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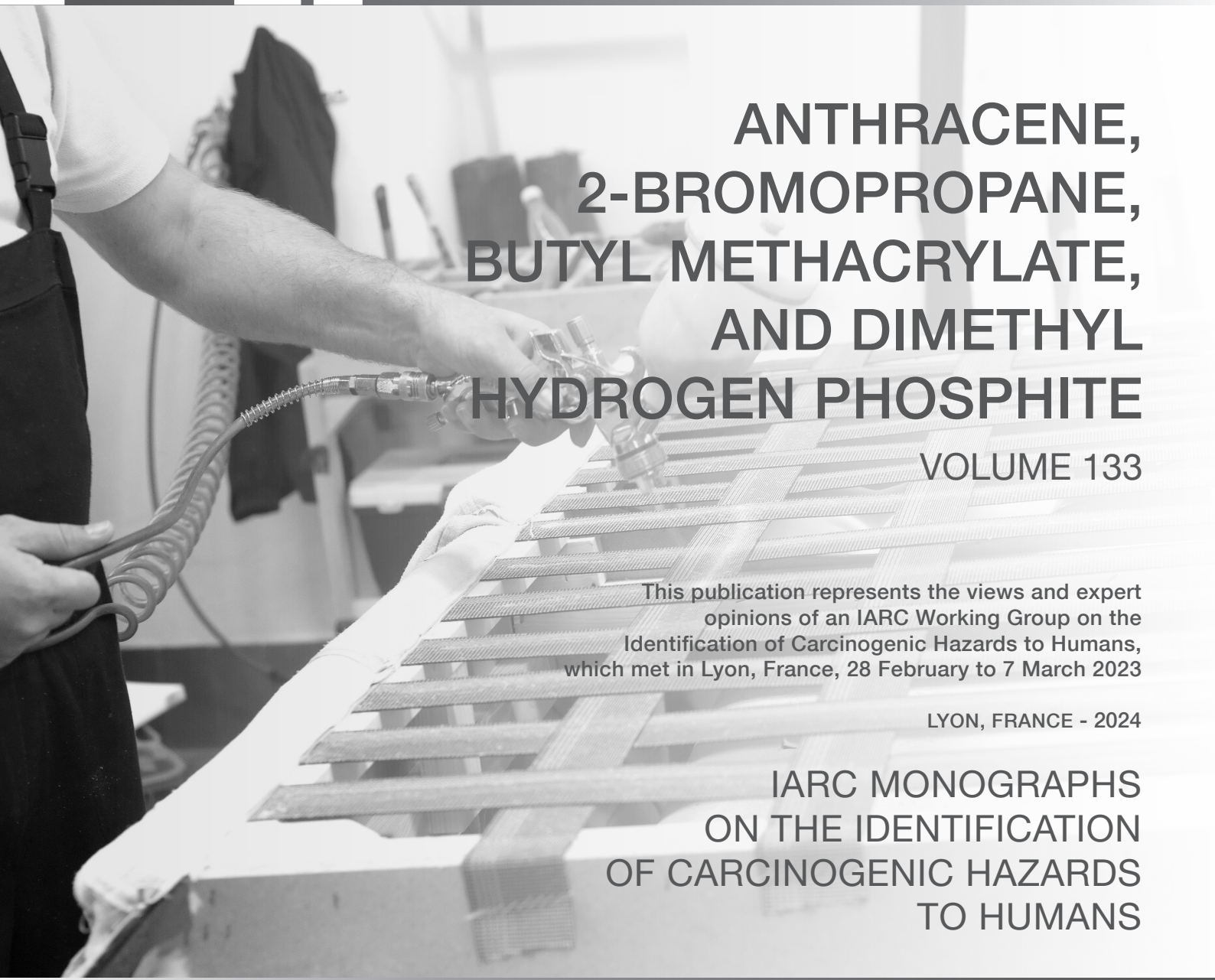

ANTHRACENE, 2-BROMOPROPANE, BUTYL METHACRYLATE, AND DIMETHYL HYDROGEN PHOSPHITE

VOLUME 133

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IARC MONOGRAPHS ON THE IDENTIFICATION OF CARCINOGENIC HAZARDS TO HUMANS

International Agency for Research on Cancer

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GENERAL REMARKS

General remarks

This one-hundred-and-thirty-third volume of the *IARC Monographs* contains evaluations of the carcinogenic hazard to humans of anthracene, 2-bromopropane, butyl methacrylate, and dimethyl hydrogen phosphite.

