ENVIRONMENTAL PROTECTION AGENCY

Chamblee Toxicology Laboratory
4770 Buford Highway
Chamblee, Georgia 30341
October 14, 1971

OCT 15 1971

PCB's

Dr. George Levinskas
Monsanto Company
800 N. Lingbergh Blvd.
St. Louis, Missouri
63166

Dear George:

Enclosed is a copy of the article on bladder cancer in the U.K. that I mentioned on the phone. Another article that discusses this problem is one by Case, R.A.M.: Tumours of the Urinary Tract as an Occupational Disease in Several Industries. Ann. Roy. Coll. Surg. Engl. 39:213-235, 1966.

Does Monsanto have a cytology screening program? If this is not the case it may be prudent to set up a cytology screening program where workers would submit about a 200 cc early morning urine specimen once a year. The freshly voided urine could be filtered immediately through a millipore filter, then stained by the "Pap" method and examined under the microscope, or it could be fixed in an equal amount of 50% ethanol and shipped to a laboratory and processed there. I do not think that collecting 24 hour urines would give any more information and would be a nuisance to collect.

For the sake of completeness I am also enclosing the summaries of two articles which I am sure you have seen. Both articles report some findings on Aroclor 1260 Lot AK-3.

Let me know if you need any Aroclor. We seem to have more than sufficient for our studies.

Sincerely yours,

Renate Kimbrough, MD

Renate D. Kimbrough, M.D.

enc: 3

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BLADDER TUMOURS IN THE ELECTRIC-CABLE INDUSTRY

JOAN M. DAVIES
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IN 1949 Case and Hosker investigated the incidence of tumours of the bladder in the rubber industry in England and Wales; this study was not sponsored by the industry, and was based largely on data from census reports, death certificates, and hospital records. The findings were communicated to the appropriate authorities and to the industry in 1949, but at that time the Rubber Manufacturing Employers' Association did not sanction publication (*Times* 1965). The results were finally published five years later (Case and Hosker 1954), and demonstrated an occupational risk among skilled rubber workers both of contracting tumour of the bladder and of dying from this disease; these findings were compatible with the hypothesis that a risk was introduced into the industry when a certain rubber-antioxidant came into use in 1928. The production of this widely used substance ceased in 1949 when the danger to those making and using it was recognised.

Case and Hosker regarded this as a preliminary study, and considered that a much more intensive survey of the rubber industry was necessary in order to ascertain whether the antioxidant in question was in fact responsible—and if so whether it was the sole agent—and to measure the risk and study its dynamics. Such a survey has never been made, and for information about the background to the disease we must turn to the survey of occupational bladder-tumours in chemical workers of Case et al. (1954), although we cannot be certain how closely the findings of this survey will apply in the context of a different industry. The survey was sponsored by the Association of British Chemical Manufacturers, and was concerned with the mortality and morbidity from bladder tumours in a group of 2466 dyestuff workers in England and Wales.

The results showed that by 1952, 1 in 10 of these men had already developed bladder tumours, and that in time the incidence was expected to reach 1 in 5. These tumours could be attributed to exposure to α-naphthylamine, β-naphthylamine, or benzidine; β-naphthylamine being the most potent carcinogen. These substances may readily enter into the body whether they are in the form of powder, liquid, or vapour, for they may be ingested, absorbed through the skin, or inhaled.

The risk to the workers increased with the amount of exposure, measured by either duration or degree of exposure in various operations with the substances. Thus at one end of the scale a small number of tumours developed among workers such as fitters and plumbers, who handled contaminated machinery or worked in contaminated atmospheres, and at the other end of the scale the disease attacked *every one* of a group of 15 workers engaged on distilling β-naphthylamine in one particular plant (Case, in the press).

The average "induction-time" between first exposure to the carcinogens and the development of the disease was 18 years; but some tumours appeared within 5 years, and some after 45 years. There was no evidence that this induction-time was shorter in those with severe exposure, or longer in those with comparatively slight exposure.

During the survey it was observed that tumours had occurred among chemical workers engaged in manufacturing the antioxidant mentioned, which contained 2·5% of free naphthylamine of which 0·25% was β-naphthylamine, and this was the observation which prompted the study of the rubber industry.

