Carcinogenicity of some nitrobenzenes and other industrial chemicals

In October, 2018, 14 experts from six countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to finalise their evaluation of the carcinogenicity of *ortho*-phenylenediamine and its dihydrochloride salt, 2-chloronitrobenzene, 4-chloronitrobenzene, 1,4-dichloro-2-nitrobenzene, 2,4-dichloro-1-nitrobenzene, 2-amino-4-chlorophenol, *para*-nitroanisole, and *N,N*-dimethylacetamide. These assessments will be published in Volume 123 of the IARC Monographs.[1]

Few quantitative data were available to characterise exposure in the workplace or general population, but occupational exposure is expected during production and use of these compounds via inhalation, skin contact (the primary exposure route for *N,N*-dimethylacetamide), or inadvertent ingestion. Drinking water and some consumer products might contain residues of some of these agents. All of the agents were classified as "possibly carcinogenic to humans" (Group 2B), on the basis of "sufficient evidence of carcinogenicity in experimental animals" and no data or "inadequate evidence" in humans. For most agents, mechanistic data were sparse.

Ortho-phenylenediamine is the parent compound of *ortho*-phenylenediamine dihydrochloride. A pH-dependent acid–base equilibrium exists between the two compounds, and the Working Group considered that in-vivo studies on either compound were informative about the carcinogenic hazard of both. *Ortho*-phenylenediamine is used in the production of agrochemicals and pharmaceuticals, and dyes and pigments used for colouring hair and furs. *Ortho*-phenylenediamine dihydrochloride is used in the manufacture of dyes, coatings, and photographic chemicals. The general population can be exposed via hair dyes (although the use of *ortho*-phenylenediamine in hair dyes has been banned in the European Union since 2007) and other products containing these agents. In rodent studies, drinking water exposure to *ortho*-phenylenediamine (tested as its dihydrochloride)[2] increased the incidence of hepatocellular adenoma (HCA) in male and female rodents, of both HCA and hepatocellular carcinoma (HCC) combined in male mice, of HCC in female mice and male and female rats, of urinary bladder transitional cell papilloma and carcinoma in male rats, and of gall bladder papillary adenoma in male and female mice. In other studies, dietary administration of *ortho*-phenylenediamine dihydrochloride[3] increased the incidence of HCC in male and female mice and male rats.

No toxicokinetic data were available about *ortho*-phenylenediamine or its dihydrochloride, nor were there mechanistic studies in which *ortho*-phenylenediamine dihydrochloride was administered. In rodents, *ortho*-phenylenediamine and its dihydrochloride produced toxicity in the haematological, hepatic, and renal systems, target organs of toxicity common to 2- and 4-chloronitrobenzene, and 1,4- and 2,4-dichloro-1-nitrobenzene. Strong evidence suggested that *ortho*-phenylenediamine is genotoxic according to positive results in mammals, mammalian cells in vitro, plants, and prokaryotes.

2-Chloronitrobenzene is used to make colourants and various other chemicals; downstream uses include lumber preservatives, corrosion inhibitors, pigments, and agricultural chemicals. 4-Chloronitrobenzene is used in the production of agricultural chemicals, pharmaceuticals, paints, pigments, colourants, plastics, and paper, and in the treatment of textiles and leather. 2-Chloronitrobenzene and 4-chloronitrobenzene have been detected at low levels in edible fish. 2-Chloronitrobenzene and 4-chloronitrobenzene have been measured in workplace air in chemical factories, and urinary metabolites of 4-chloronitrobenzene have been detected in factory workers. Haemoglobin adducts and *N*-2-hydroxy-chloroaniline and *N*-4-hydroxy-chloroaniline—metabolites of 2-chloronitrobenzene and 4-chloronitrobenzene, respectively—have been detected in human blood. Methaemoglobinaemia was seen in humans exposed to 4-chloronitrobenzene. In rats, 2-chloronitrobenzene and 4-chloronitrobenzene are absorbed, widely distributed to tissues, and excreted as metabolites in urine and faeces.

Administration of 2-chloronitrobenzene in the diet[3,4] increased the incidence of HCA, HCC, and hepatoblastoma in one study in male and female mice; of HCC in another study in male and female mice; of HCA, HCC, and renal cell carcinoma in one study in male rats; and of HCA and HCC in one study in female rats. In a study in mice, diet containing 4-chloronitrobenzene[5] increased the incidence of HCC and malignant lymphoma in male mice, and of HCC and liver haemangiosarcoma in female mice. In another study,[3] dietary administration of 4-chloronitrobenzene increased the incidence of HCC in male mice, and of vascular tumours in male and female mice. Dietary administration of 4-chloronitrobenzene[5] increased the incidences of malignant splenic tumours (eg, fibrosarcoma, osteosarcoma, and haemangiosarcoma) in both male and female rats.

