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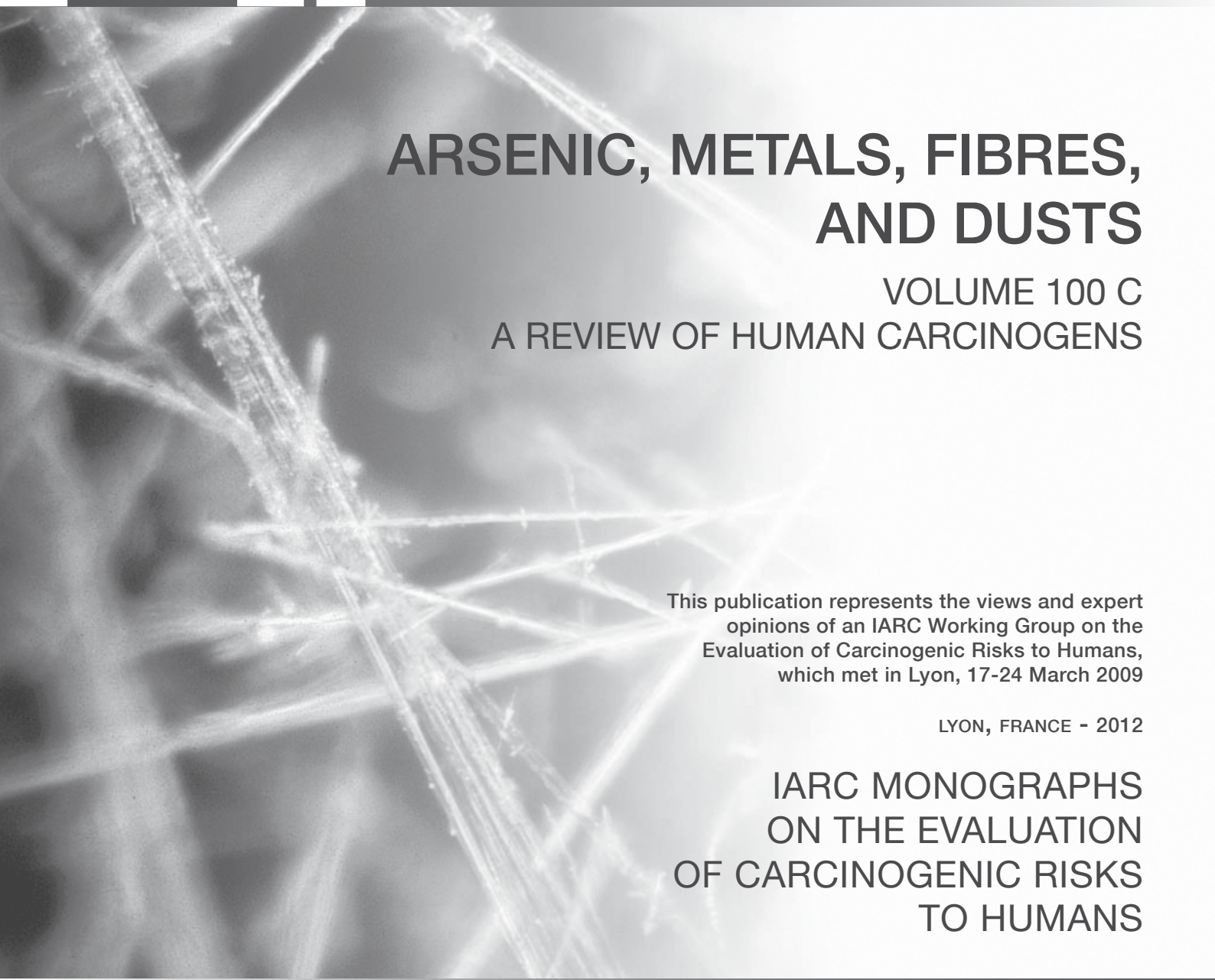

ARSENIC, METALS, FIBRES, AND DUSTS

VOLUME 100 C
A REVIEW OF HUMAN CARCINOGENS

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ARSENIC AND ARSENIC COMPOUNDS

Arsenic and arsenic compounds were considered by previous IARC Working Groups in 1979, 1987, and 2002 (IARC, 1980, 1987, 2004). Since that time, new data have become available, these have been incorporated in the *Monograph*, and taken into consideration in the present evaluation.

1. Exposure Data

1.1 Identification of the agents

Information on the physical and chemical properties of arsenic and arsenic compounds can be found in Table 1.1, for further details please refer to IARC (1980). The list is not exhaustive, nor does it comprise necessarily the most commercially important arsenic-containing substances; rather, it indicates the range of arsenic compounds available.

1.2 Chemical and physical properties of the agents

Arsenic (atomic number, 33; relative atomic mass, 74.92) has chemical and physical properties intermediate between a metal and a non-metal, and is often referred to as a metalloid or semi-metal. It belongs to Group VA of the Periodic Table, and can exist in four oxidation states: –3, 0, +3, and +5. Arsenite, As^{III}, and arsenate, As^{V}, are the predominant oxidation states under, respectively, reducing and oxygenated conditions (WHO, 2001; IARC, 2004).

From a biological and toxicological perspective, there are three major groups of arsenic compounds:

-inorganic arsenic compounds,
-organic arsenic compounds, and
-arsine gas.

Of the inorganic arsenic compounds, arsenic trioxide, sodium arsenite and arsenic trichloride are the most common trivalent compounds, and arsenic pentoxide, arsenic acid and arsenates (e.g. lead arsenate and calcium arsenate) are the most common pentavalent compounds. Common organic arsenic compounds include arsanilic acid, methylarsonic acid, dimethylarsinic acid (cacodylic acid), and arsenobetaine (WHO, 2000).

1.3 Use of the agents

Arsenic and arsenic compounds have been produced and used commercially for centuries. Current and historical uses of arsenic include pharmaceuticals, wood preservatives, agricultural chemicals, and applications in the mining, metallurgical, glass-making, and semiconductor industries.

