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Review Article

Bladder Chemical Carcinogens in the Workplace

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Michel Hery[1]

1. Independent researcher

Exposure to certain chemicals in the workplace increases the risk of developing bladder cancer. Depending on the study, between 5 and 25% of these cancers could be due to this type of exposure. So there's a real public health issue to be tackled when it comes to preventing these risks. Raising awareness among employers and workers may mean recognising these cancers as occupational diseases. The aim of this article is to provide a number of data on the basis of which such an approach can be developed.

Correspondence: papers@team.qeios.com — Qeios will forward to the authors

1. Introduction

According to the International Agency for Research on Cancer (IARC), bladder cancer is the ninth most common type of cancer worldwide. In 2022, more than 600,000 people worldwide were diagnosed with bladder cancer and more than 220,000 died from the disease. Bladder cancer is one of the most difficult and costly cancers to diagnose and treat[1]. The role of smoking, nutritional factors, radiation and infectious factors in the development of this cancer has been widely documented[2]. The influence of occupational exposure has also been shown in several studies, although estimates of the number of bladder cancers linked to occupational exposure vary widely: from around 5% in a multicentre European epidemiological study[3] limited strictly to the workplace, to 20% in studies considering both occupational and environmental exposure[4].

However, the indisputable role of smoking and the lack of knowledge among general practitioners and specialists about the working conditions of sufferers have had the effect of crushing awareness of the importance of occupational exposure in the aetiology of the disease. However, in the 2000s in France, a specific Social Security initiative carried out in one region (Normandy), which brought together doctors and occupational hygienists with a good knowledge of working conditions and occupational exposure, revealed that 15% of bladder cancer victims had been exposed to bladder carcinogens during their working lives[5]. As a result, these patients were able to file a claim for occupational disease and compensation. Given the region's industrial profile, with a major oil and petrochemical industry and significant activities in the dyes and rubber sectors, it would be risky to extrapolate these figures to the whole of France, but they do show the significant influence that work can have on the onset of disease.

The aim of this article is to help inform doctors, workers, trade unions, patients' associations and, more generally, all those who may be involved in the process of declaring an occupational disease, by providing them with data that can be used in their arguments. These ideas have been developed on the basis of the French example, but can very likely be used in a wider geographical context: certainly at European level, but also in many other countries. It also tries to take into account factors that aggravate exposure linked to work organisation (type of job held, employment status, etc.).

It is very often difficult to obtain recognition of occupational diseases, so in this article we will confine ourselves to those exposures that are most likely to be recognised in the context of medico-legal proceedings.

2. A wide variety of aetiological agents encountered in the workplace

Since the end of the 19th century, several families of chemical compounds, listed below, have been identified as likely to cause bladder cancer:

2.1. Aromatic amines

These synthetic products have had many uses in numerous industrial sectors. These include, of course, the dye industry, which in turn has been used in a wide range of production activities (textiles, leather, paper, inks, paints, etc.)[6]. Benzidine, for example, was widely used from the nineteenth century until it was banned (except for very limited uses) in 1988, leading to numerous cases of bladder (and pancreatic) cancer.

But other aromatic amines, known or suspected carcinogens, have been used (and some still are) as vulcanisation accelerators in the rubber industry or as cross-linking agents for plastics[7].

The cosmetics industry also uses aromatic amines. A number of them have been banned over the years, particularly in the 1990s, and most of them had seen their use decline over the years[8]. Other amines continue to be used: the question of their capacity to release toxic compounds (some of which could be potentially carcinogenic) is regularly raised. Over the years, the toxicity of some of them has been revised upwards. Given the inability to carry out exhaustive research into the toxicity of all aromatic amines within a reasonable timeframe, it would seem advisable to limit their use as much as possible. This precautionary measure is all the more important given that they often penetrate the skin to a high degree.

Some products, including pesticides, are likely to break down in the body and give rise to aromatic amine metabolites.

