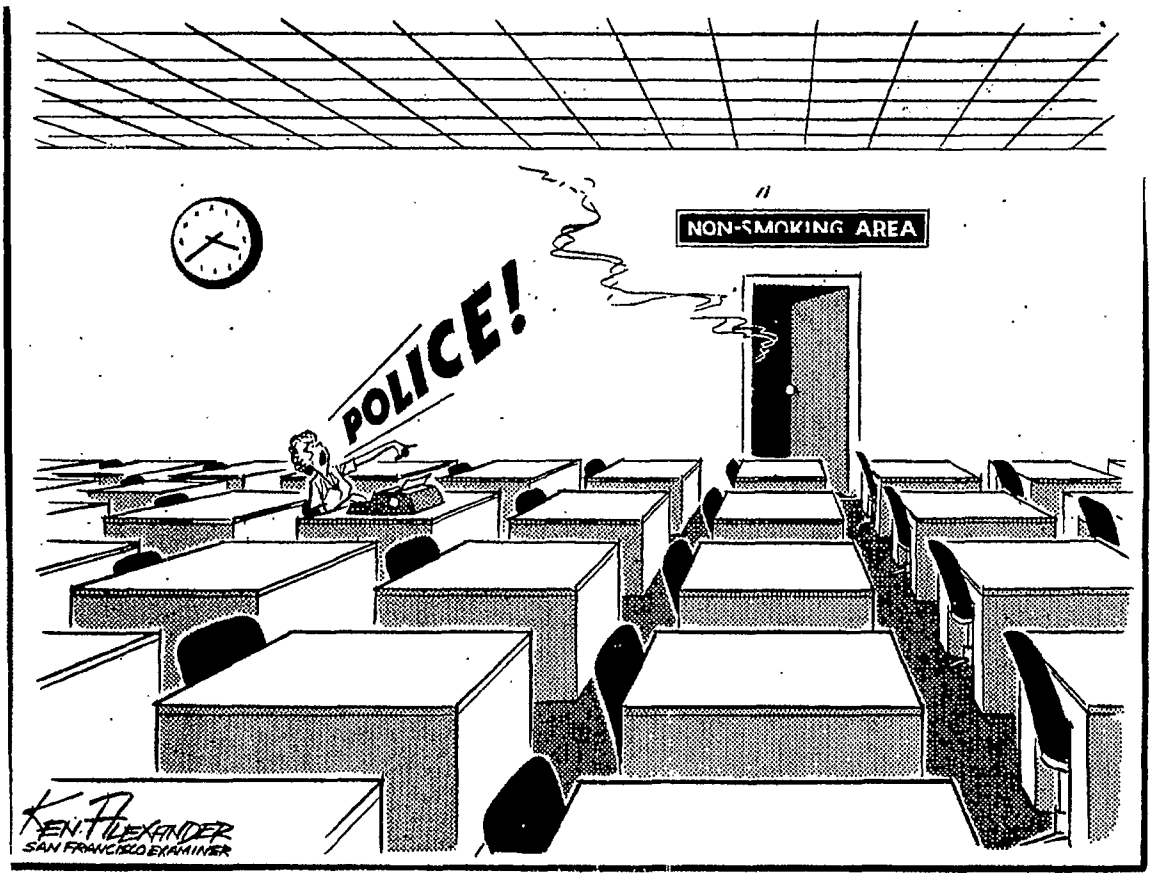

JUL 07 1983

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Fire-safe cigarettes

where the issue stands

By Lisanne Renner 34113
OF THE SENTINEL STAFF

ORLANDO, FLA.
SENTINEL
D. 185,722 S. 238,675

JUN 1 1983
BURRELLE'S

Smoldering cigarettes snuff out more than a thousand lives in the United States each year, and about 40 percent of the victims don't even smoke.

Two tinderboxes for fires sparked by cigarettes are hotels and nursing homes, both of which are plentiful in Florida. But the state has not followed 11 others in considering legislation that would require self-extinguishing cigarettes.

Here's a chain of events typical of those that started 1,685 fires, killed 24 people and caused $3.4 million in property damage in Florida last year: Someone who may be sleepy, forgetful, drunk or drugged leaves a burning cigarette unattended. Hot ashes drop into upholstered furniture and smolder for hours before flames spread late at night, when people are sleeping. Flames and toxic fumes catch people unaware.