Arsenic was used in some medicinal applications until the 1970s. Inorganic arsenic was used

Table 1.1 Chemical names, CAS numbers, synonyms, and molecular formulae of arsenic and arsenic compounds

Chemical name	CAS Reg. No.	Synonyms	Formula
Arsanilic acid	98-50-0	Arsonic acid, (4-aminophenyl)-	$C_6H_8AsNO_3$
Arsenic[a]	7440-38-2	Metallic arsenic	As
Arsenic(V) pentoxide[b]	1303-28-2	Arsenic oxide [As_2O_5]	As_2O_5
Arsenic(III) sulfide	1303-33-9	Arsenic sulfide [As_2S_3]	As_2S_3
Arsenic(III) trichloride	7784-34-1	Arsenic chloride [$AsCl_3$]	$AsCl_3$
Arsenic(III) trioxide[a,c]	1327-53-3	Arsenic oxide [As_2O_3]	As_2O_3
Arsenobetaine	64436-13-1	Arsonium, (carboxymethyl) trimethyl-, hydroxide, inner salt; 2-(trimethylarsonio)acetate	$C_5H_{11}AsO_2$
Arsine	7784-42-1	Arsenic hydride	AsH_3
Calcium arsenate	7778-44-1	Arsenic acid [H_3AsO_4] calcium salt (2:3)	$(AsO_4)_2.3Ca$
Dimethylarsinic acid	75-60-5	Cacodylic acid	$C_2H_7AsO_2$
Lead arsenate	7784-40-9	Arsenic acid [H_3AsO_4], lead (2+) salt (1:1)	$HAsO_4.Pb$
Methanearsonic acid, disodium salt	144-21-8	Arsonic acid, methyl-, disodium salt	$CH_3AsO_3.2Na$
Methanearsonic acid, monosodium salt	2163-80-6	Arsonic acid, methyl-, monosodium salt	$CH_4AsO_3.Na$
Potassium arsenate[d]	7784-41-0	Arsenic acid [H_3AsO_4], monopotassium salt	$H_2AsO_4.K$
Potassium arsenite	13464-35-2	Arsenous acid, potassium salt	$AsO_2.K$
Sodium arsenate[e]	7631-89-2	Arsenic acid, [H_3AsO_4], monosodium salt	$H_2AsO_4.Na$
Sodium arsenite	7784-46-5	Arsenous acid, sodium salt	$AsO_2.Na$
Sodium cacodylate	124-65-2	Arsinic acid, dimethyl-, sodium salt	$C_2H_6AsO_2.Na$

[a] As_2O_3 is sometimes erroneously called 'arsenic'.
[b] The name 'arsenic acid' is commonly used for As_2O_5 as well as for the various hydrated products (H_3AsO_4, $H_4As_2O_7$).
[c] As_2O_3 is sometimes called 'arsenic oxide', but this name is more properly used for As_2O_5.
[d] The other salts, K_3AsO_4 and K_2HAsO_4, do not appear to be produced commercially.
[e] The name 'sodium arsenate' is also applied to both the disodium [7778-43-0] and the trisodium [13464-38-5] salts; it is therefore not always possible to determine which substance is under discussion.

in the treatment of leukaemia, psoriasis, and chronic bronchial asthma, and organic arsenic was used in antibiotics for the treatment of spirochetal and protozoal disease (ATSDR, 2007).

Inorganic arsenic is an active component of chromated copper arsenate, an antifungal wood preservative used to make "pressure-treated" wood for outdoor applications. Chromated copper arsenate is no longer used in residential applications, following a voluntary ban on its use in Canada and the United States of America at the end of 2003.

In the agricultural industry, arsenic has historically been used in a range of applications, including pesticides, herbicides, insecticides, cotton desiccants, defoliants, and soil sterilants. Inorganic arsenic pesticides have not been used for agricultural purposes in the USA since 1993. Organic forms of arsenic were constituents of some agricultural pesticides in the USA. However, in 2009, the US Environmental Protection Agency issued a cancellation order to eliminate and phase out the use of organic arsenical pesticides by 2013 (EPA, 2009). The one exception to the order is monosodium methanearsonate (MSMA), a broadleaf weed herbicide, which will continue to be approved for use on cotton. Small amounts of disodium methanearsonate (DSMA, or cacodylic acid) were historically applied to cotton fields as herbicides, but its use is now prohibited under the aforementioned US EPA 2009 organic arsenical product cancellation. Other organic

arsenicals (e.g. roxarsone, arsanilic acid and its derivatives) are used as feed additives for poultry and swine to increase the rate of weight gain, to improve feed efficiencies, pigmentation, and disease treatment and prevention (EPA, 2000, 2006; FDA, 2008a, b).

Arsenic and arsenic compounds are used for a variety of other industrial purposes. Elemental arsenic is used in the manufacture of alloys, particularly with lead (e.g. in lead acid batteries) and copper. Gallium arsenide and arsine are widely used in the semiconductor and electronics industries. Because of its high electron mobility, as well as light-emitting, electromagnetic and photovoltaic properties, gallium arsenide is used in high-speed semiconductor devices, high-power microwave and millimetre-wave devices, and opto-electronic devices, including fibre-optic sources and detectors (IARC, 2006). Arsine is used as a doping agent to manufacture crystals for computer chips and fibre optics.

Arsenic and arsenic compounds are used in the manufacture of pigments, sheep-dips, leather preservatives, and poisonous baits. They are also used in catalysts, pyrotechnics, antifouling agents in paints, pharmaceutical substances, dyes and soaps, ceramics, alloys (automotive solder and radiators), and electrophotography.

Historically, the USA has been the world's largest consumer of arsenic. Prior to 2004, about 90% of the arsenic consumed, as arsenic trioxide, was in the manufacture of wood preservatives. Since the voluntary ban on chromated copper arsenate in residential applications came into effect at the end of 2003, the consumption of arsenic for wood preservation has declined, dropping to 50% in 2007 (USGS, 2008). During 1990–2002, approximately 4% of arsenic produced was used in the manufacture of glass, and 1–4% was used in the production of non-ferrous alloys (NTP, 2005).

1.4 Environmental occurrence

Arsenic is the 20th most common element in the earth's crust, and is emitted to the environment as a result of volcanic activity and industrial activities. Mining, smelting of non-ferrous metals and burning of fossil fuels are the major anthropogenic sources of arsenic contamination of air, water, and soil (primarily in the form of arsenic trioxide). The historical use of arsenic-containing pesticides has left large tracts of agricultural land contaminated. The use of arsenic in the preservation of timber has also led to contamination of the environment (WHO, 2000, 2001).

1.4.1 Natural occurrence

In nature, arsenic occurs primarily in its sulfide form in complex minerals containing silver, lead, copper, nickel, antimony, cobalt, and iron. Arsenic is present in more than 200 mineral species, the most common of which is arsenopyrite. Terrestrial abundance of arsenic is approximately 5 mg/kg, although higher concentrations are associated with sulfide deposits. Sedimentary iron and manganese ores as well as phosphate-rock deposits occasionally contain levels of arsenic up to 2900 mg/kg (WHO, 2001).