The function of antioxidants is to retard the perishing of the rubber in a finished article, and thus preserve its strength and elasticity. They are among the chemical agents added to raw rubber to form a rubber *mix*, which is then manipulated under heat to form a *compound*. Antioxidants are frequently used in powder form, and are usually added to the mix in the proportion of one or two parts per hundred. Subsequently the compound is *moulded* or *extruded* to the shape required, and subjected to heat (usually by steam) for the process of *vulcanisation*. If the antioxidant contains naphthylamines, they will contaminate the air of the room where any of these operations are carried out. They may be absorbed as powder or vapour not only by the workers actually handling the rubber, but by anyone in the room.

In 1948 the rubber industry purchased 1410 tons of antioxidants of all types. At that time the industry employed 77,000 persons in over 300 factories in England and Wales (Board of Trade 1952).

The Electric-cable Industry

In terms of man-power, the electric-cable industry is half the size of the rubber industry, and it is concentrated mainly in large factories in Greater London, Lancashire, and Cheshire, though there are factories in other counties. At present 31 companies in England and Wales are parties to the Joint Industrial Council for the industry, and these control about 40 factories.

Electric cables may be *communication* cables—e.g., submarine or telephone cables—or *power* cables. We are concerned only with the latter because communication cables do not usually contain rubber. Power cables vary in size according to the voltage they carry; the smallest contain a single conductor wire whilst larger ones contain many wires stranded together. In most power cables the conductor is insulated, and (except in cables carrying very high voltages) rubber was the usual insulating material until the recent introduction of thermoplastic materials such as polyethylene. The insulated conductor is covered with a protective outer sheath, and rubber remains the most suitable material for this sheath in certain types of cable—e.g., house-wiring and flexible trailing cables.

In 1949 the electric-cable industry used 10,500 tons of rubber. This was only 6% of all rubber consumed in the United

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TABLE I—DISTRIBUTION OF DEATHS BY YEARS

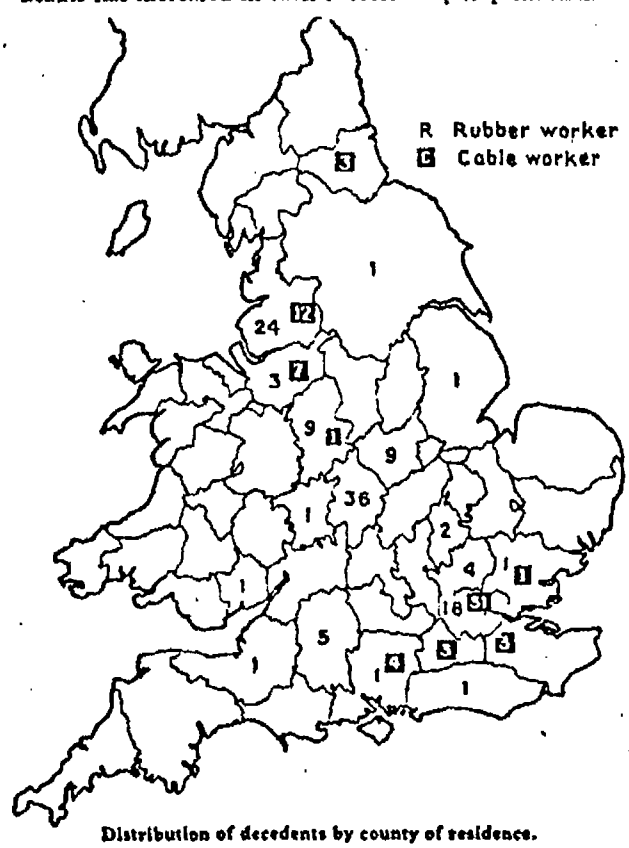
Year	No. of deaths		Total
	Cable workers	Rubber workers	
1945–49	8	9	17
1950–54	15	30	45
1955–59	20	38	58
1960–64	22	41	63
Total	65	118	183

Kingdom, and only a tenth of the amount used in the manufacture of tyres and tubes (Central Statistical Office 1952).