In southwest Orange County last month, five residents escaped as fire roared through their home around dawn, causing $25,000 in damage. Fire investigators — "archeologists of modern man's tragedies," as Orange County Fire Department investigator Robert Fischer calls them — found what started it: a pack of Kool cigarettes, matches and three cigarette butts all dumped in a paper bag.

Although cigarettes and other smoking materials start fewer than 10 percent of fires nationwide, they account for more than a third of the fire-related deaths, according to the U.S. Fire Administration.

Self-extinguishing cigarettes are the best solution, say consumer advocates, doctors, fire officials and some lawmakers. The cigarette industry disagrees.

Since 1979, two Democratic lawmakers unsuccessfully have pushed the Cigarette Safety Act, which would empower the federal Consumer Product Safety Commission to develop standards for shortening the amount of time that cigarettes burn. Rep. Joe Moakley of Massachusetts introduced the bill in the House and Sen. Alan Cranston, a presidential candidate from California, introduced it in the Senate. The bill is being considered in Congress again this year.

Fearing that the cigarette industry will continue to suppress the bill in Congress, the Burn Council in California also is pushing for state legislation. The issue, considered in 11 states so far, was killed in Virginia and Maryland — two major tobacco states — and Connecticut. Andrew McGuire, who is organizing the council's legislative efforts, says no legislation has been proposed in Florida because "I simply don't have a lot of contacts in Florida."

The federal government does not regulate cigarettes, though it taxes them and subsidizes tobacco crops. The decade-old Consumer Product Safety Commission had the power to regulate cigarettes only during its first year, before Congress amended the agency's powers. Now the commission wants that power back so it can study whether fire-safe cigarettes are practical.

The commission's chairwoman, Nancy Harvey Steorts, was in Orlando this week and said it's "hard to speculate" about whether the authority will be returned.

Even if Congress gives the commission authority to regulate cigarettes, the agency lacks the adequate staff and budget for the job.

Please see FIRE, F-4

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JUL 07 1983

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FIRE

From F-1

says Steorts. The agency's budget has been cut 25 percent and its staff has been reduced 28 percent in the past two years.

Because it can't regulate cigarettes, the safety commission — with an emphasis on voluntary compliance rather than regulation — has persuaded 94 percent of furniture makers to design fire-resistant upholstery, Steorts says.

Though the industry's Upholstered Furniture Action Council promotes showroom tags intended to inform consumers of fire-resistant features, the tags are confusing to read and "some stores cut them off," Steorts says. Most consumers remain unaware that they can compare fire-safety features when shopping for furniture.

All the fuss over self-extinguishing cigarettes is silly, says the Tobacco Institute, which represents the $23 billion industry that sold 640 billion cigarettes last year. "There is not a technologically feasible way to produce a cigarette that is fireproof and that the consumer would be willing to buy," says Tom Howard, assistant to the institute's president.

Though there have been no definitive government tests of cigarette burning rates, some cigarettes — such as More, Carlton and the specialty Sherman's — have a reputation for extinguishing themselves or for not setting furniture on fire while they burn.

The Tobacco Institute compares the United States with other industrialized countries, where fires are fewer although fire-resistant cigarettes are non-existent. There are ways to deal with fire safety without unfairly singling out the cigarette industry, says Howard.

But requiring safer cigarettes gets to the root of the problem, say advocates of the legislation. Carlton Currens, an aid to Rep. Moakley, says, "You're not going to reduce the fires really dramatically unless you go after the source of the problem, which is the cigarette."

ANGELA PETERSON/SENTINEL

Cigarettes were blamed for blaze that caused $25,000 damage to this house.

2.

Senate unit may back cigarette price change

By Chris Black
Globe Staff 2411B-LEG/S

In a move that sets the stage for a showdown with the House of Representatives, the Senate Ways and Means Committee is expected today to back a proposal to deregulate the price of cigarettes.

Gov. Michael S. Dukakis has proposed a 4-cent increase in the state cigarette tax and tied it to repeal of a 38-year-old law which establishes a minimum price for cigarettes. Dukakis said deregulation might increase competition enough to lower retail prices and offset most of the tax increase to consumers.