Anthracene and dimethyl hydrogen phosphite were each previously evaluated by the *IARC Monographs* programme as *not classifiable as to its carcinogenicity to humans (Group 3)* (IARC, 1999, 2010). Two of these agents – 2-bromopropane and butyl methacrylate – were evaluated by the *IARC Monographs* programme for the first time.

The Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024, which met in 2019, recommended that anthracene and dimethyl hydrogen phosphite be evaluated with medium priority and butyl methacrylate with low priority (IARC, 2019a; Marques et al., 2019). 2-Bromopropane was not recommended for evaluation, but it was the subject of a recent cancer bioassay that gave positive results and was thus accorded priority for evaluation in forthcoming meetings (IARC, 2019a; Marques et al., 2019).

A summary of the findings of this volume appears in *The Lancet Oncology* (Cattley et al., 2023).

Evaluation of anthracene

Exposure data for anthracene

The lack of data on anthracene concentrations from food surveys, particularly in geographical areas where agricultural lands are polluted and/or biomass is widely used for cooking (e.g. Africa), hampers the assessment of anthracene dietary intake by the general population. The Working Group considered this information highly relevant for assessing general population exposure because ingestion has been identified as one of the most significant routes of exposure to anthracene for people who do not smoke and are not exposed occupationally. There is a general lack of data on anthracene concentrations in consumer products, such as those incorporating coal tar or those derived from pitch or coal tar (e.g. over-the-counter shampoos and hair care products for the treatment of seborrheic dermatitis and psoriasis) and that are likely to contain anthracene. Dermal absorption is also poorly characterized for these products.

Anthracene's potential for phototoxicity

The Working Group noted the lack of specific epidemiological literature on (i) investigating the effects of anthracene among people who work

outside and are exposed to anthracene under sunlight; and (ii) identifying specific biomarkers. Phototoxicity is a concern for anthracene, given that common exposures are from outdoor air pollution and in sunlight; therefore, the photo-modifications that anthracene undergoes should not be overlooked when considering the carcinogenic potential of anthracene in combination with sunlight (Mujtaba et al., 2011; Choi & Oris, 2000a, b; Forbes et al., 1976). There are knowledge gaps and research opportunities for anthracene, including: (i) mechanistic studies with primary human cells; (ii) studies to evaluate the tumour promotion potential of anthracene in a two-stage initiation–promotion animal model with anthracene as the promoter; and (iii) additional exposure studies to better evaluate the effects of anthracene on human health specifically for, but not limited to, cancer.

Evaluation of 2-bromopropane

The classification of 2-bromopropane in Group 2A

In the case of 2-bromopropane, the Working Group recognized that the strict application of the framework given in the Preamble to the *IARC Monographs* (IARC, 2019b) would have led to an assignment to Group 2B (*possibly carcinogenic to humans*) and that the assignment of 2-bromopropane to Group 2A (*probably carcinogenic to humans*) was exceptional. This Group 2A evaluation was based upon two circumstances within two streams of evidence: cancer in experimental animals and mechanistic evidence. First, there was an unusually high degree of carcinogenic activity in both sexes of animals in a study that complied with Good Laboratory Practice, based upon the occurrence of malignant tumours of various types with a high incidence and at numerous sites. Second, the evidence for key characteristics of carcinogens in experimental systems, which was judged to be *strong* for "is immunosuppressive" and "modulates receptor-mediated effects", was supported by suggestive evidence for these two key characteristics in studies of exposed humans.

Addressing bias in exposure assessments for 2-bromopropane

In its evaluation of 2-bromopropane, the Working Group re-analysed a study on biomarkers of effect among workers exposed to 2-bromopropane that clearly showed that the applied individual-based assessment of exposure resulted in a strong attenuation of exposure–response associations. Re-analysing the data using a group-based approach resulted in stronger and unbiased estimates of the exposure–response association (see Fig. 4.1 in the monograph on 2-bromopropane). In addition to evaluating the quality of the exposure assessment in observational studies in humans, important bias should be addressed and, where possible, corrected (Schubauer-Berigan et al., 2023). Thus, the Working Group considered that the assessment and post hoc correction of bias caused by measurement error in observational studies in humans was essential for a proper assessment of the carcinogenic hazard of 2-bromopropane.