Antioxidants are essential ingredients in the compounding of rubber used for insulating or covering electric cables—the same antioxidants that are used in the rubber industry. The antioxidant withdrawn in 1949 was popular in the cable industry, and had been in use since 1935, and possibly earlier. This fact and its implications seem to have escaped notice for a decade. Later the possibility of a bladder-tumour hazard in the cable industry was mentioned by the British Association of Urological Surgeons (1961) and by Scott (1962), and the occurrence of deaths from bladder tumours among cable workers was noted by Case and Davies (1965). Yet, only after the publicity which followed the inquest on G. L., a former cable worker who died in January, 1965 (*Lancet* 1965a), was much attention paid to this risk, and it seems likely that its severity is still not fully appreciated.

Deaths in Cable Workers

The data analysed here were obtained by examining all death certificates on which papilloma or carcinoma of the bladder was mentioned as a cause of death of males in England and Wales from 1945 to 1964. During these 20 years the occupation given on 65 of these certificates indicated a worker in the electric-cable industry; in the same period 118 such certificates related to rubber workers. Table I gives the distribution of these deaths by date, and shows that in both industrial groups the number of deaths has increased in each successive quinquennium.



Distribution of decedents by county of residence.

The geographical distribution of the deaths is shown in the accompanying figure; nearly half the cable workers lived in the Greater London area, whereas the highest concentrations of rubber workers were in the Midlands and the North-West. In the past there has been a tendency to assume that industrial bladder tumours concerned only clinicians in the North of England; a study of the map will show that this is not the case.

If we knew the numbers and ages of all male workers engaged in the manufacture of electric cables during the same period, we could calculate an *expected* number of bladder-tumour deaths to compare with our *observed* number of 65. Unfortunately this is not possible because the only sources of such information are the Reports of the 1951 Census, and the occupation tables distinguish only a small group of some 4800 "Electric Cable and Wire Machine Drivers, Setters-up and Assistants" (codes 233, 234); all other cable-factory workers (numbering over 30,000) form part of heterogeneous groups of employees in the "Metal Manufacture, Engineering and Allied Trades".

In most cases the occupations given on the 65 death certificates indicate the cable workers' status (e.g., labourer, cable maker, foreman) rather than the departments in which they worked, and so afford few clues as to whether the deceased men were in contact with rubber. We do, however, know the histories of 8 of the men, and all but 1 of these had had contact with rubber. It must be remembered that exposure can occur without the actual handling of rubber; this was illustrated in the case of G. L., whose recorded occupation of wire stranding was probably innocuous but who incurred incidental exposure when he visited the rubber departments in his factory in the course of fire-watching duties (*Lancet* 1965a).

The figure of 65 is likely to be a considerable underestimate of the number of men who worked in cable factories and subsequently developed bladder tumours, for it excludes three groups of men:

(1) Those, such as G. L., who leave the industry and are not described on their death certificates as cable workers. Such cases do not usually come to light unless patients have been questioned about their past jobs and it is possible to link their case-histories with their death certificates.

(2) Those who develop bladder tumours but whose death certificates do not mention this condition. Case et al. (1954) found that 19% of patients with bladder tumours notified by hospitals and known to be dead had no mention of this disease on their death certificates.

(3) Those who have been successfully treated and are still living. At the Royal Marsden Hospital alone eight such patients have been treated.

Similarly the figure of 118 must be an understatement of the number of tumours among rubber workers, and there can be no doubt that the information available about the number of cases of industrial bladder tumour in the cable and rubber industries is woefully inadequate.

Bladder Tumours at a Cable Factory

Attention was first drawn to these cases when a former worker at a large cable-factory in London was treated for tumour of the bladder at the Royal Marsden Hospital and reported that 2 of his former workmates had received similar treatment. The factory had recently been closed down, but these 2 men were traced; it was found that they were alive and well, but had in the past been treated for papilloma of the bladder. All three men had worked in the rubber mill, and subsequently other cases from this department came to light.

