THE CONTROL OF INDUSTRIAL BLADDER TUMOURS

A Code of Working Practice Recommended by the British Dyestuffs Industry for the Manufacture and Use of Products Causing Tumours of the Bladder

BY

T. S. SCOTT and M. H. C. WILLIAMS

From the Papilloma Committee of the Association of British Chemical Manufacturers

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Bladder tumours have been recognized as an occupational hazard amongst dyestuffs workers for over 60 years. The news of this hazard reached Great Britain in 1912 following the visit of Thomas Legge, then H.M. Senior Medical Inspector of Factories, to Frankfurt-am-Main in 1911 (Legge, 1912, 1913), but it was not until 1926 that the first cases in England were described by members of the factory medical inspectorate (Bridge, 1927). The first contribution from the industry itself came from Wignall in 1929. By 1933 Bridge, H.M. Senior Medical Inspector of Factories, reported that 28 deaths from occupational bladder tumours had come to his notice. Goldblatt (1949) described 101 cases from a group of British factories and Scott (1952) recorded 66 cases from yet another works.

In 1947 the Dyestuffs Group of the Association of British Chemical Manufacturers (A.B.C.M.) set up and financed a major research project on industrial papilloma of the bladder. This has been described in a booklet which was circulated to managements, trades unions, and workmen (1953). A scientific committee was appointed under the chairmanship of Professor A. Haddow to guide research work into the cause, consider diagnostic methods, and examine preventive techniques. A sub-committee was invited, under the chairmanship of Mr. N. Strafford, to provide accurate methods for the analysis of suspected compounds under industrial conditions (Butt and Strafford, 1956). In 1948 a research fellow, Dr. R. A. M. Case, was appointed at the Chester Beatty Institute to conduct an investigation into the industrial data. This enquiry covered the records of over 30 years of the manufacture of dyestuffs and their intermediates in Great Britain. The results and the statistical analysis were published in 1954 (Case, Hosker, McDonald, and Pearson, 1954).

Case and his co-workers were able to produce

statistical proof that contact with alpha-naphthylamine, beta-naphthylamine and benzidine, three compounds which had previously been suspected, caused a significant incidence of bladder tumour amongst the men engaged in their manufacture or use. No evidence was found to inculcate aniline and it is now considered that under the conditions of its manufacture and use in this country it is not a significant cause of bladder tumour, and that the name aniline cancer of the bladder is an unfortunate misnomer. Suspicion, however, fell on the manufacture of magenta and auramine and further data collected and analysed confirmed that the risk also existed in connexion with their manufacture. The results of the study were at once given to the Ministry of Pensions and National Insurance, and in 1953 papilloma of the bladder was prescribed as an industrial disease in occupations involving contact with alpha-naphthylamine, beta-naphthylamine, or benzidine, and the manufacture of auramine or magenta.

Progress had already been made in many directions to improve the methods of protection from the compounds now proved to be carcinogenic, but it was obviously necessary not only to devise the safest possible method of working but also to be able to assess the efficacy of those measures in eradicating the tumours. We were, therefore, invited by the A.B.C.M. to draw up a "code of industrial practice" to cover the manufacture and use of known or suspected bladder carcinogens and the present paper is based on the recommendations made to the member firms of the Association in 1953 now brought up to date. Many of these recommendations have been made before but it is felt that repetition is not without virtue in this context.

This report is based on the following premises which are now generally accepted in Great Britain and which have been confirmed by the report on the

field survey, by other published reports, and by the industrial experience of the authors:—

- (a) That the high incidence of bladder tumours has occurred in men working on the manufacture or handling of beta-naphthylamine, benzidine, and to a lesser extent, alpha-naphthylamine.
- (b) That there is a widely variable latent period (or induction period) between entry to the industry and onset of the tumours. This may range from one to 45 years with an average of 18 years and the most common time of development is between 15 and 20 years. This does not necessarily coincide with the period of exposure, which also varies widely. Exposure periods of a few months are accepted as being sufficient to cause a tumour.
- (c) That the process of tumour development, once initiated, is irreversible and is not arrested by cessation of exposure. Thus the exposure period may, in those who leave the industry and subsequently develop a tumour, be shorter than the latent period. During this time it is not possible to demonstrate any pre-tumour changes in the bladder, nor is any method of treatment known which would prevent the development of a tumour.
- (d) That the onset of tumour and death occurs at much earlier ages in those who enter the industry before the age of 30 than in the general population or in entrants over 40. This may be applied as a rough test for occupational hazard, *i.e.*, death from bladder tumours in younger age groups would give rise to the suspicion that the tumours were of occupational origin. It is not thought that younger people are more susceptible to the disease but only that the younger the age at entry into the industry, the younger will be the victim at onset should a tumour develop. Older people are in fact more likely to develop spontaneous tumours of nearly every type including bladder tumours.
- (e) That the proportion of exposed persons who will be affected is influenced by the intensity and duration of exposure. The higher the "dose" as determined by these two factors, the greater will be the number affected.
- (f) That the mean latent period is influenced by the type of carcinogen. It had previously been thought that the severity or length of exposure might influence the latent period and this is the case in a number of recorded animal experiments. The statistical analysis, however, did not confirm this view.
- (g) That the cancer-producing potency of these substances in industry varies, technical beta-naphthylamine being about twice as potent as benzidine and four times as potent as technical alpha-naphthylamine. It is strongly recommended that all compounds which are known or suspected to be cancer-producing should, where manufacture is necessary, be manufactured and handled with equally stringent precautions as far as is technically possible.
- (h) That alpha-naphthylamine may be a carcinogen itself apart from its beta-isomer impurity. Therefore even if alpha-naphthylamine can be manufactured free of its beta-isomer impurity it should still be regarded as dangerous, unless overwhelming proof to the contrary could be adduced.
- (i) That aniline does not cause occupational tumours of the bladder in men engaged in its manufacture or use.
- (j) That there is an occupational hazard of bladder tumour in the manufacture of auramine and magenta with a latent period of the same order as the other occupational cases. This does not necessarily mean that the finished products, auramine and magenta, are themselves the causal agents and the statistical analysis could not elucidate this point.