Mechanistic considerations for 2-bromopropane and similar agents

The Working Group noted that 2-bromopropane is structurally similar to at least two other agents previously evaluated for carcinogenic hazard by the *IARC Monographs* programme – 1-bromopropane and bromodichloromethane – both of which were classified in Group 2B (*possibly carcinogenic to humans*). In addition, all three chemicals have mechanistic features in

common, including genotoxicity. The Working Group further noted similarities in reproductive toxicity among these chemicals.

End-points related to immunosuppression of 2-bromopropane

The Working Group found consistent and coherent mechanistic evidence that 2-bromopropane is immunosuppressive in experimental systems and suggestive evidence for this key characteristic in exposed humans (see Section 5.4 in the monograph on 2-bromopropane).

Host immunity represents an important barrier to tumour formation and progression, and immunosuppression is recognized as one of the 10 key characteristics commonly exhibited by human carcinogens (Smith et al., 2016). Multiple pathways are involved in evading innate and adaptive immune responses, and a broad spectrum of chemicals display the potential to adversely influence immunosurveillance (Kravchenko et al., 2015). Many of the mechanisms through which environmental chemicals or therapeutic drugs modulate immune function are well recognized, and 10 key characteristics exhibited by immunotoxic agents have recently been described (Germolec et al., 2022).

In the context of carcinogenicity, chemical-induced immunosuppression is a mechanism by which chemicals alter immune cell function such that immune cells fail to detect and destroy tumour cells, restrain tumour growth, or create a permissive environment for cancer via some other mechanism.

The immune system comprises a complex network of different cell types located in various organs and their mediators, which operate to maintain homeostasis. An immune response occurs through the coordination of many different cell types and can involve several tissues. The thymus and bone marrow are critical for immune cell development, and the lymph nodes and spleen are organs in which many immune responses occur. Chemical exposure can influence various components of the immune system via different mechanisms, eventually leading to adverse health outcomes.

Factors such as age at onset, sex, dose, duration, and route of exposure may result in differing effects on the immune system and skew the adverse response in the direction of immunosuppression or immunostimulation. Immunotoxicity can manifest in a variety of ways, with one of the most prominent effects being immunosuppression (Vos & Moore, 1977; Dean et al., 1982).

The consequences of immunosuppression after exposure to environmental chemicals or therapeutic drugs are increased sensitivity to infections and cancer (Germolec et al., 2017). A drug or chemical that causes immunosuppression might alter the number of cells (innate or adaptive); the ability of the cells to produce cytokines, chemokines, antibodies, or growth factors; the composition of the subpopulations of cells present at the site of the response; or the cell function (e.g. kill infected cells or cause proliferation). Signs of immunotoxic potential caused by agents in standard toxicology studies in experimental animals can be defined by haematological changes (i.e. leukocytopenia/leukocytosis, granulocytopenia/granulocytosis, or lymphopenia/lymphocytosis), alterations in immune system organ weights or histology, changes in serum antibodies, or changes in the incidence of infections or tumours. Specifically, the following parameters should be evaluated for signs of immunotoxicity: (i) changes in total and differential leukocyte counts; (ii) alterations in immune organ weights and histology; (iii) decreased levels of basal plasma immunoglobulins; (iv) increased incidence of infection; (v) increased occurrence of tumours in the absence of genotoxicity, hormonal effects, or liver enzyme induction; and (vi) retention of

Table 1. Testing battery to assess chemical-induced immunotoxicity in rodents (according to National Toxicology Program guidelines)

Screen (tier I)	Immunopathology (haematology, organ weights, spleen cellularity, histopathology) Cell quantification (surface marker analysis in spleen) Humoral immunity (IgM TDAR) Cell-mediated immunity (CTL, DTH) Nonspecific immunity (NK cell assay)
Definitive (tier II)	Humoral immunity (IgG TDAR) Nonspecific immunity (macrophage function) Host-resistance assays

TDAR, T-cell dependent antibody response; CTL, cytotoxic T lymphocytes; DTH, delayed-type hypersensitivity; NK, natural killer; IgM, immunoglobulin M.
Adapted from Hinton (2000), Luster et al. (1988).

the chemical in organs or cells of the immune system.

Myelotoxicity or bone marrow toxicity is characterized by a decrease in the production of cells responsible for providing immunity (leukocytes), carrying oxygen (erythrocytes), and/or those responsible for normal blood clotting (thrombocytes) (in each monograph, this information is reported in Section 3, Cancer in experimental animals, and Section 4, Mechanistic evidence). In the context of immunotoxicity, myelotoxicity would refer to toxicity to precursors of immune cells. Compounds that are capable of damaging or destroying the bone marrow will have a profound immunotoxic effect, since the effectors of the immune system itself will no longer be available. Therefore, if a compound is myelotoxic, according to the specific assay performed, the chemical will de facto be an immunotoxicant (Gennari et al., 2005; OECD, 2022).