2.2. Polycyclic aromatic hydrocarbons (PAHs)

These compounds are found systematically in coal products, petroleum products, combustion residues and also in the degradation products of organic compounds at temperatures above 500°C. This term covers a large number of molecules which have in common the fact that they are made up of at least two condensed aromatic rings[9].

Their physico-chemical and toxicological properties vary widely: some molecules are powerful carcinogens, others are only suspected of being carcinogenic, while others appear to have no such properties. On the other hand, they are always present together in tars, bitumens, pitches and combustion products, in varying proportions depending on the product. These mixtures must therefore be considered as containing carcinogens, but in highly variable concentrations depending on their origin or their physical state at the time[10]. Their toxicity is generally estimated on the basis of their benzo[a]pyrene content, a very powerful carcinogen. The switch from coal-based products to petroleum-based products represented a major advance in occupational risk prevention, as the latter are much less rich in PAHs.

These pollutants are present in a large number of industrial sectors:

- Iron and steel industries and foundries: coking plants, blast furnaces, steelworks, foundries, electrometallurgy;
- Metal machining using whole oils;
- Construction (sealing surfaces, especially roofs; concrete demoulding) and public works (road surfacing);
- Rubber industry (upstream of vulcanisation);
- Application of anti-corrosion products;
- etc.

These applications involve a wide range of materials: clogging compounds, refractory bricks, resins for making bricks and cores, carbon electrodes bonded to coal tar pitch, tar/bitumen and fluxing oils, machining oils and their degradation products, and so on. The methods of use are therefore very different. However, exposure can also occur in circumstances where the product is not an industrial product, such as for fire-fighters during fire-fighting or during surveillance operations after the fire has been extinguished.

Exposure can occur via the respiratory route or by ingestion, but also very significantly via the cutaneous route[11].

2.3. Nitrosamines

These compounds have long gone unnoticed because of the analytical difficulties involved in identifying and measuring them. They result from the chemical reaction between a secondary amine and nitrosating compounds (e.g. nitrogen oxides in the atmosphere which may come from diesel engines, or nitrites in solution used to prevent the development of bacteria in machining fluids).

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In animal experiments, most nitrosamines have shown carcinogenic properties in various organs[12].

Their presence has been demonstrated in various industrial sectors:

- In the rubber industry, where they are likely to be formed from vulcanisation accelerators supplying the necessary amines;
- In the tyre industry;
- In metal machining, where nitrosamines can be formed in aqueous cutting fluids by the reaction between secondary amines (diethanolamine, morpholine, etc.) and nitrites or nitro compounds;
- In foundries;
- In the food industry: smoked fish, fish meal, meat curing and smoking.

2.4. Chlorinated solvents

Several epidemiological studies link exposure to tetrachloroethylene (perchloroethylene) and bladder cancer. The same is true of trichloroethylene and kidney cancer. For other chlorinated solvents (isomers of tetrachloroethane, di- and trichloroacetic acids), while the level of evidence is insufficient in humans, it is proven in animals. Dichloromethane is considered by the International Agency for Research on Cancer (IARC) to be ‘possibly carcinogenic in humans’[13].

These products have mainly been used as solvents in sectors as diverse as metal degreasing and dry cleaning, but also for a variety of other uses involving smaller volumes (building paint, mechanical engineering, etc.). Given the environmental and occupational health problems they pose, they have been the subject of more or less advanced substitution measures. In order to identify work-related cancers, we need to be alert as soon as the use of these products is documented.

3. Today's occupational cancers are the result of yesterday's exposures ... but also the legacy of the past and the emergence of new exposing activities

In many industrial sectors, awareness has been raised and occupational exposure has fallen sharply in recent decades. However, we must be aware that today's occupational cancers, and bladder cancers in particular, are the result of exposure that may have occurred twenty or thirty years ago, when working conditions may have exposed workers to higher concentrations of pollutants than today. In certain industrial sectors (the rubber industry, metalworking), workers may also have been exposed simultaneously to several compounds likely to cause bladder cancer, or to a bladder carcinogen and other carcinogens likely to affect other organs. Little is known about these ‘cocktail effects’ and they have not been well documented[14]: it is reasonable to wonder about their role in the occurrence of cancers whose location may vary.