The pricing law requires a minimum 14-cent markup on the price of a package of cigarettes, and vendors who sell cigarettes below the minimum price of 84 cents stand to lose their licenses. Even though the minimum is lower than retail prices that currently range between 95 cents and $1.25 per pack, supporters of repeal believe it would stimulate competition nevertheless.

The House Ways and Means Committee eliminated repeal of the pricing law from the governor's package of tax increases and revenue-raising measures, arguing that fixed prices protect small retail stores. An attempt to restore the deregulation language on the House floor failed on a 92-56 vote last week.

When the Senate Ways and Means Committee meets to consider the House version of Dukakis' Revenue Enforcement and Protection (REAP) package today, however, administration officials and legislative aides say the repeal section, along with others eliminated by the House, will be put back in the bill.

Leading members of the Senate, including Ways and Means Chairman Chester G. Atkins (D-Concord) and Taxation Committee Chairman John W. Olver (D-Amherst), strongly support repeal of minimum pricing.

"Cigarettes are the only commodity on which we set and attempt to enforce any kind of minimum price. It's obviously price-fixing. It's obviously anticonsumer," said Olver.

Rep. Thomas F. Brownell (D-Quincy), who made the unsuccessful attempt to restore the repeal language in the House last week, said powerful interest groups, including the tobacco industry and owners of convenience store chains, opposed the measure.

"The franchises, the big-money interests and the manufacturers have a vested interest in protecting minimum pricing," he said. "It's good for them. They can't lose. They don't have to compete with the rest of the world. Why should they get special treatment?"

Supporters of the current law have argued that price competition on cigarettes would hurt small variety stores which depend upon cigarette sales.

Harold Garber of Garber Brothers in Boston, a cigarette wholesaler, said wholesalers support regulation because open pricing would hurt some of their customers. "Without regulation, everyone would be charging different prices and people in certain catgegories would be using [cigarettes] as loss leaders. That wouldn't be fair to the store that depends upon them for a living," he said. "Our customers depend on it for their livelihood." A loss leader is an item on which a store deliberately takes a loss in order to attract customers.

Garber referred other questions to William F. Coyne, lobbyist for the Tobacco Institute and the Massachusetts Candy and Tobacco Distributors Inc. Coyne did not return several calls.

"We have been victimized by the price structure," Brownell said. "It very effectively drives people to New Hampshire for cigarettes. New Hampshire is number one in the collection of cigarette tax revenues. I think that is because there is free competition there."

New Hampshire stopped enforcing its minimum-pricing laws in 1975 and repealed the laws in 1977, said New Hampshire Revenue Comr. Lloyd Price. He said elimination of the law had no effect on either the retail price of cigarettes or the number of retail outlets selling cigarettes.

Dukakis had attempted to repeal the minimum- pricing law in 1975, during his first administration, when he raised the cigarette tax by 5 cents to its current level of 21 cents a pack. The tobacco lobby was credited with killing that proposal at the time.

The Senate is also expected to restore to the revenue package a prohibition on the use of the ink stamp meters used by 72 of the state's 90 registered cigarette wholesalers to mark each package of cigarettes to indicate the tax has been paid. The change would require all wholesalers to mark cigarettes with decals, which Revenue Department officials say are a more effective guard against counterfeiting.

The Boston Globe
BOSTON, MASS.
D. 504,492 SUN. 740,720

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Washington Outlook

JULY 4, 1983/EDITED BY LEE WALCZAK

THE TEAMSTERS VETO A TRUCKING BILL

President Reagan has a reputation as an ardent believer in free-market policies, but as the election draws near, Reagan is about to take a strategic detour from his commitment to deregulation. Under heavy pressure from the Teamsters—one of the few major unions to endorse Reagan's candidacy in 1980—the Administration is about to back away from proposed legislation that seeks to end all remaining Interstate Commerce Commission regulation of trucking within a few years.

New Teamsters President Jackie Presser has made it clear that his No. 1 priority is restoration of economic regulation of the trucking industry. Says one insider: "The message has been passed to the White House that if a deregulation bill is sent to Congress, Reagan can forget about Teamsters support." The White House seems to be listening.

The controversy centers on a draft proposal that was initially approved by former Transportation Secretary Drew Lewis and that has been pushed by his successor, Elizabeth H. Dole. The bill would complete the reforms of the 1980 Motor Carrier Act, which gave truckers new flexibility to enter the business, set rates, and determine routes. "There is little justification for continuing many of the remaining transportation regulatory functions," says Dole, who predicted in May that the Transportation Dept. "will be proposing complete deregulation."