Case and others (1954) give a statistical estimate of the number of cases that may be expected in the future from the people who have already been exposed. Case (1953) has also set out a method by which it is possible for a firm in Britain to estimate the number of deaths that might arise by the non-occupational risk of the disease. A comparison of this with the observed number can be used to detect dangers associated with unsuspected processes and eventually to test the efficacy of new precautions. Case and Lea (1955) have described a more general and simpler method of achieving this object, and, in conjunction with Case and Pearson's tables (Registrar General's office, in the press), the method can be applied to other forms of cancer as well.

Description of the Disease

Occupational tumours of the bladder present all clinical and histological stages between benign papillomata and infiltrating carcinomata. A papilloma may undergo malignant change. The tumours occasionally occur in the ureter or the pelvis of the kidney (Macalpine, 1947). There is no demonstrable difference between those contracted by chemical workers and those arising in the general population.

Recurrences are frequent and tumours may recur as papillomata or as carcinomata irrespective of the nature of the original lesion. It is thought that many of these so-called recurrences are fresh tumours arising in an already activated bladder mucosa. The usual complications, such as haemorrhage and infections, occur with either type of tumour.

The onset is insidious and the disease may be advanced or even incurable before any symptoms or signs appear, but, on the other hand, it is common for severe symptoms to occur in the early stages when treatment is likely to effect a cure. Usually, the first sign is haematuria, but bleeding may not be visible even in advanced disease. Another sign is pyuria caused by the tumour surface ulcerating or becoming infected. Other signs or symptoms such as dysuria or frequency may arise, depending on the stage to which the tumour or its complications has advanced. It will be obvious from this that any haematuria, even in microscopic amounts, must be regarded with suspicion and this is extremely important in early diagnosis.

Because of the tendency to recurrence, it follows that once a tumour has been treated it is necessary to have regular follow-up examinations and review of each case at suitable intervals. Even when apparent cure has been maintained over many years at least annual re-examination should be continued. In view of the long latent period, in some cases over 30 years, it also follows that once a man has been exposed for a sufficient time to chemicals which can cause bladder cancer he remains at risk for the rest of his life, whether he continues to work with them or not. We consider that a period of six months' exposure can be sufficiently long but even shorter periods may come to be accepted as sufficient to induce a tumour.

PART I

Medical Recommendations

This section deals with the medical control of the hazard, with selection and education of workers, the methods of protection, and the keeping of records. Our recommendations for ensuring the early diagnosis of tumours in industrial workers at risk are the subject of a separate paper (Crabbe, Cresdee,

Scott, and Williams, 1956), which should be studied in conjunction with these recommendations.

Medical Control.—Medical control is essential to ensure (1) proper selection and adequate medical supervision of workers; (2) early diagnosis of bladder tumours; (3) liaison with the family doctor, the urologist, and the hospital; (4) the follow-up of men with established tumours from the point of view of their treatment, regular reviews, and working capacity; (5) general supervision of the health of workers, supervision of plant hygiene, investigation of the records to determine the incidence of sickness due to bladder disease.

It is recommended, therefore, that where there is a hazard there should be a medical officer, either full-time or part-time, depending on the amount of work involved. It is desirable that all investigation and treatment should be undertaken with the cooperation of the workman's family doctor and that, if possible, all the cases in one area should be treated by the same surgeon or unit, who would thus gain valuable experience of industrial tumours. To this end the works doctor should approach the man's family doctor to arrange through him the necessary investigation or treatment by the surgeon with whom he would also be in touch.

It is an important part of the treatment and rehabilitation of these cases that they should be enabled to continue at work and not become chronic invalids; here again it is essential to have skilled medical advice on their capacity for work and placement in a job.

Records.—The following records should be maintained in relation to each suspected carcinogenic substance:

1. (a) Plant and processes. Chemical and physical form of products during process and isolation (*e.g.*, base, sulphate or hydrochloride, etc.)
- (b) Quantities manufactured and handled
- (c) Methods of manufacture and handling with dates of changes
- (d) Type and design of plant used with dates of changes
- (e) Plant hygiene precautions
- (f) Duration and types of shift worked

2. The following records should be maintained in relation to each man working with these compounds:—

- (a) Name and address
- (b) National Insurance number
- (c) Date of birth
- (d) Date of entry into the industry
- (e) Date of starting hazardous occupation

- (f) Previous significant occupational history
- (g) Works history
- (h) Any significant accidental contamination
- (i) Particulars of death certificate

The information compiled from these records is essential for a precise assessment of the hazard in the future. They need not necessarily be kept by the medical officer but should be available to him. Many of these particulars will already be recorded by the technical and labour departments.

Where no records have existed previously a register should be compiled with these particulars, as far as they can be ascertained, in respect of present and past workers. This is similar to the nominal rolls supplied by the member firms for the A.B.C.M. field survey. This register should be continued in the future and kept up to date. From it may be calculated, by the methods mentioned earlier, the number of cases of tumour likely to arise by the ordinary risk of the disease. The actual incidence may, now or in the future, be compared with this and hence may indicate the existence of a hazard and whether the measures applied for control have been effective. Arrangements have been made for the appropriate records to be maintained in the future by H.M. Senior Medical Inspector of Factories.

Selection.—New entrants to jobs which involve risk of tumour, either in manufacture or use of carcinogenic substances, should be selected by the works medical officer, bearing in mind the following considerations:—

Age.—The age of onset of bladder tumours in those who develop them is almost entirely dependent upon the age of entry into the industry, occurring after a latent period of usually 15 to 20 years. Men over the age of 30 should be chosen when practicable in order to reduce the likelihood of onset and mortality from these tumours at early ages. Men over 40 should be given preference.

Personal Hygiene.—A high standard of personal hygiene is essential to reduce the absorption of chemical by the skin and mouth to the minimum. Generally speaking, those whose standard of hygiene is poor will be unlikely to cooperate in the personal preventive measures such as clean working, bathing, and changing. The dirty should obviously be rejected; nail-biting increases the risk of ingestion; septic teeth and mouths suggest poor hygiene; the bearded should be excluded because of the possibility of the beard becoming contaminated and so increasing the risk of absorption by the mouth and nose; mouth breathers with nasal obstruction should also be excluded as they may tend to remove masks.

Intelligence.—A sufficient standard of intelligence is necessary to understand the hazard, to profit by training in methods of prevention, and to apply the self-discipline necessary to cooperate in the measures prescribed for personal hygiene and protection.