1.4.2 Air

Arsenic is emitted to the atmosphere from both natural and anthropogenic sources. Approximately one-third of the global atmospheric flux of arsenic is estimated to be from natural sources (7900 tonnes per year). Volcanic activity is the most important natural contributor, followed by low-temperature volatilization, exudates from vegetation, and windblown dusts. Anthropogenic sources are estimated to account for nearly 24000 tonnes of arsenic emitted to the global atmosphere per year. These emissions arise from the mining and smelting of base metals, fuel combustion (e.g. waste and low-grade brown

coal), and the use of arsenic-based pesticides (WHO, 2000, 2001).

Arsenic is present in the air of suburban, urban, and industrial areas mainly as inorganic particulate (a variable mixture of As^{III} and As^{V}, with the pentavalent form predominating). Methylated arsenic is assumed to be a minor component of atmospheric arsenic (WHO, 2000). Mean total arsenic concentrations in air range from 0.02–4 ng/m^3 in remote and rural areas, and from 3–200 ng/m^3 in urban areas. Much higher concentrations (> 1000 ng/m^3) have been measured in the vicinity of industrial sources, such as non-ferrous metal smelters, and arsenic-rich coal-burning power plants (WHO, 2001).

1.4.3 Water

Arsenic, from both natural and anthropogenic sources, is mainly transported in the environment by water. The form and concentration of arsenic depends on several factors, including whether the water is oxygenated (for example, arsenites predominate under reducing conditions such as those found in deep well-waters), the degree of biological activity (which is associated with the conversion of inorganic arsenic to methylated arsenic acids), the type of water source (for example, open ocean seawater versus surface freshwater versus groundwater), and the proximity of the water source to arsenic-rich geological formations and other anthropogenic sources (WHO, 2000, 2001).

The concentration of arsenic in surface freshwater sources, like rivers and lakes, is typically less than 10 µg/L, although it can be as high as 5 mg/L near anthropogenic sources. Concentrations of arsenic in open ocean seawater and groundwater average 1–2 µg/L, although groundwater concentrations can be up to 3 mg/L in areas with volcanic rock and sulfide mineral deposits (WHO, 2001).

Exposure to high levels of arsenic in drinking-water has been recognized for many decades in some regions of the world, notably in the People's Republic of China, Taiwan (China), and some countries in Central and South America. More recently, several other regions have reported having drinking-water that is highly contaminated with arsenic. In most of these regions, the drinking-water source is groundwater, naturally contaminated from arsenic-rich geological formations. The primary regions where high concentrations of arsenic have been measured in drinking-water include large areas of Bangladesh, China, West Bengal (India), and smaller areas of Argentina, Australia, Chile, Mexico, Taiwan (China), the USA, and Viet Nam. In some areas of Japan, Mexico, Thailand, Brazil, Australia, and the USA, mining, smelting and other industrial activities have contributed to elevated concentrations of arsenic in local water sources (IARC, 2004).

Levels of arsenic in affected areas may range from tens to hundreds or even thousands of micrograms per litre, whereas in unaffected areas, levels are typically only a few micrograms per litre. Arsenic occurs in drinking-water primarily as As^{V}, although in reducing environments significant concentrations of As^{III} have also been reported. Trace amounts of methylated arsenic species are typically found in drinking-water, and higher levels are found in biological systems. More complete data on arsenic in water may be found in the previous *IARC Monograph* (IARC, 2004).

1.4.4 Soil and sediments

Natural and anthropogenic sources contribute to the levels of arsenic found in soil and sediments. Mean background concentrations in soil are often around 5 mg/kg, but can range from as low as 1 mg/kg to as high as 40 mg/kg. This variation in levels of naturally occurring arsenic in soils is associated with the presence of geological formations (e.g. sulfide ores, mineral sediments beneath peat bogs). Soils contaminated with arsenic from anthropogenic sources (e.g. mine/

smelter wastes, agricultural land treated with arsenical pesticides) can have concentrations of arsenic up to several grams per kilogram. Mean sediment arsenic concentrations range from 5–3000 mg/kg, with the higher levels occurring in areas of anthropogenic contamination (WHO, 2001).

1.5 Human exposure

1.5.1 Exposure of the general population

The primary route of arsenic exposure for the general population is via the ingestion of contaminated food or water. The daily intake of total arsenic from food and beverages is generally in the range of 20–300 µg/day.

Inhalation of arsenic from ambient air is generally a minor exposure route for the general population. Assuming a breathing rate of 20 m^3/day, the estimated daily intake may amount to about 20–200 ng in rural areas, 400–600 ng in cities without substantial industrial emission of arsenic, about 1 µg/day in a non-smoker and more in polluted areas, and up to approximately 10 µg/day in a smoker (WHO, 2000, 2001).

1.5.2 Occupational exposure

Inhalation of arsenic-containing particulates is the primary route of occupational exposure, but ingestion and dermal exposure may be significant in particular situations (e.g. during preparation of timber treated with chromated copper arsenate). Historically, the greatest occupational exposure to arsenic occurred in the smelting of non-ferrous metal, in which arseniferous ores are commonly used. Other industries or industrial activities where workers are or were exposed to arsenic include: coal-fired power plants, battery assembly, preparation of or work with pressure-treated wood, glass-manufacturing, and the electronics industry. Estimates of the number of workers potentially exposed to arsenic and arsenic compounds have been developed by the NIOSH in the USA and by CAREX in Europe. Based on the National Occupation Exposure Survey (NOES), conducted during 1981–83, NIOSH estimated that 70000 workers, including approximately 16000 female workers, were potentially exposed to arsenic and arsenic compounds in the workplace (NIOSH, 1990). Based on occupational exposure to known and suspected carcinogens collected during 1990–93, the CAREX (CARcinogen EXposure) database estimated that 147569 workers were exposed to arsenic and arsenic compounds in the European Union, with over 50% of workers employed in the non-ferrous base metal industries (n = 40426), manufacture of wood and wood and cork products except furniture (n = 33959), and construction (n = 14740). CAREX Canada estimates that 25000 Canadians are exposed to arsenic in their workplaces (CAREX Canada, 2011). These industries include: sawmills and wood preservation, construction, farms, non-ferrous metal (except aluminium) production and processing, iron and steel mills and ferro-alloy manufacturing, oil and gas extraction, metal ore mining, glass and glass-product manufacturing, semiconductor manufacturing, and basic chemical manufacturing.

1.5.3 Dietary exposure

Low levels of inorganic and organic arsenic have been measured in most foodstuffs (typical concentrations are less than 0.25 mg/kg). Factors influencing the total concentration of arsenic in food include: food type (e.g. seafood versus meat or dairy), growing conditions (e.g. soil type, water, use of arsenic-containing pesticides), and food-processing techniques. The highest concentrations of arsenic have been found in seafood (2.4–16.7 mg/kg in marine fish, 3.5 mg/kg in mussels, and more than 100 mg/kg in certain crustaceans), followed by meats, cereals, vegetables, fruit, and dairy products. Inorganic arsenic

is the predominant form found in meats, poultry, dairy products and cereal, and organic arsenic (e.g. arsenobetaine) predominates in seafood, fruit, and vegetables (WHO, 2000, 2001).