TABLE II—YEAR OF BIRTH

Year of birth		0
	<1 mo.	1
1880–92	..	
1893–1902	..	
1903–12	3	
1913–22	2	
1923–32	7	
Total	12	

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Case no.	Period of e in the m
1	1912–4
2	1914–c
3	1920–c
4	1922–c
5	1924–c
6	1923–c

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TABLE II—YEAR OF BIRTH AND LENGTH OF EXPOSURE OF MILL WORKERS

Year of birth	Length of exposure					Total
	0–5 yr.			5–10 yr.	>10 yr.	
	<1 mo.	1 mo. to 1 yr.	1–5 yr.			
1880–92	..	1	6	1	9	17
1893–1902	..	8	4	1	9	22
1903–12	3	7	4	4	6	24
1913–22	2	23	15	7	6	53
1923–32	7	10	6	..	..	23
Total	12	49	35	13	30	139

The factory manufactured rubber-insulated power cables, and used the antioxidant referred to from 1935 to 1949, and possibly earlier. The operations carried out in the rubber mill included the weighing out of the additives that were mixed with the raw rubber (these included the antioxidant, in powder form), the mixing process, and the subsequent rolling of the rubber compound to a required thickness. The coating of the conductor wire with rubber and the process of vulcanisation were carried out in other departments.

The firm concerned gave access to the records of former workers at the factory, and from these records a list of men said to have worked in the rubber mill at some time during the years 1935–49 was compiled. There were 139 such men excluding foremen and other "staff" workers. Many of them also worked in the mill before 1935 and/or after 1949, but we are concerned only with the length of their exposure to the antioxidant, and this length of exposure is defined as the period of service in the mill between January, 1935, and December, 1949. Table II shows the years of birth and length of exposure of the 139 men; it can be seen that 30 men had over 10 years' exposure.

Examination of death certificates for England and Wales showed that 4 deaths from bladder tumours had occurred among the 139 men during the 19-year period 1946–64. The expected number of such deaths, calculated from national age-specific rates, was found to be 0·2. This difference is highly significant ($p \simeq 0{\cdot}0001$). In addition to these 4 deaths there are the two cases of papilloma already mentioned, making a total of 6 cases of bladder tumour.

All 6 cases occurred among the group of men with more than 10 years' exposure, and details of these cases are given in table III. All the deaths occurred under the age of 60 years. There are no grounds for believing that the end of this epidemic has been reached, for 3 of the 4 deaths occurred last year, and 1 of the 2 papillomas recurred a few months ago.

No deaths from bladder tumours have occurred so far among the 109 men with shorter periods of exposure. However, it should be noted that 25 out of the 35 men with 1–5 years' exposure did not enter the mill until after 1944, and that tumours would be expected to develop in this group some 10 years later than in men whose first exposure was in 1935.

No comprehensive search has been made for cases of bladder tumour among workers in other departments of this factory, but 6 cases have come to light, and three of these patients have died (in 1959, 1964, and 1965). 2 of the men concerned were members of the scientific staff of the firm and spent some of their time at this particular factory; 1 man was a laboratory technician; 1 worked on the process of vulcanisation, and 2 worked in the stranding department. The first 3 are believed to have actually handled the antioxidant; the vulcaniser was presumably exposed to vapour from rubber compounded with this substance; the stranders may never have handled rubber, but it is known that one of them had occasion to go into the rubber departments, and the other probably did likewise. The period when the antioxidant was used included the whole of the 1939–45 war, and it is likely that there was increased movement between departments at this time. Indeed, it would be difficult to exclude exposure in the case of anyone who worked at this factory during the war, for at one stage the rubber mill served as an air-raid shelter because it was on the ground floor of one of the strongest buildings of the factory.

TABLE III—BLADDER TUMOURS IN RUBBER-MILL WORKERS

Case no.	Period of work in the mill	Year of onset	Age at onset (yr.)	Year of death	Age at death (yr.)
1	1912–53	Unknown	Unknown	1953	55
2	1939–60	1954	56	Alive	..
3	1929–60	1956	45	Alive	..
4	1932–60	1961	46	1964	49
5	1934–60	Unknown	Unknown	1964	53
6	1923–60	1964	58	1964	58

Discussion

The results shown above strongly suggest that the risk of contracting occupational tumours of the bladder, already known to exist in the rubber industry, extends into the electric-cable industry. One of the causal agents is almost certainly an antioxidant of which manufacture ceased in 1949, but we have no assurance that this is the only source of danger.