Previous Health.—Special attention must be paid to any previous disease of the genito-urinary system and to any previous history of cancer of any type or of any organ. An applicant with such a history must be rejected because of the risk of non-occupational disease which would confuse the assessment of the hazard and the diagnosis of industrial tumour. There is no evidence that a family history of cancer predisposes to bladder tumour and we do not recommend rejection merely on this ground.

Present Health.—Men selected should be free from gross disease, especially of the genito-urinary system, and from cancer or any pre-cancerous lesions of any organ or of the skin. The urine should be examined for albumin and blood and pus cells, partly to assist in excluding genito-urinary disease and partly to avoid confusion in the interpretation of urine tests after the applicant has started work.

Occupational History.—It is most important to ascertain whether there has been any previous exposure to carcinogens. Men who have previously worked in occupations in which they have been exposed to other carcinogens should be excluded from starting work with these compounds. This would also entail the rejection of men with a previous industrial history of work in tar products, gas works, rubber works, coke ovens, and in other chemical plants carrying a carcinogenic risk. On a plant where the hazard is suspected but not proved it is undesirable to employ men who have had previous exposure to carcinogens.

Apart from the above considerations, the standard of fitness required will be determined by the type of work to be done. The physique or strength of a man or the general state of his health is no indication of his resistance to bladder tumour.

Education and Training.—The worker selected should have explained to him clearly and simply (a) what the hazard is, (b) where and how it arises, (c) the measures which are taken on the plant to prevent risk, (d) how he should use the measures provided for his personal protection.

We consider that it is not possible to justify the concealment of such a risk from men who are being exposed to it. Better cooperation can be expected if they understand what is being done to attain safe working conditions and why it is being done. A simple explanation of the situation, including reference to medical care, engenders confidence in the

worker's mind. Particular care should be attached to supervision and training during the first few weeks of a man's employment on such a plant.

Protective Measures.—In industry these compounds enter the body by two main routes—inhalation and absorption through the skin—but it should be borne in mind that they can also be ingested. Thus the aim of all preventive measures must be to reduce to the minimum, and where possible to eliminate, all contacts between operator and carcinogens. The first and basic method of ensuring this end must be by plant design and operation. The second line of defence is the provision of personal protection for the workmen but the hygiene of the plant and of the working environment is more important than any measure which depends for its efficiency on the cooperation or discipline of the operator or on any measure which is under his control (Legge, 1934).

Working Clothing.—No man should wear any of his own clothing while exposed to carcinogens. A complete set of working clothing should be supplied and should include underwear, footwear, socks, and outer-wear. They should be changed immediately on accidental contamination, and should be changed and washed at regular intervals depending on the plant conditions and on the degree of exposure but not less than once a week in any circumstances. A daily change will avoid the absorption of amine which has impregnated the clothing on the previous day. For laundering a slightly acid synthetic detergent is preferable to alkaline soap as the latter leads to the formation of the insoluble base which may dry in the clothes. The clothing should be tested at frequent intervals for the presence of amines by the methods which have been described by Butt and Strafford (1956). This forms a useful check on the efficacy of the measures taken to prevent absorption of the noxious substances. The working clothing supplied should be taken off at the end of each shift and must be left at the factory. On no account should it be taken home. Separate lockers should be provided for home and working clothes so that no cross contamination takes place. A clean smock or coat can be worn during meals so that tables and food are not contaminated from working clothes.

Protective Clothing.—The protective clothing, which should be supplied and worn in addition to the working clothing described above, will vary according to the process and the type of plant and the resultant potential exposure, but will generally consist of overalls of closely woven cotton or wool (or blouse and trousers of similar material), rubber boots, rubber or plastic gloves with gauntlet fitting

or long sleeves attached, and a cap which can be washed.

GLOVES.—PVC and rubber withstand the amines, but if new carcinogens are discovered care must be taken to ensure that protective materials are resistant to them. Gloves contaminated on the inside must be destroyed. The outside of gloves should be washed by the operative during and after work but the laundering of gloves for re-issue is not recommended because of the danger of accidental re-use and incomplete decontamination. Cotton gloves are inadequate and may result in longer absorption than brief contact with bare hands followed by immediate washing. This latter practice may be necessary where delicate manual operations are carried out by fitters. Impervious armlets can be worn with gloves in dealing with molten carcinogens or solutions.

APRONS.—Light impervious aprons for handling molten carcinogens or solutions should extend up to the neck and below the tops of the rubber boots.

FOOTWEAR.—Rubber safety boots are preferable to clogs as they are more impervious and they can be worn to knee length if liquids are being handled. Turning down the tops of boots is wrong, particularly when aprons are worn, as liquid is apt to run inside the boots.

MASKS.—Should vapour or dust give rise to heavy atmospheric contamination, hoods with clean compressed air supplies should be used. Dust respirators are not always dependable because of the unreliability of individual fit and the risk of skin absorption from the face and neck. Cotton wool pads are not adequate protection against these dusts or vapours.

Baths.—Suitable changing and bathing facilities with adequate hot water, soap, and towels must be available at the factory. Shower baths are the most satisfactory and are usually preferred, but some workers, especially the older ones, prefer a slipper bath. The main objection to the slipper bath is that in cases of contamination some amine may remain on the skin from the bath water; there may also be some danger of inhaling amine volatilized by the hot water while lying in the bath.

(1) A bath or shower must be taken at the end of each shift so that small quantities of amine which may be present on the skin will be removed. This must be obligatory and the bathing time should be paid for. Twenty minutes is regarded as adequate time.

(2) These compounds can be absorbed directly through the skin in any physical form as salt or base, molten liquid or solution, or at any temperature, so that if there is accidental contamination

or if contamination occurs during plant maintenance or cleaning, it is essential that the workman is bathed immediately and his clothing completely changed. If contamination is very heavy and a slipper bath is used, a second bath is advisable as the water in the first becomes heavily charged with amine. A scrubbing brush will help to remove chemical from rough skin or fissures and care should be taken to ensure that the nails are cleaned. The hair should also be washed and it should be remembered that spectacles, if worn, may be contaminated.

Hours of Work.—Process operation should be so adjusted as to limit the time of exposure to a minimum. (a) No overtime should be worked except in an emergency and an emergency should be regarded as being an occasional isolated incident and not a continuous period. (b) If men work with these amines for part of a day or shift they should bath and change before going on to other work to complete their shift.