Regional differences are seen in the daily intake of total arsenic through food, and are mainly attributable to variations in the quantity of seafood consumed. For example, the daily dietary intake of total arsenic in Japan is higher than that in Europe and the USA (WHO, 2000). Based on the limited data available, it is estimated that approximately 25% of daily dietary arsenic intake is from inorganic sources. Arsenic intake is typically higher in men than it is in women and children, with estimated levels ranging from 1.3 μg/day for infants under 1 year of age, 4.4 μg/day for 2-year olds, 9.9 μg/day for 25–30-year-old men, 10 μg/day for 60–65-year-old women, and 13 μg/day for 60–65-year-old men (WHO, 2001).

1.5.4 Biomarkers of exposure

Arsine generation atomic absorption spectrometry (AAS) is the method of choice for biological monitoring of exposure to inorganic arsenic (WHO, 2000). The absorbed dose of arsenic can be identified and quantified in hair, nail, blood or urine samples. Because arsenic accumulates in keratin-rich tissue, total arsenic levels in hair, fingernails or toenails are used as indicators of past exposures. In contrast, because of its rapid clearing and metabolism, blood arsenic, urine arsenic, and urine arsenic metabolites (inorganic arsenic, monomethylarsonic acid [MMA^V] and dimethylarsinic acid [DMA^V]) are typically used as indicators of recent exposure.

The concentration of metabolites of inorganic arsenic in urine generally ranges from 5–20 μg/L, but may exceed 1000 μg/L (WHO, 2001). Time-weighted average (TWA) occupational exposure to airborne arsenic trioxide is significantly correlated with the inorganic arsenic metabolites in urine collected immediately after a shift or just before the next shift. For example, at an airborne concentration of 50 μg/m^3, the mean concentration of arsenic derived from the sum of the three inorganic arsenic metabolites in a post-shift urine sample was 55 μg/g of creatinine. In non-occupationally exposed subjects, the sum of the concentration of the three metabolites in urine is usually less than 10 μg/g of creatinine (WHO, 2000).

2. Cancer in Humans

The epidemiological evidence on arsenic and cancer risk comes from two distinct lines of population studies, characterized by the medium of exposure to arsenic. One set of studies addresses the cancer risk associated with inhalation. These studies involve populations that are largely worker groups who inhaled air contaminated by arsenic and other agents, as a consequence of various industrial processes. The second set of studies was carried out in locations where people ingested arsenic in drinking-water at high concentrations over prolonged periods of time.

2.1 Types of human exposure circumstances studied

2.1.1 Arsenic exposure by inhalation

The cohort studies and nested case–control studies considered in this *Monograph* that are relevant to airborne arsenic include workers in metal smelters and refineries, and miners of various ores. Case–control studies within the general population addressed occupational exposures more generally. Consequently, the exposure to inhaled arsenic was accompanied by exposures to other potentially toxic and carcinogenic by-products of combustion, such as sulfur oxides with copper smelting, polycyclic aromatic hydrocarbons, and particulate matter.

Most studies did not attempt to estimate separately exposures to the full set of agents in the inhaled mixtures, leaving open the possibility of some confounding or modification of the effect of arsenic by synergistic interactions.

2.1.2 Arsenic exposure by ingestion

For most human carcinogens, the major source of evidence contributing to causal inferences arises from case–control and cohort studies. In contrast, for arsenic in drinking-water, ecological studies provide important information on causal inference, because of the large exposure contrasts and the limited population migration. For arsenic, ecological estimates of relative risk are often so high that potential confounding with known causal factors could not explain the results. Although food may also be a source of some ingested arsenic, in several regions of the world where the concentrations of arsenic in drinking-water is very high, arsenic intake through food consumption contributes a relatively small cancer risk to the local residents (Liu *et al.*, 2006a).

The strongest evidence for the association of human cancer with arsenic in drinking-water comes from studies in five areas of the world with especially elevated levels of naturally occurring arsenic: south-western and north-eastern Taiwan (China), northern Chile, Cordoba Province in Argentina, Bengladesh, West Bengal (India), and other regions in the Ganga plain. Although data contributing to our understanding also come from many other places, the current review is largely restricted to the major studies from these regions. Some of the oral exposure may occur via seafood. However, no epidemiological studies were available with regard to the cancer risk associated with arsenic exposure via seafood, in which arsenic may occur as particular organic compounds such as arsenobetaine and arsenocholine.

(a) Taiwan (China)

Exposure to arsenic was endemic in two areas of Taiwan (China): The south-western coastal area (Chen *et al.*, 1985), and the north-eastern Lanyang Basin (Chiou *et al.*, 2001). Residents in the south-western areas drank artesian well-water with high concentrations of arsenic from the early 1910s to the late 1970s, with levels mostly above 100 µg/L (Kuo, 1968; Tseng *et al.*, 1968). In the Lanyang Basin, residents used arsenic-contaminated water from household tube wells starting in the late 1940s. Arsenic in the water of 3901 wells, tested in 1991–94 ranged from undetectable (< 0.15 µg/L) to 3.59 mg/L (median = 27.3 µg/L) (Chiou *et al.*, 2001).

(b) Northern Chile

The population-weighted average concentration of arsenic in drinking-water in Region II, an arid region of northern Chile, was about 570 µg/L over 15 years (1955–69) (Smith *et al.*, 1998). With the introduction of a water-treatment plant in 1970, levels decreased. By the late 1980s, arsenic levels in drinking-water had decreased to less than 100 µg/L in most places. With minor exceptions, water sources elsewhere in Chile have had low concentrations of arsenic (less than 10 µg/L) (Marshall *et al.*, 2007).

(c) Cordoba Province, Argentina

Of the 24 counties in Cordoba Province, two have been characterized as having elevated exposure to arsenic in drinking-water (average level, 178 µg/L), six as having medium exposure, and the remaining 16 rural counties as having low exposure (Hopenhayn-Rich *et al.*, 1996, 1998).

(d) Bangladesh, West Bengal (India), and other locations in the Ganga plain

Millions of tube wells were installed in West Bengal (India), Bangladesh, and other regions in the Ganga plain of India and Nepal starting in the late 1970s to prevent morbidity and mortality

from gastrointestinal disease (Smith *et al.*, 2000). Elevated arsenic in wells in Bangladesh was confirmed in 1993 (Khan *et al.*, 1997). In a Bangladesh survey by the British Geological Survey of 2022 water samples in 41 districts, 35% were found to have arsenic levels above 50 µg/L, and 8.4% were above 300 µg/L, with an estimate of about 21 million persons exposed to arsenic concentrations above 50 µg/L (Smith *et al.*, 2000).