The severity of the risk demonstrated in one group of rubber mill workers should help to dispel any doubts about the necessity for tracing exposed workers and offering them cytological screening tests. There is no reason to suppose that the epidemic of tumours at this factory is unique, for we know of clusters of 3 or more cases at some other factories. It is possible that thorough searches would reveal cases at most cable and rubber factories that had used this antioxidant. Hitherto most factory managements have not been conscious of this risk to their workers, and many cases of industrial bladder tumour have gone unnoticed by them. No firm should assume that its workers have escaped this risk unless a scrutiny has been made of the causes of death of all present and former employees who have died during the past 10 or 20 years. Bladder tumour is not a common cause of death and the number of naturally-occurring cases that may be expected to occur under the age of 65 is very small; this is illustrated by the expectation of 0·2 deaths among the 139 mill workers over a period of 19 years.

It seems inevitable that further cases of this disease will occur as the result of past exposure, but at least we may hope that early diagnosis will save or prolong the lives of some of the future victims.

The probable industrial origin of many cases of bladder tumour among cable workers appears to have gone unnoticed not only by factory managements, but also by the doctors who treated these cases. We have noted that of 65 bladder-tumour deaths that occurred among cable workers some are definitely known to be of industrial origin, and yet none of these 65 men was certified as dying of industrial disease. The most likely explanation for this omission is that the deaths were not reported to coroners as being of possible industrial origin because the certifying doctors failed to notice this aspect of their patients' disease.

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An unfortunate result of this lack of awareness among doctors is that in many instances where the cable workers were entitled to benefit for a prescribed industrial disease (no. 39, papilloma of the bladder) nobody advised the men that they were eligible for this benefit, and unnecessary hardship may have resulted; it is believed that from 1954 until mid-1963 only one cable worker was granted benefit. As old cases of this industrial disease come to light a number of claims are being made retrospectively, some by cable workers themselves and some by their widows (for industrial widows' pensions).

To a lesser extent this lack of awareness applies to cases of bladder tumour among rubber workers, and the dearth of research and published information are largely responsible for this ignorance. Disquiet may be felt over the recent response of the Medical Research Council (*Lancet* 1965b) to the request for an independent investigation into bladder tumours in the rubber industry: not only has the Council declined to carry out such an investigation itself, but it has suggested that a more limited study of the incidence of tumours should be made by the Rubber Manufacturing Employers' Association—a body which opposed the publication of the original study of this problem, and which has not published any of the valuable information it must possess from the first 7 years' results of its cytological screening service.

The basic reason why a thorough investigation of the rubber (and cable) industries is sought remains the same as when this was first proposed in 1949: there is no certainty that all the dangerous substances have been identified and withdrawn from use. This doubt has been strengthened by findings such as the continuing rise in the number of certified deaths from bladder tumour in cable and rubber workers.

It has been seriously suggested that the naphthylamine content of certain antioxidants may not have been the only dangerous constituent of these products. The very high incidence of bladder tumours in one group of cable workers lends some support to this suggestion, for these men were in contact with an antioxidant containing a mere 2·5% of naphthylamines of which only 0·25% was the β-isomer, so that their exposure to these carcinogens was almost certainly much less severe than that of groups of chemical workers with a similar tumour incidence. The implication is that we may have to deal with a completely new and unsuspected class of chemical carcinogens.

Clemmesen (1965) discusses the fact that the survey of bladder tumours among chemical workers was made only long after the risk in this industry had been first suspected, and comments "... it may be difficult to future workers to understand that so many decades should pass before a statistically sound evaluation of risk was carried out". It seems all too likely that this remark may apply equally to any comprehensive study of the rubber industry.

Summary

A high incidence of bladder tumours among skilled rubber workers was demonstrated in 1949 and may have been caused at least in part by an antioxidant used between 1928 and 1949. This high incidence has never been fully investigated.

Factories manufacturing electric power cables also used this antioxidant. Examination of death certificates for England and Wales for the years 1945–64 revealed 65 cases of bladder tumour where the deceased was described as a cable worker.

In one large cable factory 30 workers in the rubber mill had had more than 10 years' exposure to the antioxidant, and 6 of these men developed bladder tumours. No cases were observed among 109 mill workers with shorter periods of exposure, but 6 further cases occurred among workers in other parts of the factory. In 7 of the 12 cases the disease proved fatal.