Limitation of Numbers Exposed.—The total number of men exposed regularly to these carcinogens should be limited as far as conditions allow.

(a) Only men who have been selected by the medical officer should be allowed to work on processing or handling operations.

(b) Temporary or casual process workers and handlers should be kept to a minimum and avoided if possible.

(c) Cross transfers from one hazardous plant to another should not normally be allowed so that confusion as to the relative risks of each plant or process may be avoided. But, in small factories, it may be better to employ one man, or a small number of men, to operate all the plants where there is a risk rather than to increase the numbers exposed.

(d) Similarly, the handling of these substances in any plant should be confined if possible to one man or, if the scale of work is too large for this, to a limited number of men who would handle, weigh, and charge all the dangerous material where mechanical methods cannot be installed.

(e) Selected deputies should be appointed to cover the absence of regular men. No other men should be allowed to do the job.

All men engaged on these processes should be employed on a voluntary basis and no industrial sanctions should be applied to persuade men to undertake this work or to remain on it.

In plants where radical improvements have been carried out or in new plant which has been built with due regard to safe working, we recommend that men of suitable age who have not previously been exposed to carcinogens should be employed

whenever possible, although it may be necessary to employ certain key men who have previous experience and possibly previous exposure.

Cases of tumour developing after a few months of heavy exposure to benzidine and beta-naphthylamine have been reported. Safe working should be achieved by appropriate plant design and methods of working and no reliance should be placed on the practice of employing men for short periods, as advocated by earlier writers, as this would only increase the numbers of men at risk.

PART II

Plant and Operating Precautions

This section will deal with the industrial and technical measures recommended in the manufacture and use of alpha-naphthylamine, beta-naphthylamine, benzidine and its homologues, and a number of other processes. Before discussing the details peculiar to each process it is proposed to lay down the basic principles which must lie behind all efforts to eradicate this hazard completely from the industry.

Buildings.—In the design of new plants the ceiling should be sufficiently high to allow adequate ventilation. Where possible, pressure vessels containing molten carcinogen should be isolated in the open air. The walls should be made of a material which cannot become impregnated with chemicals. The floors should have an adequate slope to drain and be constructed of a material which will withstand both physical and chemical damage. If wear and tear occurs so that pools form, these must be filled in since they can form a constant source of atmospheric contamination as well as a cause of splashes. Where a high level of exposure is liable to occur no wood should be used in the construction of stairs, platform floors, or hand-rails, all of which should be made of metal. Floor grids must be easily removable and drains should have a sufficient gradient to ensure quick flow. Although it may be difficult to alter old sheds, these recommendations represent the standard to be aimed at.

Ventilation.—Forced ventilation will be desirable for all buildings where carcinogens are regularly handled in a manner where there is any possibility, however remote, that the general atmosphere may become contaminated with vapour or dust. In order to achieve adequate air changes in the lower floors of some buildings, it may be necessary to provide air suction trunks from the roof to each floor in order to achieve the desired effect. It must be made clear that the need for forced ventilation of the general working space is much more necessary

where volatile hot carcinogens are being handled than where the hazard is in the form of dust. Likewise, forced ventilation is least necessary where there is no hot process and the final product is handled as a paste. All general airflow should be arranged so that the air current moves away from the man.

No plant item containing hot molten carcinogen should be vented within the working space and if a number of such vent pipes are necessary a common scrubber system should be provided so that contaminated air does not enter other sheds nearby or re-enter the shed from which the contamination originated. If no such scrubber system is installed the vent pipes must be carried well above any point where air is entering the working space, such as windows or ventilators.

Plant.—The object in all plant design must be to contain the carcinogens within an enclosed system wherever possible whether they are present as dust, vapour, or liquid. Every plant item should be considered with regard to its enclosure and ventilation outside the working space. Lagging liable to be contaminated should be encased in an impervious material, so that spillages can be effectively removed. Hot contaminated lagging is a danger and care should be taken during its repair. Catwalks should be provided where necessary to avoid damage to lagging. All operations involving manual handling of carcinogens whether in concentrated form or when they are present only as an impurity should be studied with a view to the establishment of automatic enclosed types of plant. All such plant should be designed so that decontamination can be carried out before it is handled by fitters. Sharp angles of pipes should be avoided to minimize the chance of blockages, and in pipe design special attention should be paid to ease of replacement.

When these improvements have been carried out there remains the risk of these carcinogens being in contact with the workroom atmosphere during final packaging in manufacture, or in charging if these intermediates are being used. Bulk handling of material in enclosed pipelines as molten liquid, slurry, or solution will often close this last loophole. If manual handling is inevitable in charging or isolating the material, adequate draughting and full protective clothing must be relied upon. It is realized that bulk handling will only be possible where considerable quantities of carcinogens are being handled. Evidence available suggests that by far the greatest risk exists on plants which handle carcinogens consistently every day. Where dust is likely to occur floors should be kept wet to prevent it from rising into the atmosphere. A pipe with

multiple holes can be fitted so that the floor can be kept constantly wet.

Sampling of Product.—Where sampling of hot carcinogens within an enclosed system is necessary for process control, a device can be installed to carry out a melting point determination without opening up the plant. Where samples have to be withdrawn this should be done in a small vented cabinet. The use of dip pans for sampling is unsatisfactory because hot amine is given off to the atmosphere during withdrawal and transport. The use of dip sticks to determine the depth of liquid in vessels containing carcinogens is dangerous and automatic depth recorders should be installed.

Batch Weighing.—Tumours have occurred amongst weighmen. Adequate draughting should be provided where any batch weights of intermediates are made up and suitable protective clothing should be worn by the operator.

Isolation of Solids.—Filter presses and open nutsches are unsatisfactory for the isolation of carcinogens or of materials where the carcinogens are present as impurities, unless a completely impervious one-piece suit with compressed air supply is worn by the operator. When the operation is completed the clothing must be scrupulously decontaminated before the man emerges from the suit. Rotary filters, pressure filters, vacuum nutsches, and automatically discharging whizzers, all totally enclosed, are more suitable. The emptying of closed nutsches by shovel easily leads to contamination of skin and clothes and re-slurrying is the only satisfactory method of discharge. Attention should be paid to the possibility of pastes drying out and giving rise to dust hazards. Flakers should be totally enclosed and their discharge points draughted.