2.2 Cancer of the lung

2.2.1 Exposure via inhalation

Several ecological studies were conducted on populations exposed to arsenic through industrial emissions. The worker studies primarily provide information on lung cancer. The case–control studies are also mostly directed at lung cancer, with one on non-melanoma skin cancer (see Table 2.1 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.1.pdf).

The cohort studies reviewed previously and here consistently show elevated lung cancer risk in the various arsenic-exposed cohorts compared with the general population or other comparison groups, with most values in the range of 2–3 (see Table 2.2 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.2.pdf and Table 2.3 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.3.pdf).

The studies incorporate diverse qualitative and quantitative indices of exposure that include measures of average airborne concentration of exposure, cumulative exposure across the work experience, and duration of exposure. There is consistent evidence for a positive exposure–response relationship between the indicators of exposure and lung cancer risk. Case–control studies nested within occupational cohorts provided similar evidence with regard to exposure–response relationships.

Several analyses further explored the relationship between arsenic exposure and lung cancer risk using models based on either empirical, i.e. descriptive, or biological data (see Table 2.4 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.4.pdf).

Using data from the Tacoma, Washington smelter workers, Enterline *et al.* (1987) modelled the relationship between lung cancer risk and airborne arsenic exposure using power functions, and found that the exposure–response relationship was steeper at lower concentrations than shown in conventional analyses, and was concave downwards at higher concentrations. By contrast, the relationship of risk with urine arsenic concentration was linear. Lubin *et al.* (2000, 2008) analysed the exposure–response relationship of lung cancer risk with arsenic exposure in the cohort of Montana smelter workers, now followed for over 50 years. Overall, a linear relationship of risk with cumulative exposure was found; however, the slope of the relationship increased with the average concentration at which exposure had taken place, that is, the effect of a particular cumulative exposure was greater if received at a faster rate.

For a comparison of the different studies, see Table 2.5 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.5.pdf.

2.2.2 Exposure via ingestion

A summary of the findings of epidemiological studies on arsenic in drinking-water and risk for lung cancer are shown in Table 2.6 (water exposures) available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.6.pdf, and online Tables 2.1 to 2.4 (air exposures).

(a) Ecological studies

Ecological studies, based on mortality records, were conducted in the arseniasis endemic area of south-western Taiwan (China) (Chen *et al.*, 1985, 1988a; Wu *et al.*, 1989; Chen & Wang, 1990; Tsai *et al.*, 1999). All studies found elevated risks for lung cancer mortality associated with levels of arsenic in drinking-water, or surrogate measurements.

In Chile, Rivara *et al.* (1997) found an elevated relative risk (RR) for mortality from lung cancer in 1976–92 in Region II compared with Region VIII, a low-exposure area. Smith *et al.* (1998) found an elevated standardized mortality ratio (SMR) of approximately 3 for lung cancer for both sexes in Region II, using the national rate as standard. In Cordoba Province, Argentina, significant increases in lung cancer mortality were associated with increasing exposure to arsenic (Hopenhayn-Rich *et al.*, 1998). Smith *et al.* (2006) found an elevated lung cancer mortality (RR, 7.0; 95%CI: 5.4–8.9) among the 30–49-year-old residents of Antofagasta and Mejillones born in the period 1950–57, just before the period of exposure to high arsenic levels (1958–70). They were exposed in early childhood to high levels of arsenic through the drinking-water. The temporal pattern of lung cancer mortality rate ratios in Region II compared with that in Region V (a low-exposure area) from 1950 to 2000, showed an increase about 10 years after the onset of high arsenic exposure, and peaked in 1986–87, with relative risks of 3.61 (95%CI: 3.13–4.16) and 3.26 (95%CI: 2.50–4.23) for men and women, respectively (Marshall *et al.*, 2007).

(b) Case–control and cohort studies

In northern Chile, a case–control study of 151 cases and 419 controls reported significantly increasing risks with increasing levels of arsenic during the 1958–70 high-exposure period, with an odds ratio increasing to 7.1 (95%CI: 3.4–14.8) (Ferreccio *et al.*, 2000).

In a cohort from south-western Taiwan (China), Chen *et al.* (1986) observed a dose–response relationship between the duration of consumption of artesian well-water containing high levels of arsenic and lung cancer mortality risk, showing the highest age- and gender-adjusted odds ratio among those who consumed artesian well-water for more than 40 years compared with those who never consumed artesian well-water. Another cohort study from south-western Taiwan (China) endemic for arsenic found a smoking-adjusted increased risk for lung cancer in relation to increasing average concentrations of arsenic and increasing cumulative exposure to arsenic (Chiou *et al.*, 1995).

A further study of combined cohorts in south-western (n = 2503) and north-eastern (n = 8088) Taiwan (China) found a synergistic interaction between arsenic in drinking-water and cigarette smoking (Chen *et al.*, 2004).

A case–control study from Bangladesh, conducted in 2003–06, found an elevated risk (odds ratio [OR], 1.65; 95%CI: 1.25–2.18) for male smokers consuming tube well-water with arsenic levels of 101–400 µg/L (Mostafa *et al.*, 2008). In non-smokers, the study did not report an increased risk with increasing arsenic exposure. [The Working Group noted the ecological nature of the exposure estimates, the possibility of greater sensitivity to arsenic exposure among smokers, and the relatively short latent period, with almost two-thirds of the wells put in place in 1990 or later.]

2.3 Cancer of the urinary bladder and of the kidney

The results of the epidemiological studies on arsenic in drinking-water and the risk for cancers of the urinary bladder and of the kidney are summarized in Table 2.7 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.7.pdf.

2.3.1 Ecological studies

In south-western and north-eastern Taiwan (China), the relation between cancer of the urinary bladder and of the kidney and drinking-water containing arsenic was evaluated in many of the studies cited above (Chen *et al.*, 1985, 1988a; Wu *et al.*, 1989; Chen & Wang, 1990; Tsai *et al.*, 1999). Each reported an elevation in mortality from these cancers during various time periods in 1971–94 associated with levels of arsenic in well-water from rural artesian wells, with many reporting a dose–response relationship among both men and women. An additional study, based on incidence records, found comparable risks for bladder cancer (Chiang *et al.*, 1993).