DOLE IS A SAVVY POLITICIAN, but she underestimated the furor that her "phase II" deregulation bill stirred up within the Teamsters. After two months of seemingly routine analysis, the legislation was suddenly yanked off the calendar at a June 8 Cabinet meeting by White House aides who got nervous about alienating the union's hierarchy. Says C. Boyden Gray, counsel for Vice-President George Bush's Task Force on Regulatory Relief: "They wanted to do some more checking on the politics of this thing."

Key opposition to the initiative was spearheaded by Labor Secretary Raymond J. Donovan, who keeps in close contact with Teamsters boss Presser. The Labor Secretary is said to have argued that total deregulation would further threaten the jobs of Teamsters members, who have been hit hard by the combination of the recession and deregulation. Teamsters officials believe that the proliferation of lower-cost, nonunion operators who have entered the trucking business since the 1980 deregulation law was passed has undermined the union's dominance. According to Teamsters spokesmen, 100,000 of the union's truckers have been laid off since the industry was opened to competition.

But Donovan alone could not have turned the tide. Industry observers suspect that the real power behind the shift was Michael K. Deaver, Reagan's Deputy Chief of Staff. As a public relations consultant, Deaver once represented California trucking interests. And he was instrumental in drafting the strategy that enabled Reagan to nail down Teamsters support in 1980.

Ever since that crucial endorsement, the White House has carefully courted the union. For example, the Administration appointed Nevada attorney Reese H. Taylor Jr., the Teamsters' hand-picked candidate, to head the ICC. As chairman, Taylor has consistently sought to slow the pace of deregulation.

WITH BLUE-COLLAR SUPPORT for Reagan eroded by the recession, the prospect of a Teamsters endorsement in 1984 has taken on growing significance within the Administration. No one on Reagan's staff believes that Presser can get his wish of "re-regulation," given how far Congress has moved to promote trucking industry competition in recent years. That leaves the White House with the delicate task of extricating itself from the Dole proposal while preserving the President's image as a free-market champion.

The White House could decide to ditch the Dole plan on the grounds that the ICC is doing an adequate job of deregulating trucking through administrative action. Such a move, however, would undercut Dole's credibility on Capitol Hill just as she is settling into her new job. A more graceful exit would be to submit a watered-down second-phase deregulation bill to Congress and to refrain from any serious lobbying for enactment. Either way, with the White House shifting into political overdrive in advance of next year's campaign, efforts to inject more competition into the trucking industry appear to be doomed for the foreseeable future. Says one Republican aide: "The Reagan people are going to bury this."

CAPITAL WRAPUP

PEOPLE

Washington attorney Katherine B. McGrath will be named director of the Securities & Exchange Commission's investment management division, the office that oversees mutual funds. McGrath was an SEC staffer for nine years before leaving in 1978. . . . Herbert Hetu, a former information official of the Central Intelligence Agency, is the leading candidate to succeed Henry E. Catto Jr. as Assistant Defense Secretary for public affairs. Hetu previously was an adviser to the Presidential commission studying deployment of the MX missile.

POLITICS

By the end of the year, North Carolina Governor James B. Hunt Jr., a popular Democrat, will declare his intention to challenge Republican Senator Jesse Helms in 1984. Arch-conservative Helms has been expecting the announcement. His Senate campaign committee has already raised $1.5 million for the upcoming battle. . . . The National Conservative Political Action Committee (NCPAC)—a group that received notoriety but few results with its 1982 negative advertising campaign to unseat Democratic liberals—will take a more traditional approach next year. Sensing few opportunities to defeat Senate Democrats, NCPAC officials may opt to spend up to $7 million on a campaign to support President Reagan's expected reelection bid.

WORKPLACE SAFETY

The Occupational Safety & Health Administration faces a crossfire over its plan to issue a controversial proposal to reduce exposure to asbestos. Under pressure from congressional committees and organized labor, OSHA Administrator Thorne G. Auchter says that a tough asbestos standard is a top priority. But industry opposition to stricter exposure rules is fierce. OSHA aides suspect that skeptical Office of Management & Budget officials may team up with industry opponents and try to kill the proposal.