There is no certainty that all the substances responsible for this risk have been identified and withdrawn; only a full investigation can elucidate this point.

I should like to thank Dr. P. E. Thompson Hancock, director of the department of clinical research, and Mr. D. M. Wallace, consultant urologist, Royal Marsden Hospital, for permission to interview patients and to use clinical records; several other urologists for information about their patients; the management of a large cable-making firm for their ready cooperation and for providing detailed records; and the Ministry of Labour for providing access to their records of deaths from bladder tumours.

REFERENCES

Board of Trade (1952) Final Report of the Census of Production for 1948: Vol. 11, Trade A, Rubber. London.
British Association of Urological Surgeons (1961) *Br. J. Urol.* 33, 1.
Case, R. A. M. The *Scientific Basis of Medicine: Annual Reviews*, 1966 (in the press).
— Davies, J. (1965) *Br. J. prev. soc. Med.* 19, 48.
— Hosker, M. E. (1954) *ibid.* 8, 39.
— — McDonald, D. B., Pearson, J. T. (1954) *Br. J. industr. Med.* 11, 75.
Central Statistical Office (1952) Annual Abstract of Statistics. London.
Clemmesen, J. (1965) Statistical Studies in the Ætiology of Malignant Neoplasms. 1: Review and Results; p. 581. Copenhagen.
Lancet (1965a) i, 306, 328.
— (1965b) i, 1106.
Scott, T. S. (1962) Carcinogenic and Chronic Toxic Hazards of Aromatic Amines. Amsterdam.
Times (1965) Jan. 30.

HIGH-ALTITUDE PULMONARY HYPERTENSION

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Rotta et al. (1956) first reported that people living at high altitudes in the Peruvian Andes had moderate pulmonary hypertension. It was less evident in temporary residents with a year's continuous stay at high altitude, and most evident in patients with chronic mountain sickness. Their findings in permanent residents of the Peruvian Andes were confirmed by Sime et al. (1963) and by Peñaloza et al. (1963) and by findings in the continental United States by Vogel et al. (1962).

We have been concerned mostly with high-altitude pulmonary hypertension in temporary residents in the Himalayas. The following is an account of our experience of 102 cases.

Predisposing Factors

The exposed population consisted of men aged between 18 and 47 years.

For 98 temporary residents from sea-level the vulnerable altitude began at 11,500 feet. For 1 person it was 8000 feet, and for 2 persons born and brought up at an altitude of 11,500 feet the vulnerable altitude was 12,500 feet and 14,800 feet. 1 man was a local resident living at 12,000 feet.

In 61 men symptoms of pulmonary hypertension began after five to forty-two months' stay at high altitude. In 7 men this high-altitude stay was continuous for five to six months, and in

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400 ppm 2000 ppm.

TOXICOLOGY AND APPLIED PHARMACOLOGY 17, 656–668 (1970)

Comparative Toxicologic Study with Polychlorinated Biphenyls in Chickens with Special Reference to Porphyria, Edema Formation, Liver Necrosis, and Tissue Residues

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Received November 3, 1969

Comparative Toxicologic Study with Polychlorinated Biphenyls in Chickens with Special Reference to Porphyria, Edema Formation, Liver Necrosis, and Tissue Residues. VOS, J. G. and KOEMAN, J. H. (1970). *Toxicol. Appl. Pharmacol.* 17, 656–668. In a comparative 60-day oral toxicity test (400 ppm) in chickens, three 60%-chlorinated commercial polychlorinated biphenyl (PCB) preparations were used: compound I (Phenoclor DP 6), compound II (Clophen A60), and compound III (Aroclor 1260). Using mortality, mean survival time, mean weight, and pathological observations (hydropericardium, abdominal, and subcutaneous edema and centrolobular liver necrosis) as parameters, a significant difference in toxicity was found between the compounds: compounds I and II showed the highest, compound III the lowest, toxicity. Microscopically centrolobular liver necrosis was found in chicks fed compounds I and II. Atrophy of the spleen was found in all test groups. Chemical porphyria was found as a general PCB effect: increased fecal excretion of coproporphyrin and protoporphyrin and fluorescence of tissues occurred in all test groups. Additional experiments with compound I (2000 ppm) in Japanese quail and rats confirmed the porphyrogenic action. Gas chromatographic analyses of liver and brain of dead chicks gave PCB levels that varied between 120 and 2900 ppm. The relationship of hydropericardium (chick edema) and liver necrosis to the differences in toxicity observed between the technical PCB mixtures is discussed.