3.1. Progress in occupational risk prevention: banning or substitution of certain products, improvement in exposure levels, etc.

Numerous preventive measures have been taken in recent decades. For example, coal products have been replaced by petroleum products, which contain far fewer PAHs. Measures have also been taken to regularly monitor the concentrations of carcinogenic compounds in products: for example, in the case of machining fluids, PAH concentrations increase with the use of the product, and in the case of other types of machining fluids, the absence of nitrites is monitored to prevent the formation of nitrosamines. Similarly, the rubber and tyre industries have implemented substitution measures to avoid exposure to aromatic amines and nitrosamines. It is beyond the scope of a short article such as this to give a more precise description of this reduction in exposure, which is quantified in an estimate by P. Goutet[15].

3.2. The strong influence of working conditions and employment status on occupational exposure

As we have seen, there has been a clear improvement in exposure conditions in traditional industries. However, it is important to remain realistic: not all companies are moving at the same pace, and gains are not uniform within the same sector of activity. What's more, some tasks are still more exposed than others: often maintenance, cleaning, and sometimes packaging of finished products. This inequality in terms of exposure is often reinforced by the status of the workers performing these tasks: they often belong to subcontracting companies and do not always benefit from protection as effective as that available to workers from the company managing the site. In terms of recognition of occupational disease, these are also workers whose exposure may be difficult to reconstruct, as it is less well documented in a large number, sometimes very large number, of different

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companies[16][17]: there is a real inequality here in the medico-legal possibilities for compensation for the harm suffered, linked to the worker's status. While the recognition process is arduous for permanent jobs in permanent structures, it often becomes impossible for workers who regularly change workplace and professional environment.

3.3. Exposure may appear with changes in manufacturing processes

The opinion that exposure to bladder carcinogens has disappeared in recent decades is fairly widespread. As we saw earlier, knowledge of the bladder carcinogenicity of certain molecules is fairly recent. Recent periods (around 2000) have also seen the appearance or modification of new activities or processes such as cementation furnaces[18], the manufacture of carbon disks[19] or clay pigeons, which have resulted in new exposures (particularly through percutaneous contact) to PAHs[20]: it would therefore be wrong to consider that exposure to bladder carcinogens is a thing of the past and that occupational causes are becoming negligible.

Similarly, work on public works sites or during the removal of tar coatings (very rich in PAHs) laid several decades ago can lead to high levels of exposure[21]. Work on a drinking water network whose pipes had been coated with an anti-corrosion varnish based on coal tar pitch generated very high levels of exposure, particularly when carried out in enclosed spaces[22]. Various studies have also shown that the banning of certain products in France does not prevent their presence. For example, an investigation by Unitex (a textile trade association) revealed the presence of azo dyes in imported fabrics, in concentrations sometimes thirty times higher than authorised. These dyes, which are poorly fixed, are likely to release aromatic amines that are carcinogenic or suspected of being carcinogenic[23]. In a context of free trade and self-monitoring of product quality, this type of problem is likely to occur quite often before it is detected. When it is... A similar problem has been highlighted with the use of a cleaning cream containing an alkaline reducer on stains caused by azo dyes, with the same release of amines (benzidine, dichloroaniline)[24].

4. Conclusion: A need for vigilance

As we have seen, the identification of the occupational component in the occurrence of bladder cancer in France is highly inadequate. Despite the progress that has been made in preventing exposure to these pollutants, there is every reason to believe that a certain number of current diseases are due to exposure that occurred twenty or thirty years ago, but also more recently, as new exposure circumstances have emerged. Urologists can also refer patients to associations for the defence of work-related victims.

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