In Region II of Chile, two studies found markedly high SMRs for cancer of the urinary bladder and of the kidney in 1950–92 (Rivara *et al.*, 1997) and in 1989–93 (Smith *et al.*, 1998). In the latter study, mortality from chronic obstructive pulmonary disease was at the expected level, suggesting that smoking was not involved. The temporal pattern of bladder cancer mortality in Region II from 1950–2000 was compared with that in Region V (Marshall *et al.*, 2007). Increased relative risks were reported about 10 years after the start of exposure to high arsenic levels, with peak relative risks of 6.10 (95%CI: 3.97–9.39) for men, and 13.8 (95%CI: 7.74–24.5) for women in the period 1986–94. In Cordoba Province, Argentina, positive trends in SMRs were reported for bladder and kidney cancers associated with estimates of exposure to arsenic in drinking-water (Hopenhayn-Rich *et al.*, 1996, 1998), again with no findings for chronic obstructive pulmonary disease.

[The Working Group noted that kidney cancers consist of both renal cell carcinoma and transitional cell carcinoma of the renal pelvis, the latter often being of the same etiology as bladder cancer. As arsenic causes transitional cell carcinoma of the bladder, merging of the two types of kidney cancer may result in a dilution of the risk estimate for total kidney cancer.]

2.3.2 Case–control and cohort studies

In a case–control study using death certificates (1980–82) from the area in Taiwan (China), endemic for Blackfoot disease, Chen *et al.* (1986) reported increasing trends in odds ratios with increasing duration of consumption of artesian well-water containing arsenic. The highest risks were seen for over 40 years of exposure, with an odds ratio of 4.1 ($P < 0.01$) for bladder cancer in a multivariate analysis, after adjusting for smoking and other factors from next-of-kin interviews.

In case–control studies of incident bladder cancer that included analysis of arsenic species in urine samples, a higher risk associated with arsenic was found among persons with higher MMA^V:DMA^V ratios or, alternatively, with a higher percentage of MMA^V (Chen *et al.*, 2003, 2005a; Steinmaus *et al.*, 2006; Pu *et al.*, 2007a; Huang *et al.*, 2008).

Cohort studies from south-western and north-eastern Taiwan (China) (Chen *et al.*, 1988b; Chiou *et al.*, 1995, 2001; Chen & Chiou, 2001) Japan (Tsuda *et al.*, 1995), and the United Kingdom (Cuzick *et al.*, 1992) each observed elevated bladder cancer risk following long-term exposure to ingested arsenic, with dose–response relationships found where the numbers of cases permitted such an analysis. The study from Taiwan (China), also found an elevated risk of kidney cancer (OR, 2.8; 95%CI: 1.3–5.4, based on nine cases) (Chiou *et al.*, 2001).

2.4 Cancer of the skin

The recognition of arsenic as a carcinogen first came from case series describing skin cancers following the ingestion of medicines containing arsenicals (Hutchinson, 1888; Neubauer, 1947), and exposure to arsenical pesticide residues, and arsenic-contaminated wine (Roth, 1957; Grobe,

1977) or drinking-water, originating from many countries. The characteristic arsenic-associated skin tumours include squamous cell carcinomas arising in keratoses (including Bowen disease), and multiple basal cell carcinomas.

Findings of epidemiological studies on arsenic in drinking-water and risk for skin cancer are summarized in Table 2.8 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.8.pdf.

2.4.1 Ecological studies of prevalence

In south-western Taiwan (China), Tseng *et al.* (1968) found an 8-fold difference in the prevalence of skin cancer lesions from the highest (> 600 µg/L) to the lowest category (< 300 µg/L) of arsenic concentration in artesian wells, after an extensive examination survey of 40421 inhabitants in 37 villages.

2.4.2 Ecological studies based on mortality from cancer of the skin

Studies in Taiwan (China) (Chen *et al.*, 1985, 1988a; Wu *et al.*, 1989; Chen & Wang, 1990; Tsai *et al.*, 1999) analysed skin cancer mortality in relation to levels of arsenic in well-water. These investigations found consistent gradients of increasing risk with average level of arsenic in drinking-water, as measured on the township or precinct level.

Rivara *et al.* (1997) observed an SMR for skin cancer of 3.2 (95%CI: 2.1–4.8), comparing mortality from skin cancer in 1976–92 between Region II and the unexposed control Region VIII of Chile. Later, Smith *et al.* (1998) found SMRs of 7.7 (95%CI: 4.7–11.9) among men and 3.2 (95%CI: 1.3–6.6) among women for the years 1989–93 in Region II of Chile, using national mortality rates as reference. [The Working Group noted that the histological type of skin cancer was reported in only a few instances. Although skin cancer mortality can be influenced by access to health care, the SMRs reported here are so large as to not be explained by any possible confounding.]

2.4.3 Cohort studies

A retrospective cohort study of 789 (437 men, 352 women) of Blackfoot disease patients in Taiwan (China) reported an SMR of 28 (95%CI: 11–59) for skin cancer deaths (based on seven observed deaths), using Taiwan (China) regional rates as reference (Chen *et al.*, 1988b).

In a cohort of 654 persons in south-western Taiwan (China), an observed incidence rate of 14.7 cases of skin cancer/1000 person–years was found (Hsueh *et al.*, 1997), with risks significantly related to duration of living in the area endemic for Blackfoot disease, duration of consumption of artesian well-water, average concentration of arsenic, and index for cumulative exposure to arsenic. Similar findings were observed in a nested case–control study conducted within this cohort (Hsueh *et al.*, 1995).

In Region II of Chile, a decrease in incidence rates of cutaneous lesions (leukoderma, melanoderma, hyperkeratosis, and squamous cell carcinoma) was observed during 1968–71 after a lowering of waterborne arsenic levels from a filter plant, which started operation in 1970 (Zaldívar, 1974).

2.5 Cancer of the liver

2.5.1 Ecological studies

The relation between liver cancer risk and drinking-water contaminated with arsenic was evaluated in many of the studies from south-western Taiwan (China), cited above (Chen *et al.*, 1985, 1988a; Wu *et al.*, 1989; Chen & Wang, 1990; Chiang *et al.*, 1993; Tsai *et al.*, 1999; see Table 2.9 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.9.pdf), with positive associations found in all studies.

In northern Chile, Rivara *et al.* (1997) observed a relative risk for liver cancer mortality of 1.2 (95%CI: 0.99–1.6) in arsenic-exposed Region II compared with Region VIII. Liver cancer mortality in Region II of northern Chile during the period 1989–93 among persons ≥ 30 years of age was not significantly elevated, using national rates as reference (Smith *et al.*, 1998). SMRs were 1.1 (95%CI: 0.8–1.5) both for men and for women. Liaw *et al.* (2008) found an elevated relative risk (10.6; 95%CI: 2.9–39.3, $P < 0.001$) for liver cancer among children in Region II of Chile born in 1950–57 and exposed *in utero* or shortly thereafter, compared to rates in Region V of Chile.