1,4-Dichloro-2-nitrobenzene and 2,4-dichloro-1-nitrobenzene are intermediates in the manufacture

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Upcoming meetings
Nov 12–14, 2018: Advisory Group to recommend an update to the Preamble
March 25–27, 2019: Advisory Group to recommend priorities for the IARC Monographs during 2020–2024
June 4–11, 2019, Volume 124: Shift work that involves circadian disruption

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Declaration of interests
J W Cherrie did some consulting work for the Italian oil company ENI (owner of ENICHEM-Fibre, a company that uses N,N-dimethylacetamide). The work lasted 10–15 days and was in relation to a criminal court case linked to asbestos exposure of workers in a refinery. The income from the work was paid directly to his university, he did not personally benefit from the work, and the consultancy was unrelated to dimethylacetamide or ENICHEM-Fibre. All other working group members declare no competing interests.

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None

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Declaration of interests
All representatives declare no competing interests.

Observer
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Declaration of interests
J O'Connor is employed by DuPont, a company that uses one of the chemicals under discussion (*N,N*-dimethylacetamide), which is used in the manufacture of some DuPont products. DuPont covered the cost of his attendance at the meeting and pays him a salary/benefits as part of his employment.

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For the **Preamble to the IARC Monographs** see http://monographs.iarc.fr/ENG/Preamble/index.php

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of diazo pigments, agrochemicals, ultraviolet absorbents, and pharmaceuticals. In rodents, dietary administration of 1,4-dichloro-2-nitrobenzene[6] increased the incidence of HCA, HCC, and hepatoblastoma in male and female mice, and of Zymbal gland adenoma, HCA, HCC, and renal cell adenoma or carcinoma (combined) in male rats. Diets containing 2,4-dichloro-1-nitrobenzene[7] increased the incidence of HCA, HCC, hepatoblastoma, and peritoneal haemangiosarcoma in male and female mice, of renal cell adenoma and carcinoma in male and female rats, and of preputial gland adenoma in male rats. 1,4-Dichloro-2-nitrobenzene increased the incidence of proximal tubule hyaline droplets and granular casts in male rats, and male and female rats fed 2,4-dichloro-1-nitrobenzene developed atypical hyperplasia and chronic progressive nephropathy. Neither compound satisfied the seven IARC criteria[8] for an α_{2u}-globulin-associated tumorigenic response.

2-Amino-4-chlorophenol is used in the manufacture of dyes used in textiles and other consumer products (although it is banned for use in hair dyes in several countries), and in the manufacture of pharmaceuticals. In rodents, dietary administration of 2-amino-4-chlorophenol[9,10] increased the incidence of forestomach squamous cell papilloma in male and female mice, of forestomach squamous cell papilloma and carcinoma in male and female rats, and of urinary bladder transitional cell carcinoma in male rats. Methaemoglobinaemia was reported in exposed workers and in chronically exposed rats. There is weak evidence that 2-amino-4-chlorophenol is genotoxic, including some positive results in vitro, thus the relevance of the observed forestomach tumours to humans[11] could not be ruled out.

Para-nitroanisole is a nitrobenzene that is used in the manufacture of synthetic dyes used for cosmetics and other consumer products. In rodents, dietary administration of *para*-nitroanisole[12,13] increased the incidence of HCA in female mice, of HCC and hepatoblastoma in male and female mice, of uterine adenocarcinoma in female rats, and of HCA in male and female rats. In humans and rodents, *para*-nitroanisole is metabolised rapidly to *para*-nitrophenol, followed by catechol formation, conjugation, and excretion. *Para*-nitroanisole induced chronic progressive nephropathy in male and female rats, and hepatotoxicity in male and female mice.

N,N-Dimethylacetamide is used in the manufacture of textile fibres, agrochemicals, pharmaceuticals, fine chemicals, coatings and films, and as a solvent for resins. *N,N*-Dimethylacetamide and its metabolites have been measured in workplace air and in urine of workers employed in synthetic-fibre production facilities. One epidemiological study that assessed cancer mortality related to *N,N*-dimethylacetamide exposure, with various limitations, was considered inadequate for the evaluation of carcinogenicity in humans. *N,N*-Dimethylacetamide is absorbed from the skin, lungs, and gastrointestinal tract, and its metabolites include acetamide. *N,N*-Dimethylacetamide induced hepatotoxicity in humans and in rodents. In inhalation studies,[14,15] *N,N*-dimethylacetamide increased the incidence of HCA in male and female mice and male rats, and of HCC in female mice and male rats.

IARC Monographs Vol 123 Group
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