Disposal of Still Residues.—Tar or pitch must not be allowed to set hard on the inside of stills. On no account must a man enter a still to chip out such pitch unless he is protected by a completely impervious suit with a fresh-air feed hood. This latter practice should only be an emergency measure. This risk can be eliminated entirely if molten still residues are fed directly to a furnace which must destroy the carcinogen and not distil it to the outside atmosphere.

Drying.—The hazard to workmen on driers in the dyestuffs industry is real and may arise in the drying either of concentrated carcinogens or of products derived from them which contain unreacted carcinogenic amines. It is recommended that where complete dryness is not essential, tray drying should be avoided and the materials should be isolated as pastes from enclosed filters or from

enclosed high-speed automatically discharging whizzers. Where possible no unreacted carcinogenic amine should remain in the products derived from carcinogenic intermediates and routine analyses may be necessary to check this.

Where these measures are technically impossible and heat drying has to be used, the most dangerous and undesirable of the methods of drying is that in which a man has to enter the drying space where he may breathe or be in contact with any vapourized amine which is in the atmosphere. Hence tunnel stoves are quite unsuitable. Stoves with forced air flow must not be vented into the working space. Dust and sublimed material tend to blow from ill-fitting doors and to collect in the flues, so that this method of drying is not without hazard, apart from the detraying of a dusty product. Vacuum stoves are liable to produce high atmospheric contamination when the doors are first opened. All forms of tray drying carry a heavy risk because of the dusting of the material on discharge from the trays. If tray drying of small amounts of material containing carcinogens is inevitable, special exhaust ventilation should be provided and protective clothing with a fresh-air hood should be worn. Drum driers which are totally enclosed produce a large amount of dust which may contaminate the operator because of the need for frequent blade adjustment and overhaul but an enclosed draughted "venuleth" drier may be used.

Enclosed self-discharging driers with the discharge point adequately draughted are the best type available at the moment. It must be remembered that if any unreacted bases are present, some will be volatilized during drying and will be deposited in the ventilation system.

Grinding.—If possible grinding of carcinogens or materials containing carcinogens should be avoided altogether since even the best enclosed draughted mill produces some dust. If it is possible to whizz the material down to a sufficiently low water content for subsequent use, this should be the method of isolation preferred. Checks should be made to ensure that aerosols are not produced by the whizzer and that maintenance is efficient.

Maintenance.—However effective plant design and operation can be made, it is eventually necessary to open up plant for inspection or repair. Unless stringent precautions are taken there is a high potential risk to maintenance and engineering personnel. All plant items should, therefore, be cleared of carcinogen where possible before being dismantled for maintenance. This may be achieved either by steaming out an enclosed system ensuring that steam laden with amine is not sent to atmo-

sphere, or by washing with cold water followed by chemical inactivation of any carcinogen remaining. Where the carcinogen is an amine, inactivation may be carried out with hypochlorite or formaldehyde or by diazotization and destruction of the amine. In the event of maintenance of a contaminated plant item being inevitable, as in the setting of flaker blades, complete impervious protective clothing is necessary together with the use of a fresh-air feed hood. Changes of clothing and washing facilities are as necessary for fitters on these processes as for processmen. Where contamination is likely to occur, protective clothing and plant decontamination must likewise be provided for other tradesmen, such as electricians, instrument fitters, and construction engineers.

Transport and Packaging.—Where dry flaked carcinogens are being packaged, drums with tight-fitting lids are advocated as the best method of transport. Damaged drums which do not fit standard draughted devices should not be used as dust may escape due to the setting up of uneven air currents.

Wooden casks must be avoided if possible. Where acid pastes are being handled, however, casks may have to be used but specially lined drums are preferred. Individual casks should have the lids fitted immediately after filling so that the paste does not have time to form a dust on the surface. The use of a handle in the centre of the lid may help to avoid contamination of the lid with the contents of the cask during heading up. If a cask used in the transfer of carcinogenic materials becomes unusable, it should be burned rather than sent for repair since it is impossible to remove dust from the cracks in a broken cask. Casks which have contained a carcinogen must be washed with cold water since tumours have occurred amongst cask washers who inhaled steam vaporized carcinogens from hot washing. Remote control hot water washing can be used if cold water fails to clean the vessel but care should be taken to ensure that the steam is adequately removed and does not drift towards the operator.

In the event of transfer of hot or molten material, special drums with indwelling dip legs can be used. In the event of such a drum containing a solid this will have to be melted in a draughted compartment before emptying. Drums requiring welding should be specially cleaned before repair so as to avoid vaporization of carcinogen during this work.

Where bulk handling is used special devices will be necessary to catch drips and ensure clean coupling of charging and discharging pipes. Local draughting will ensure that vapour does not arise

from the open ends of pipes after use. Bulk transport lorries should be supplied with warnings and full instructions for safe handling of material spilt after accidents, together with the necessary protective clothing. If such solid material sets on the road, its cold chipping with full protective clothing will be necessary after the police have been informed.

DETAILED CONSIDERATION OF MANUFACTURE AND USE

Having discussed the basic principles to be adopted in considering the elimination of this hazard from the dyestuffs industry, it is now proposed to devote a section to each relevant process. These sections may repeat some of the general principles but it is intended to point out to the manufacturer the main and also the subtle dangers associated with the operation of each process. Explanations based on experience of factory conditions are included where necessary as well as any relevant results of animal experiments.

Beta-naphthylamine

The manufacture of beta-naphthylamine has proved to be by far the most hazardous occupation in the dyestuffs industry. It was felt that no plant could be economically devised which could be operated with any degree of certainty that tumours would not occur. The cessation of its manufacture and use in 1952 in Great Britain is considered to be one of the most important measures in the prevention of industrial bladder tumours.

Its main use was in colour manufacture for which beta-naphthylamine was sulphonated. The sulphonated compounds, which are not considered to be carcinogenic, can be made effectively by the amination of the appropriate sulphonated beta-naphthols.

The use of beta-naphthylamine to make rubber chemicals and colours has also been abandoned in Great Britain. In the case of the rubber chemicals and small colour manufacturers, alternative products with similar or improved technical effects have been developed using non-carcinogenic intermediates.

