



**SOME NITROBENZENES
AND OTHER INDUSTRIAL
CHEMICALS**

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**IARC MONOGRAPHS
ON THE EVALUATION
OF CARCINOGENIC RISKS
TO HUMANS**

GENERAL REMARKS

This one-hundred-and-twenty-third volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of several industrial chemicals to which workers or the general population are or can potentially be exposed. They include: *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 chemicals were recommended for evaluation primarily because new studies of cancer in experimental animals had become available. Epidemiological data for each of the chemicals included in the present volume were either lacking or scant. Mechanistic data were sparse for most of these chemicals, and did not alter the overall evaluations for any agent. 2-Chloronitrobenzene and 4-chloronitrobenzene were both previously evaluated as *not classifiable as to its carcinogenicity to humans* (Group 3) by the Working Group in Volume 65 of the *IARC Monographs* ([IARC, 1996](#)); new data that have become available since these evaluations have been included and considered in the present volume. The other chemicals considered in the present volume have not been previously evaluated by the Working Group. A summary of the findings of this volume appears in *The Lancet Oncology* ([Van den Berg et al., 2018](#)).

Limitations on data on production and use, and quantification and relative contributions of sources of exposure

Despite the fact that seven of the agents evaluated (*ortho*-phenylenediamine, 2-chloronitrobenzene, 4-chloronitrobenzene, 1,4-dichloro-2-nitrobenzene, 2,4-dichloro-1-nitrobenzene, *para*-nitroanisole, and *N,N*-dimethylacetamide) are “high production volume” chemicals, few quantitative data were available to characterize exposure in the workplace or general population. Occupational exposure is expected during production and use 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.

The Working Group particularly noted the poor information available on production and use of, and exposures to these chemicals in workers or in other populations in low- and middle-income countries (especially India and

China). Regarding production and use, data are not generally available in the peer-reviewed literature because of the barriers of language and unfamiliarity with systems for regulating chemicals and recording such data. There are few researchers from low- and middle-income countries publishing data on occupational and environmental exposure to chemicals.

Common effects for structurally related chloronitrobenzenes

Four of the chemicals evaluated in this volume were structurally related chloronitrobenzenes: 2-chloronitrobenzene, 4-chloronitrobenzene, 1,4-dichloro-2-nitrobenzene, and 2,4-dichloro-1-nitrobenzene. Both similarities and differences were observed in the major toxicological and carcinogenic effects induced by these related compounds. For all four chemicals, hepatocarcinogenicity, hepatotoxicity, and haematotoxicity were observed in rats and mice, and renal toxicity was seen in rats. For 2-chloronitrobenzene and the dichloronitrobenzenes, renal carcinogenicity in rats was also apparent, and hepatocarcinogenicity in mice was characterized by the induction of hepatoblastoma.

2-Chloronitrobenzene appeared to be the most potent hepatotoxicant of the agents considered, while 4-chloronitrobenzene was a potent haematotoxicant, and also induced malignant splenic tumours (e.g. fibrosarcoma, osteosarcoma, and haemangiosarcoma) in rats and liver haemangiosarcoma in mice. 2,4-Dichloro-1-nitrobenzene caused peritoneal haemangiosarcomas in mice.

High-throughput screening data

Of the compounds considered, all except *para*-nitroanisole have been evaluated in at least some of the high-throughput screening assays of the United States Environmental Protection Agency and National Institutes of Health ([EPA, 2018](#)). In addition, assay results were available for several key metabolites of these compounds. Data obtained from high-throughput screening have certain strengths, and may provide additional evidence to support mechanistic conclusions made on the basis of other types of assay. However, there are limitations to the applicability and utility of such data for the evaluations made by the *IARC Monographs Working Group* (see also [Chiu et al., 2018](#); [Guyton et al., 2018](#)), including that xenobiotic metabolism in these assays is lacking or poor (and uncharacterized), restricting observations primarily to effects elicited by the parent compounds. In addition, for compounds of lower relative molecular mass it may be difficult to attain the concentrations required for bioactivity in these assays ([Hopkins, et al., 2004](#)); four of the compounds evaluated by the present Working Group (*N,N*-dimethylacetamide, *para*-nitroanisole, *ortho*-phenylenediamine, and 2-amino-4-chlorophenol) have a relative molecular mass of less than 150, with that of the other compounds being slightly above. Furthermore, these large-scale screening programmes were designed to aid prioritization of large chemical libraries for additional toxicity testing rather than to identify the hazards of a specific chemical or chemical group. Thus, presenting the data for all agents under evaluation in one place, as is done in the first monograph of this volume, is useful as it facilitates comparisons. However, in addressing the strength of mechanistic evidence for individual agents, it may be useful to consider the results of high-throughput screening assays in the context of the sensitivity and specificity of

other available in vitro and in vivo assays relevant to the key characteristics of carcinogens.

High-throughput screening results are currently presented as active assay end-points mapped to key characteristics of carcinogens (see Table 4.4 of the monograph on 2-chloronitrobenzene). However, experimental coverage is not consistent across agents or within key characteristics of carcinogens (Chiu et al., 2018). Gaps were significant for the agents evaluated in the present volume; for five of the agents, data were available for only 54 of the 229 assay end-points mapped to the key characteristics (see Table 4.4, and supplementary information available in Annex 1). There was also variability in coverage across assays (the experimental unit), the platform (the type of assay), and the cell type; these factors may contribute to the activity patterns seen. For example, for the 225 assay end-point results available for *ortho*-phenylenediamine, the data spanned 70 individual experiments (assays) performed on eight different platforms in various cell types. Most results were from assays performed across six primary human cell cultures and a number of immortalized human cell lines (including kidney, cervix, ovary, pituitary, intestinal, liver, and breast cell lines), with a few other results from a Chinese hamster ovary cell line (CHO-K1), or from a cell-free platform. Analyses that move beyond counts (or ratios of counts) of active assay end-points may aid further characterization of the variability associated with individual experiments, cell type, and platform. This may also aid in determining whether and when individual or nested high-throughput screening assay results can be more fully integrated with other in vitro and in vivo assays typically evaluated within the section on mechanistic evidence, Section 4, of each monograph.

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