Special Report: Policy

Carcinogenicity of some aromatic amines, organic dyes, and related exposures

Upcoming meetings
June 17–20, 2008
Advisory group to recommend priorities for IARC monographs
October 14–21, 2008
Pharmaceuticals (meeting A of the Volume-100 series)
http://monographs.iarc.fr/

In February, 2008, 17 scientists from seven countries met at the International Agency for Research on Cancer (IARC), Lyon, France, to reassess the carcinogenicity of some aromatic amines and organic dyes. Additionally, occupational exposures of hairdressers and barbers and exposure from personal use of hair colourants were reviewed. These assessments will be published as volume 99 of the IARC Monographs.[1]

Some aromatic amines have long been known to cause bladder cancer in human beings, and several others are suspected of being carcinogenic. Aromatic amines also cause bladder cancer whenever they are tested in dogs. The Working Group identified several additional aromatic amines that are carcinogenic to human beings.

ortho-Toluidine is used in the production of dyes, pigments, and rubber chemicals, and as a biological stain. It is present in the urine of most people, but its origin remains unknown. In patients treated with the anaesthetic prilocaine, *ortho*-toluidine was detected in urine as a metabolite. Occupational exposure occurs mainly via dermal contact, and occupational cohort studies have reported greatly increased risks of bladder cancer, which could not be explained by smoking. In two of these studies,[2,3] known bladder carcinogens were present only in trace amounts and the highest risk of bladder cancer was noted in the subgroup with the longest duration of exposure. Furthermore, *ortho*-toluidine-haemoglobin adducts have been identified in exposed workers,[4] as well as in patients treated with prilocaine.[5] *ortho*-Toluidine also causes tumours at many sites in rodents, including bladder tumours in female rats. *ortho*-Toluidine was classified as "carcinogenic to humans" (Group 1).[6]

4-Chloro-*ortho*-toluidine, which is used in the production of organic dyes and is a known metabolite of the insecticide chlordimeform, was reaffirmed as "probably carcinogenic to humans" (Group 2A)[6] on the basis of limited evidence of carcinogenicity in human beings and sufficient evidence in laboratory animals.

4,4′-Methylenebis(chloroaniline) (MOCA) is widely used as a curing agent in the polyurethane industry. Occupational exposure in industries that manufacture or use MOCA occurs mainly via dermal absorption. MOCA causes tumours at many sites in mice and rats and bladder tumours in dogs, and is also genotoxic in many in-vitro test systems. Bioactivation of MOCA by *N*-oxidation produces metabolites that form adducts with DNA and haemoglobin.[7] DNA adducts were detected in the urothelial cells of one heavily exposed worker.[8] Additionally, MOCA causes the formation of sister chromatid exchange in lymphocytes[9] and micronuclei in urothelial cells and lymphocytes of exposed people.[10] Overall, the toxicological profile of MOCA is similar to that of monocyclic aromatic amines, such as *ortho*-toluidine. On the basis of these considerations, the Working Group classified MOCA as "carcinogenic to humans" (Group 1).[6]

Benzidine-based dyes are used mainly for colouring paper, textiles, and leather. The production of these dyes is banned in most developed countries, but they are still produced in and imported from other countries. Because benzidine is known to cause bladder cancer in human beings,[11] there is concern that benzidine-based dyes would pose a similar cancer hazard. Indeed, these dyes are known to be metabolised to benzidine, because free benzidine and benzidine conjugates have been measured in the urine of workers exposed to these dyes, generally in higher concentrations than could be explained by the small amounts of residual benzidine present in the dyes.[12] Studies in rhesus monkeys, dogs, hamsters, and rats exposed to benzidine-based dyes consistently showed the presence of free or acetylated benzidine in the urine, in some cases in near-equimolar concentrations.[13,14] Azoreductase activity, responsible for cleavage of the azolinkage of the dye, has been shown in anaerobic bacteria in the intestine of mice, rats, and human beings,[15,16] in human skin bacteria,[17] and in human liver.[18] On the basis of these data, the Working Group concluded that dyes metabolised to benzidine are "carcinogenic to humans" (Group 1).[6]

The Working Group reaffirmed the carcinogenicity of benzidine, 4-aminobiphenyl, and 2-naphthylamine, identifying each as "carcinogenic to humans" (Group 1),[6] and as a known cause of bladder cancer in human beings. The Working Group also reaffirmed magenta production (where *ortho*-toluidine is used as an intermediate) and auramine production as "carcinogenic to humans" (Group 1)[6] and as known causes of bladder cancer.[19] Magenta, technical-grade auramine, Michler's base (an intermediate in auramine production), and Michler's ketone (a hydrolysis product of auramine) all cause tumours at many sites in rodents and were classified as "possibly carcinogenic to humans" (Group 2B).[6]

Modern hair dyes are classified as permanent, semipermanent, or temporary dyes. The permanent (or oxidative) hair dyes represent about 80% of the market and consist of colourless primary intermediates (para-substituted aromatic amines) and

couplers (meta-substituted aromatic amines and others) that, in the presence of peroxide, form the dye by a chemical reaction. Dark hair dyes tend to contain the highest concentrations of the colouring ingredients. As a result of positive findings in rodent carcinogenicity assays, the use of some colouring ingredients was discontinued in the 1970s.

Many new epidemiological studies on cancer in hairdressers, barbers, and beauticians have been published since the last IARC assessment. A small, but consistent, increase in the risk of bladder cancer was reported in male hairdressers and barbers. Because of few supporting findings by duration or period of exposure, the Working Group considered these data as limited evidence of carcinogenicity and re-affirmed occupational exposures of hairdressers and barbers as "probably carcinogenic to humans" (Group 2A).[6]

The Working Group also reviewed the epidemiological evidence on personal use of hair dyes with respect to cancer at several sites, on the basis of data from developed countries. For bladder cancer, the findings from cohort and case–control studies were inconsistent. One case–control study from the USA[20] suggested a possible association between personal use of permanent hair dyes and the risk of bladder cancer, which was stronger for slow acetylators. However, a recent study from Spain,[21] which had a similar study design, did not corroborate these findings. With regards to haematological malignancies, several independent studies showed modest increases in risk for different subgroups of lymphomas and leukaemias. In some of these studies, the increased risk became significant after stratification for permanent hair-dye use, hair-dye use starting before 1980, longer duration of use, or use of dark-coloured hair dyes. However, no consistent pattern emerged for a specific subgroup of lymphoma or leukaemia or by exposure strata. A recent pooled analysis[22] showed a 10% increase in relative risk of non-Hodgkin lymphoma (NHL) in women for ever-use of hair dyes and a 30% increase in women who started using hair dyes before 1980, compared with non-users. After stratification by NHL subtype, the relative risk was 1·4 for follicular lymphoma and 1·5 for chronic lymphocytic leukaemia and small lymphocytic lymphoma. No clear pattern by type of dye (dark *vs* light or permanent *vs* semi-permanent), period of use, or duration of use was noted.

The Working Group considered the epidemiological evidence inadequate, and concluded that personal use of hair colourants is "not classifiable as to its carcinogenicity to humans" (Group 3).[6]

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The IARC authors declared no conflicts of interest.

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None

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