Tobias Acid (2 Naphthylamine-1-Sulphonic Acid)

Since crude and technical Tobias acid contain a trace of beta-naphthylamine as an impurity, this compound must be treated with certain precautions. This impurity can be reduced to a minimum by appropriate control of process conditions. The beta-naphthylamine is present as the sulphate so that no free amine is volatilized during drying. However, the final dry powder may constitute a potential hazard, both in manufacture and use. Efficient draughting should be provided at the

packaging point and a type of enclosed drier is recommended as opposed to any form of tray drying. The product is very apt to "fly" and it is doubtful if tray drying can be achieved with complete safety.

Full protective clothing for the workman with dust masks or fresh-air hoods should be adequate for charging this powder for use in subsequent processes, but pneumatic handling is preferable if large amounts are regularly used. Anti-dusting treatment of the powder should not be relied upon.

No tumours have been attributed to Tobias acid manufacture in any country to date, but in view of the vast increase in manufacture accompanying the cessation of beta-naphthylamine manufacture, exposure to it will certainly be increased greatly and the recommended precautions must be taken.

Benzidine

The findings of Case *et al.* (1954) removed any doubt previously held as to the hazard associated with the manufacture of this chemical. No alternative has been found, however, to the use of benzidine in colour manufacture as has been the case with beta-naphthylamine. The hazard is believed to exist after the conversion of hydrazobenzene to benzidine. In some factories, where the reduction of nitrobenzene to hydrazobenzene and the subsequent conversion to benzidine have been entirely separated, no tumours have been recorded amongst men carrying out the reduction process, whilst many tumours have occurred amongst those working on the conversion and isolation of benzidine itself. However, in many cases reduction and conversion are carried on in the same building and, therefore, full-scale precautions are recommended for both. Whether the reduction is effected by zinc dust, sodium amalgam, or electrolytic means, enclosure of all plant items should be aimed at. If it is necessary to isolate the hydrazo compound, enclosed types of filter should be used. The conversion vessel should be totally enclosed and dip pot sampling should be avoided. The material should be handled in an enclosed system as a slurry before isolation in an enclosed filter. The distillation of benzidine base and the isolation of the product in solid form as base is liable to result in contamination of the atmosphere with vapour which can be entirely avoided by final isolation as a salt. The final product must be packed with all necessary precautions against dust and skin contact. The salts of benzidine can be absorbed easily through the skin and no refuge must be sought in the suggestion that the salts are less dangerous. Tumours have occurred amongst men handling all the salts and the base in various factories in the world. Isolation of benzidine

as salt, however, avoids almost completely the possibility of vapour contamination but a potential dust and skin hazard still exists.

The isolation of this compound from an open nutsche filter press or any open filter device is dangerous. In the event of the product being manufactured as base, the grinding of the final product as opposed to flaking is strongly deprecated. The best conditions are most likely to be attained with the isolation of the final product as a salt paste but the whizzing of base in an enclosed centrifuge can be performed safely. Special attention must be paid to the provision of protective clothing to the workman lidding drums in this manufacture. If attempts to isolate a very dry paste are made, a dust hazard immediately arises and a user hazard is also created as the packages are difficult to empty safely.

Benzidine Azo Colours

Tumours have occurred amongst a number of men manufacturing azo colours from benzidine. It is interesting and important to note that these benzidine azo colours are the only ones using carcinogenic intermediates made continuously throughout the year. The incidence of tumours amongst azo process men is largely confined to the manufacture of these large-scale benzidine colours. This would result in these particular workmen getting a considerably higher total dose of carcinogen than those employed for short and occasional periods on other work using carcinogens as intermediates.

If benzidine itself is manufactured in a user factory, then there is no doubt that bulk handling of an amine slurry or tetrazo solution is to be preferred to filling and emptying containers. In emptying a package with a shovel in azo manufacture there is no doubt that the clothing will become contaminated. In the case of smaller manufactures where handling drums or casks is inevitable an automatic device can be installed which will wash out the benzidine from the container by high pressure cold water. This can be operated quite safely and the water is used to make the solution for the subsequent tetrazo reaction. It may prove most effective to charge all the benzidine used in an azo shed to one well-protected point using such a device. Subsequently, slurry or tetrazo solution can be pumped to different units as is advocated in the case of factories where benzidine is manufactured within the same works. Great care will be necessary in obtaining samples from such a central source for assessment of the strength of the slurry. An automatic enclosed device should be installed for obtaining such samples without using a dip tin which would drip on the surrounding floor and perhaps splash the man taking the sample. It is not

recommended that batch weights of benzidine should be made up but if this has to be done, full-scale impervious clothing must be worn together with a fresh-air hood.

Tests for residual benzidine in the final product should be made to avoid atmospheric contamination during its drying or grinding.

o-Tolidine, Dianisidine, and Dichlorbenzidine

Although animal experiments on the rat suggest that the homologues and derivatives of benzidine are considerably less carcinogenic than the parent amine, it is felt that in industrial practice the homologues should be treated in a similar fashion to benzidine itself if large amounts are handled. Whereas there are records of men developing tumours who have been exposed to benzidine without its homologues, no population is known which has been exposed to the homologues of benzidine without the parent amine also being manufactured in the same plant.

Thus, in the manufacture of azo colours from o-tolidine, dianisidine, dichlorbenzidine, or benzidine disulphonic acid, an emptying device employing high-pressure water jets should be used for charging these intermediates to the azo vats. Benzidine disulphonic acid is not believed to be a carcinogen.

The final colour should be analyzed to ensure that no free amine is volatilized during drying.

Alpha-naphthylamine

The manufacture of alpha-naphthylamine has been associated with an incidence of tumours of the bladder amongst workers employed on it under poor conditions where very heavy exposure was encountered. Even under these conditions, exposure of five years or more was necessary for a tumour to develop. Statistical evidence suggests that it is of considerably lower potency than benzidine or beta-naphthylamine as a carcinogen in man. The commercial product usually contains about 4% beta-isomer but this level may be higher in some cases. Hazards exist during reduction of alphanitro-naphthalene and distillation and isolation of the final product. Completely enclosed plant should be used for the reduction with special attention paid to the gland of the agitator shaft. Any residue should be transferred through an enclosed system to a vessel where the amine can be completely destroyed. Special devices should be used for obtaining samples in order to ascertain the state of the reduction and the use of a dip pot for obtaining such samples is strongly deprecated. Where large quantities of material are to be handled by the user the final product should be transferred molten in tankers but some flaking will be necessary

for the smaller user. The flaker should be totally enclosed and draughted. Attention to the flaking conditions can increase the size of flake and reduce the amount of fine dust in the final product.