Thus, useful information on potential immunosuppressive hazard can be derived from histopathology of immune organs, enumeration of immune cells, or mostly from functional immune tests, which may be used in various tiers (Hinton, 2000; Luster et al., 1988). An example of a testing battery to assess chemical-induced immunotoxicity, from the National Toxicology Program guidelines for immunotoxicity evaluation in rodents, is shown in Table 1.

Standard assessments of immunotoxicity use both in vitro and ex vivo assays that evaluate different functional parameters of the immune response; of these assays, those for lymphocyte proliferation, mixed lymphocyte reaction, cytotoxic T lymphocytes, and natural killer cell activity are relevant to immunosurveillance of cancer (Germolec et al., 2017).

Modulation of receptor-mediated effects by 2-bromopropane

Together with myelotoxicity, there is suggestive evidence that 2-bromopropane modulates receptor-mediated effects, a key characteristic of carcinogens; this is based on alterations in serum levels of several hormones, namely, follicle-stimulating hormone (FSH), luteinizing hormone-releasing hormone (LHRH), luteinizing hormone (LH), estradiol, and testosterone in exposed workers. Alterations in hormone levels can have significant effects on their respective target receptors. However, the Working Group considered that there is only very limited evidence of cancer causation associated with levels of LH and LHRH, since their role is yet to be fully elucidated. In addition, while there are known associations between estradiol and cancers in the female reproductive tract and between testosterone and cancers in the male reproductive tract,

these are generally shown as positive associations with increased receptor activity. The Working Group observed increased levels of FSH and LH and decreased levels of estradiol in women, and decreased levels of testosterone in men. For this reason, and because of the lack of further information on the activities of various receptors, the evidence for modulation of receptor-mediated effects, and the link to carcinogenesis, was found to be only suggestive for 2-bromopropane.

Carcinogenicity in experimental animals

Trend tests

In its evaluation of studies of cancer in experimental animals for three of the agents considered (anthracene, 2-bromopropane, and butyl methacrylate), the Working Group took into account, in addition to the Cochran–Armitage trend test, the data analysis methodology applied by the Japan Bioassay Research Center (JBRC, 1998, 2018a, b, 2019). This included three Peto test methods: the standard method (referred to as "death analysis"), the prevalence method (referred to as "incidental tumour test"), and combined analysis (referred to as "death analysis plus incidental tumour test"). The Working Group considered that a significant *P* value in any trend test was relevant for the detection of treatment-related increases in tumour incidence.

Combination of tumours

When considering the data for anthracene and 2-bromopropane, the Working Group consulted a publication by Brix et al. (2010) on appropriate combinations of lung neoplasms and combinations of mammary gland neoplasms in rodents for the purposes of evaluating the statistical and biological significance of these neoplasms. Specifically, the incidence data for squamous cell neoplasms of the lung should not be combined with those for bronchioloalveolar neoplasms. Similarly, the incidence data for fibroadenoma of the mammary gland should not be combined with those for adenoma, except when there is evidence that an adenoma or carcinoma of the mammary gland has arisen from a fibroadenoma. In the studies by the Japan Bioassay Research Center, no information was provided regarding why these tumour types were combined or the criteria used (JBRC, 1998; 2019). Therefore, these combinations of tumour incidence data were not considered by the Working Group in its evaluation of the evidence on carcinogenic activity.

Scope of the systematic review

Standardized searches of the PubMed database (NCBI, 2023) were conducted for each agent and for each outcome (cancer in humans, cancer in experimental animals, and mechanistic evidence, including the key characteristics of carcinogens). For cancer in humans, searches were also conducted in the Web of Science (Clarivate, 2023) and Embase (Elsevier, 2023) databases. The literature trees for the agents, including the full set of search terms for the agent name and each outcome type, are available online.[a]

[a] The literature trees for the present volume are available at: https://hawcproject.iarc.who.int/assessment/660/ (anthracene), https://hawcproject.iarc.who.int/assessment/695/ (2-bromopropane), https://hawcproject.iarc.who.int/assessment/696/ (butyl methacrylate), and https://hawcproject.iarc.who.int/assessment/697/ (dimethyl hydrogen phosphite).

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