In recent years the presence of polychlorinated biphenyls (PCB) has been exhibited in fish and wildlife in many countries, including the United States, Great Britain, Sweden, and The Netherlands (Jensen, 1966; Holmes *et al.*, 1967; Holden and Marsden, 1967; Koeman *et al.*, 1967; Risebrough *et al.*, 1968; Koeman *et al.*, 1969).

Commercial PCB preparations are oily fluids consisting of a mixture of different chlorinated biphenyls. These chemicals are extremely stable with very low aqueous solubility. They are used as lubricants, as fluids for heat transfer and dielectric media, in protective coatings for wood, metal, and concrete, and for many other applications. Which of these applications has contributed to the present widespread environmental contamination has not been elucidated. The occupational hazards in the use of PCB have been known for years; normal handling of these compounds has not given rise to great difficulties (Irish, 1963).

Animal experiments with rats and guinea pigs have shown that the ingestion of PCB

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TOXICOLOGY AND APPLIED PHARMACOLOGY 19, 617–633 (1971)

Dermal Toxicity Studies of Technical Polychlorinated Biphenyls and Fractions Thereof in Rabbits

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Received October 5, 1970

Dermal Toxicity Studies of Technical Polychlorinated Biphenyls and Fractions Thereof in Rabbits. Vos, J. G., and Beems, R. B. (1971). *Toxicol. Appl. Pharmacol.* 19, 617–633. A significant difference in toxicity between 3 polychlorinated biphenyl (PCB) preparations was found in a prior study: Clophen A 60 and Phenoclor DP6 showing the highest, Aroclor 1260 the lowest, toxicity (Vos and Koeman, 1970). A subsequent study revealed the presence of tetra- and pentachlorodibenzofuran in Phenoclor and Clophen (Vos *et al.*, 1970). In the present study, application of 118 mg of the 3 PCB's (5 times per wk, for 38 days) on the back skin of rabbits also resulted in differences in toxicity.

PCB-induced skin lesions were hyperplasia and hyperkeratosis of the epidermal and follicular epithelium. Histopathology of the liver included centrolobular degeneration, centrolobular liver cell atrophy, focal necrosis, and cytoplasmic hyalin degeneration. Definite hyperplasia and hyperkeratosis of the follicular epithelium of the ear skin were seen after the topical application of fractions of Phenoclor and Clophen eluted from chromatographic columns with 25% diethylether in hexane. The fraction from Aroclor caused a minimal hyperplasia and hyperkeratosis of the follicular epithelium. PCB-induced kidney lesions were hydropic degeneration of the convoluted tubules and tubular dilatation with the presence of casts. This dilatation was demonstrated also by a significantly increased relative percentage of the diameter which corresponds to the space of Bowman. Moreover, thymus atrophy and lymphopenia were found. Fecal coproporphyrin and protoporphyrin excretion was increased.

Polychlorinated biphenyls (PCB) have been identified in tissues of fish and wildlife in many countries (Jensen, 1966; Holmes *et al.*, 1967; Holden and Marsden, 1967; Koeman *et al.*, 1967; Risebrough *et al.*, 1968; Koeman *et al.*, 1969; Jensen *et al.*, 1969; Duke *et al.*, 1970; Prestt *et al.*, 1970).

PCB preparations are extremely stable, oily fluids with very low aqueous solubility. They are used as lubricants, as heat transfer media, in protective coatings for wood, metal, and concrete, and for many other applications. Which of these applications has contributed to the present environmental contamination has not yet been established.

Inhalation and feeding experiments in rats with 65% chlorinated PCB resulted in liver injury (Drinker *et al.*, 1937; Bennett *et al.*, 1938). Liver damage and skin lesions have been described after inhalation, ingestion, and application to the skin using rabbits, guinea pigs, and mice (von Wedel *et al.*, 1943). Hydropericardium occasionally accompanied by abdominal edema was found in chicks fed PCB (McCune *et al.*, 1962; Flick

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