Alpha-naphthylamine Sulphate

This manufacture carries with it not only the risk in the charging of the initial amine, but also the risk of handling the final product. Thus, the charging point should be adequately ventilated to avoid contamination of the general atmosphere with dust or the material can be handled molten in an enclosed system to avoid this hazard completely. The hazard in the filtration and drying of this product is one of skin contact and inspiration of dust. During the drying, vapour will not be given off but dust will collect in the vents from the drying space. A continuous enclosed drier is recommended and the use of any form of tray drying is strongly deprecated.

Alpha-naphthol

Although this chemical is made from alpha-naphthylamine it is not believed to be carcinogenic. Bulk use of molten alpha-naphthylamine in a totally enclosed system to avoid atmospheric contamination is recommended. Analytical estimations of alpha-naphthylamine in the final product should be maintained to ensure its safety.

Naphthionic Acid

There is no evidence to suggest that naphthionic acid itself is carcinogenic but its manufacture involves the handling of alpha-naphthylamine. The amine charging point is the first hazard. In the event of a bulk supply of molten alpha-naphthylamine being available, heated enclosed measure vessels and weigh-scales can be used so that no problem of charging solid alpha-naphthylamine arises. If alpha-naphthylamine flake or alpha-naphthylamine sulphate is used efficient draughting and full protective clothing will be necessary. Alpha-naphthylamine flake packs in the drum on standing so that no automatic emptying device is suitable, and for the same reason it is not suitable for pneumatic handling.

The sulphonation is never quite complete so that the naphthionic acid dust is contaminated with amine. Further, the sulphonation is preferential to the alpha-isomer so that the unsulphonated amine will contain more of the beta-isomer than the original amine charged to the sulphonator. This high proportion of beta-isomer constitutes a very real hazard. During the washing of the acid these amines are present in the liquors together with tar. This tar, contaminated with beta-naphthylamine,

should not be removed in an open vessel or filter press. An enclosed filter with automatic discharge is the most suitable means of purifying naphthionic acid liquors. The recovered amine must be collected in a drum or vessel and either destroyed chemically or disposed of at sea. It is unsafe to use regular amounts of this recovered amine for any other process in the industry.

If a solvent bake process is used, a major problem of distillation of the solvent for use again arises. The recovered amines have to be removed from the still as well as tar. Leakages will contaminate the atmosphere with beta-naphthylamine. A direct run of tar and amines from the still to a muffle furnace for destruction appears to be the most satisfactory method of disposal of these waste products. Full protective clothing is adequate for the subsequent use of naphthionic acid in the dyestuffs industry.

Sodium Naphthionate

This chemical is not thought to be carcinogenic but precautions must be taken to enclose all plant items which contain even a small trace of unsulphonated amine, particularly when they are hot. Equally, all residues from the plant should be handled molten in an enclosed system before disposal or destruction.

Phenyl-alpha-naphthylamine

This secondary amine can be made from alpha-naphthylamine but this involves charging a carcinogen to the phenylation vessel. Furthermore, the condensation with aniline is not complete and free carcinogen in the final product constitutes a hazard in isolation and its subsequent use. All these hazards can be easily eliminated by making phenyl-alpha-naphthylamine from alpha-naphthol. Attention should be paid to the purity of the alpha-naphthol used, as this is made from alpha-naphthylamine and can contain this carcinogen as an impurity. Phenyl-alpha-naphthylamine is not believed to be carcinogenic.

Ethyl-alpha-naphthylamine

This secondary amine can also be made from alpha-naphthylamine, but again this involves charging a carcinogen and also the removal of unreacted starting material. Complete safety can be ensured by making it from alpha-naphthol and monoethylamine. Ethyl-alpha-naphthylamine is not believed to be carcinogenic.

Rubber Chemical Manufacture from Alpha-naphthylamine

Condensates of alpha-naphthylamine and aldehydes have been made as rubber chemicals. The

condensation is never quite complete and their manufacture has been discontinued in Great Britain because of the hazard in manufacture and isolation and the potential hazard of their use in the rubber industry due to the presence of uncondensed carcinogen (Case and Hosker, 1954). Only by the use of a solvent process is it possible to reduce the unreacted amine to negligible quantities, but this involves the hazard of redistilling the solvent and removing the carcinogen therefrom.

Alpha-naphthylamine Condensation Colours

These condensations do not go to completion so that special measures must be taken to remove unreacted carcinogens from the final product. Otherwise these impurities may constitute a hazard in isolation, drying, and grinding of the final colour.

Phenyl-beta-naphthylamine

It is appropriate here to mention phenyl-beta-naphthylamine because it is sometimes suspected owing to its name. It is not made from beta-naphthylamine and is not considered to be carcinogenic. No tumours have been reported amongst the men engaged in its large-scale manufacture in a number of countries for many years.

Alpha-naphthylamine Azo Colours

Where large amounts of alpha-naphthylamine are being used for azo manufacture the bulk handling of molten amine is recommended. With the use of enclosed heated measure vessels, contact with the material is entirely avoided. Where small amounts are handled, efficient exhaust ventilation must be provided at the point where batch weighings are carried out and adequate ventilation provided at the charging point to the azo vat. Some azo reactions are not complete and analytical tests should be carried out to ensure that no free amine is left in the final product. Tumours have occurred amongst a number of persons carrying out colour drying and this is attributed to the vaporization of uncoupled amine during drying. Such a hazard will be passed on to the grinding and standardizing of these colours if unreacted amine is not controlled.

Auramine Manufacture

Although Müller (1933) attributed two cases of bladder tumour to auramine, it was not recognized that an occupational hazard was associated with the manufacture of this substance until the statistical investigations of Case and Pearson (1954) were published. As yet it is impossible to indict any particular part of the process but it is recommended that a review should be made of the handling of all intermediates and the final product in this process;

a generally higher standard of housekeeping and working practice should be instituted. The object should be to cut down contact with all chemicals in the process to a minimum until more specific data on the exact cause of these tumours are available. The possibility must not be overlooked that these tumours may have been due to other chemicals handled in the auramine sheds in the factories where tumours have occurred. Further examination of this possibility would seem to be necessary before carrying out any drastic alterations.