In Cordoba Province, Argentina, SMRs were not related to arsenic exposure (Hopenhayn-Rich *et al.*, 1998).

[The Working Group noted that the finding of an association with liver cancer in Taiwan (China), but not in South America may reflect a more sensitive population in the former region, due to endemic hepatitis B. The elevated risk of those exposed *in utero* and as young children may reflect a combination of greater biological vulnerability in early life (Waalkes *et al.*, 2007) plus the fact that young children consume 5–7 times more water per kilogram body weight per day than adults (NRC, 1993).]

2.5.2 Case–control studies

In a case–control study investigating the consumption artesian well-water containing high concentrations of arsenic and mortality from liver cancer in four townships of south-westernern Taiwan (China), Chen *et al.* (1986) observed an exposure–response relationship between the duration of consumption of the contaminated well-water and risk for liver cancer, adjusted for cigarette smoking, habitual alcohol and tea drinking, and consumption of vegetables and fermented beans.

2.6 Cancer of the prostate

Studies conducted in Taiwan (China) (Chen *et al.*, 1985, 1988a; Wu *et al.*, 1989; Chen & Wang, 1990; Tsai *et al.*, 1999) analysed prostate cancer mortality in relation to levels of arsenic in well-water, with some overlap among the respective study populations. Using several methodological approaches and comparison populations including direct and indirect standardization of rates, all studies reported significant dose–response relationships between the level of arsenic in drinking-water and the risk for prostate cancer mortality (see Table 2.10 available at http://monographs.iarc.fr/ENG/Monographs/vol100C/100C-01-Table2.10.pdf).

In Chile, Rivara *et al.* (1997) found a relative risk of 0.9 (95%CI: 0.54–1.53) for prostate cancer, comparing the 1990 mortality rate for prostate cancer of Region II with that of Region VIII.

2.7 Synthesis

The Working Group reviewed a large body of evidence that covers ecological studies, case–control studies and cohort studies in a variety of settings and populations exposed either by ingestion (primarily to As^{III} and As^{V} in drinking-water) or inhalation (with exposure to a mixture of inorganic arsenic compounds). The evidence also relates to historical exposure from pesticidal and pharmaceutical uses. The epidemiological evidence from drinking-water exposure permits the evaluation of the carcinogenicity that is related to exposure to As^{III} and As^{V}. The epidemiological evidence from inhaled arsenic mixtures permits the evaluation of the carcinogenicity that is related to inorganic arsenic compounds. However, it does not allow a separation of the carcinogenic risk associated with particular arsenic species that occur in these mixtures.

The observed associations between exposure to arsenic in drinking-water and lung cancer, and between exposure to arsenic in air and lung

cancer, cannot be attributed to chance or bias. The evidence is compelling for both the inhalation and ingestion routes of exposure. There is evidence of dose–response relationships within exposed populations with both types of exposure.

The observed association between exposure to arsenic in drinking-water and bladder cancer cannot be attributed to chance or bias. There is evidence of dose–response relationships within exposed populations.

The observed association between exposure to arsenic in drinking-water and skin cancer cannot be attributed to chance or bias. There is evidence of dose–response relationships within exposed populations. The evidence is primarily for squamous cell carcinoma of the skin.

Although the data for kidney cancer are suggestive of a relationship with exposure to arsenic in drinking-water, overall, the small possibility of chance or bias cannot be completely ruled out.

The evidence for an association between liver cancer and long-term exposure to arsenic in drinking-water relies on mortality data. Although the data strongly suggest a causal association with some evidence of a dose–response relationship, the Working Group could not rule out possible chance or bias. The evidence comes mainly from Taiwan (China) where hepatitis B is highly prevalent.

The evidence for an association for prostate cancer and long-term exposure to arsenic in drinking-water relies on mortality data. In the studies from Taiwan (China), there is some evidence of a dose–response relationship. However, the data from South America are not consistent with this observation. Although the evidence on prostate cancer suggests the possibility of a causal association, the Working Group could not rule out the possibility of chance or bias.

3. Cancer in Experimental Animals

Over the years, it has proved difficult to provide evidence for the carcinogenesis of inorganic arsenic compounds. More recent work has focused on methylated arsenic metabolites in humans or exposure to inorganic arsenic during early life, and has provided the information to show potential links between arsenic and carcinogenesis.

Studies published since the previous *IARC Monograph* (IARC, 2004) are summarized below.

3.1 Oral administration

3.1.1 Mouse

The oral administration of sodium arsenate in drinking-water for 18 months increased lung tumour multiplicity and lung tumour size in male strain A/J mice (Cui *et al.*, 2006; see Table 3.1).

Similarly, drinking-water exposure to the organo-arsenical DMA^V for 50 weeks or more increased the incidence and multiplicity of lung adenoma or carcinoma in strain A/J mice (Hayashi *et al.*, 1998), and increased lung tumours in mutant *Ogg*–/– mice (which cannot repair certain types of oxidative DNA damage) but not in *Ogg*+/+ mice (Kinoshita *et al.*, 2007; see Table 3.2).

3.1.2 Rat

In male F344 rats, the oral administration of DMA^V in drinking-water for up to 2 years produced clear dose–response relationships for the induction of urinary bladder transitional cell carcinoma and combined papilloma or carcinoma (Wei *et al.*, 1999, 2002).

When DMA^V was added to the feed of male and female F344 rats for 2 years, a clear dose–response relationship for urinary bladder benign and/or malignant transitional cell tumours

Table 3.1 Studies of cancer in experimental animals exposed to sodium arsenate (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen, Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, A/J (M) 18 mo Cui *et al.* (2006)	0, 1, 10, 100 ppm arsenate in drinking-water, *ad libitum* 30/group	Lung (adenomas): 0/19, 0/13, 0/15, 4/30 (13%)	[NS, (any dose)][a]	Age at start, 5 wk Purity, NR Redundant Student *t*-test used for multiple comparisons of lung tumour multiplicity and size Survival significantly increased at high dose Non-dose-related, modest changes in bw, lung weight, and lung bw ratio
		Lung (adenocarcinomas): 9/19 (47%), 10/13 (77%), 11/15 (73%), 19/30 (63%)	[NS, (any dose)][a]	
		Average tumours/mouse lung: 0.59, 1.1, 1.3, 1.4[b]	$P < 0.01$ (all doses)	
		Average number tumours > 4 mm/mouse lung: 17, 32, 44, 60[b]	$P < 0.01$ (all doses)	

[a] Performed during review. One-sided Fisher Exact test–control versus all treated.
[b] Numbers are estimates at review because data are presented graphically in original work.
bw, body weight; M, male; mo, month or months; NR, not reported; NS, not significant; wk, week or weeks

occurred in female but not male rats (Arnold *et al.*, 2006). Preneoplasia (urothelial cell hyperplasia) was clearly increased in female rats (Arnold *et al.*, 2006; see Table 3.2).