Magenta Manufacture

The finding by Case and Pearson (1954) that a hazard has existed in Great Britain in magenta manufacture falls into line with the German experience in the early days of the chemical industry in that country.

In considering the appropriate protective measures to be taken it must be remembered that no tumours have been attributed to magenta in Germany amongst men starting work later than 1910. A general improvement of working conditions, together with a high standard of chemical handling, have apparently completely eliminated the hazard of this process in German factories without the installation of special totally enclosed plant such as is recommended for the manufacture of benzidine and alpha-naphthylamine. It is not possible to say at this moment whether the cause of the tumours in England is due to intermediates, to impurities in the magenta process, or to the final product itself. It would appear that a general review of working conditions in the manufacture of magenta, with special care to avoid atmospheric contamination and skin contact with chemicals employed in the processes, should result in the complete elimination of this hazard. In view of German experience it is not suggested that the building of special totally enclosed plant is necessary. A high standard of handling of chemicals should be sufficient to produce a result similar to that prevailing in Germany to-day.

Xenylamine (4-Aminodiphenyl)

4-Aminodiphenyl (referred to as xenylamine in the U.S.A.) has never been manufactured in Great Britain because experiments in rats and dogs demonstrated its carcinogenicity before its proposed manufacture (Walpole, Williams, and Roberts, 1952, 1954). Subsequently, Melick Escue, Naryka, Mezera, and Wheeler (1955) confirmed the existence of an industrial hazard in a report of tumours in men engaged in its manufacture in the U.S.A. Its manufacture has been discontinued there and it is recommended that manufacture should not be started in Great Britain. There is also the possibility that a

hazard may also have been associated with the manufacture of 4-nitrodiphenyl due to the reduction in the body of the nitro compound to the corresponding amine.

ASSESSMENT OF RESULTS ACHIEVED BY IMPROVEMENTS

It is most important to ensure that the improvements in plant and working which have been introduced are effective. It must be borne in mind that the chemical industry is always changing and some so-called improvements may open up new sources of contamination.

Butt and Strafford (*loc. cit.*) have established methods of analysis of air, clothing, and liquors for the presence of benzidine and beta-naphthylamine. By their method routine sampling of atmosphere can be achieved at specific points by the use of 24-hour bubblers and spot samples can also be taken where an unusual practice carrying a risk of atmospheric contamination is being carried out. Similarly, atmospheric sampling is recommended for any other compounds which are thought to be suspect in any of the processes considered in this report. Analysis of clothing for contamination with carcinogens can also be used as an additional check on safe working as well as a means of ensuring the efficacy of laundering. The maximum concentration of carcinogen allowable in the air or on clothing which can be regarded as completely safe is not known and these tests are recommended as a means of assessing the efficiency of preventive measures or of giving warning of a process defect which is not otherwise obvious.

An additional check is afforded by the examination of the urine of workers for the presence of excess amines. Methods have been described by Kuchenbecker (1920) and by Glassman and Meigs (1951). High amine content in urine may indicate absorption due to unsatisfactory operating technique, accidental contamination, or dirty working.

CONCLUSIONS

The above recommendations have been made in the belief that if they are implemented the incidence of bladder tumours in workers in these processes will be reduced to a level no greater than that which prevails in the general population. Although this report incorporates the precautions which are thought to be necessary in the light of present-day knowledge, it must be realized that, as our knowledge of this hazard increases, further amendments and additions may become necessary as, for instance, when new chemicals or processes come into use or when other sources of hazard hitherto undetected become apparent.

It is hoped that the recommendations contained in this report will be carried out by the industry as soon as is practicable, but it must be remembered that the benefits to be reaped will not necessarily be visible for many years to come.

SUMMARY

Safe methods of working practice recommended to the Association of British Chemical Manufacturers for the manufacture and use of chemical compounds likely to induce tumours of the bladder are described. The present position of knowledge of industrial bladder tumours in Great Britain is given and the data from which the recommendations have been derived are detailed.

Medical supervision is essential to ensure proper control of the hazard. Desiderata for selection and education of the workers and for their personal protection are laid down. The need for maintaining accurate medical and industrial records is stressed. Limitation of exposure and of the number of men at risk should lessen the possible incidence. The early diagnosis, treatment, and follow-up of established cases of tumour are imperative.

Design and ventilation of buildings and plant are of primary importance. Completely enclosed plant with the carcinogens totally contained in the system is the ideal. The isolation, sampling, weighing, distilling, drying, grinding, or packaging of products and the disposal of residues can all be dangerous and measures to prevent contamination of the operators are recommended. Maintenance and cleaning of buildings, plant, and plant items can lead to serious exposure and men engaged in these operations must also be protected.

Detailed consideration of the manufacture and use of each relevant compound is presented. The dangers associated with each are pointed out and specific precautionary measures are given in detail in each case.

Beta-naphthylamine and 4-aminodiphenyl (xenylamine) should not be manufactured as no safe economical method can be devised. Safer alternatives which have been developed should be applied.

Benzidine should be manufactured in a closed system. The base and the salts are all dangerous and bulk handling as a slurry or as tetrazo solution is preferred in user factories.

The homologues and derivatives of benzidine are considered to be less carcinogenic than the parent amine but if large amounts are involved, they should be treated with equal care.

Alpha-naphthylamine should be manufactured in a closed system and bulk handling of molten amine in enclosed containers or tankers is the safest method for the large user.

The possible hazards associated with the manufacture of certain other compounds, not themselves believed to be carcinogenic, such as alpha-naphthol, naphthionic acid, sodium naphthionate, several secondary amines, and some condensation colours from the naphthylamines are considered. Aniline and phenyl-beta-naphthylamine are not accepted as causes of bladder tumours.

The hazard associated with auramine and magenta is examined.

Estimations of amine in atmosphere, on the clothing, and in the urine of workers can be used to assess the degree of contamination and absorption and the efficiency of preventive measures.

Other dangers not yet recognized may come to light and new compounds or processes may create new sources of risk in the future.

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