In male F344 rats, the oral administration of trimethylarsine oxide in drinking-water for 2 years caused a significant increase of benign liver tumours (adenoma) (Shen *et al.*, 2007; see Table 3.3).

Oral exposure to MMA^V for 2 years was negative in a comprehensive dose–response study including male and female rats and mice, although body weight suppression and reduced survival with the higher doses confounded the rat segment of the study (Arnold *et al.*, 2003; see Table 3.4).

A 2-year dose–response study with sodium arsenite showed some evidence of renal tumour formation in female Sprague-Dawley rats but not in males (Soffritti *et al.*, 2006). Tumour incidence did not reach significance (see Table 3.5).

3.2 Intratracheal administration

3.2.1 Hamster

Repeated weekly intratracheal instillations of calcium arsenate, at levels sufficient to caused moderate early mortality, increased lung adenoma formation in male Syrian golden hamsters when observed over their lifespan (Pershagen & Björklund, 1985).

In a similarly designed study, male hamsters received multiple weekly intratracheal instillations of calcium arsenate at the start of the experiment, and developed an increased incidence of lung adenoma formation, and combined lung adenoma or carcinoma formation over their lifespan (Yamamoto *et al.*, 1987; see Table 3.6).

Intratracheal instillations of calcium arsenite increased the incidence of respiratory tract carcinoma and combined adenoma, papilloma and adenomatoid lesion formation in male Syrian Hamsters (Pershagen *et al.*, 1984; see Table 3.7).

Table 3.2 Studies of cancer in experimental animals exposed to dimethylarsinic acid, DMA^V (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, A/J (M) 50 wk Hayashi *et al.* (1998)	0, 50, 200, 400 ppm DMA^V in drinking-water, *ad libitum* 24/group	Number of mice with lung papillary adenomas or adenocarcinomas: 2/14 (14%), 5/14 (36%), 7/14 (50%), 10/13 (77%)	$P < 0.01$ (high dose)	Age at start, 5 wk Purity, NR Survival unremarkable [Only histologically confirmed tumours were considered by the Working Group]
Mouse, *Ogg1*-/- and *Ogg1*+/+ (M, F) 72 wk Kinoshita *et al.* (2007)	0, 200 ppm DMA^V in drinking-water, *ad libitum*; controls received tap water 10/group (*Ogg1*-/-) 12/group (*Ogg1*+/+)	***Ogg1*-/-:** Tumour-bearing mice (any site): 0/10, 10/10 (100%) *Lung lesions–* Hyperplasias: 10/10 (100%), 10/10 (100%) Adenomas: 0/10, 2/10 (20%) Adenocarcinomas: 0/10, 3/10 (30%) Total lung tumours: 0/10, 5/10 (50%) Tumours/mouse: 0, 0.5 ***Ogg1*+/+:** Tumour-bearing mice (any site): 5/10 (50%), 6/10 (60%) *Lung lesions–* Hyperplasias: 2/10 (20%), 10/10 (100%) Adenomas: 1/10 (10%), 0/10 Adenocarcinomas: 0/10, 0/10 Total tumours: 1/10 (10%), 0/10 Tumours/mouse: 0.1, 0 Tumours/mouse: 0.1, 0	$P < 0.01$ NS $P < 0.05$ $P < 0.05$ [$P < 0.01$[b]] NS NS NS NS NS	Age at start, 14 wk Purity, 99% Bw and food and water consumption unremarkable Left lobe and visible lung nodules used for histopathological tumour analysis Treated *Ogg1*–/– showed modest decreased survival (~20%) late compared to phenotypic control Small groups

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M) 104 wk Wei *et al.* (1999)[d], 2002)	0, 12.5, 50, 200 ppm DMA^V in drinking-water, *ad libitum* 36/group	Urinary bladder (hyperplasias): 0/28, 0/33, 12/31 (39%), 14/31 (45%) Urinary bladder (papillomas): 0/28, 0/33, 2/31 (2%), 2/31 (2%) Urinary bladder (carcinomas): 0/28, 0/33, 6/31 (19%), 12/31 (39%) Urinary bladder (papillomas or carcinomas): 0/28, 0/33, 8/31 (26%), 12/31 (39%)	$P < 0.01$ (middle and high dose) NS $P < 0.05$ (middle dose) $P < 0.01$ (high dose) $P < 0.01$ (middle and high dose)	Age at start, 10 wk Purity, 99% Survival and food intake unaltered Transient bw suppression early with high and middle dose but then similar to control Water intake increased at highest two doses Incidence rates based on rats at risk (surviving to time of the first bladder tumour at 97 wk) Extensive necropsy
Rat, F344 (M, F) 104 wk Arnold *et al.* (2006)	0, 2, 10, 40, 100 ppm DMA^V in feed, *ad libitum* 60/group	**Females** Urothelial cell (hyperplasias, simple, nodular and papillary): 0/60, 1/59 (2%), 0/60, 29/59 (49%), 48/60 (80%) Urinary bladder (papillomas): 0/60, 0/59, 0/60, 0/59, 4/60 (7%) Urinary bladder (carcinomas): 0/60, 0/59, 0/60, 0/59, 6/60 (10%) Urinary bladder (papillomas and carcinomas combined): 0/60, 0/59, 0/60, 0/59, 10/60 (3%) **Males** Urothelial cell (hyperplasias, simple, nodular and papillary): 0/60, 0/59, 0/60, 6/58 (10%), 40/59 (68%) Urinary bladder (papillomas): 0/60, 0/59, 1/60 (2%), 1/58 (2%), 0/59 Urinary bladder (carcinomas): 0/60, 1/59 (2%), 0/60, 0/58, 2/59 (3%) Urinary bladder (papillomas and carcinomas combined): 0/60, 1/59 (2%), 1/60 (2%), 1/58 (2%), 2/59 (3%)	$P < 0.01$ (trend) [$P < 0.01$ (highest, and second highest dose)][b] [NS (high dose)][b] $P < 0.01$ (trend)[c] [$P < 0.05$ (high dose)][b] $P < 0.01$ (trend)[c] [$P < 0.05$ (high dose)][b] $P < 0.01$ (trend) [$P < 0.01$ (high dose)][b] [NS (high dose)][b] $P < 0.01$ (trend)[c] [NS (high dose)][b] $P < 0.01$ (trend)[c] [NS (high dose)][b]	Purity > 99%; age, 5 wk Complete necropsies performed No treatment-related differences in mortality or bw Sporadic changes in food consumption not treatment-related Water consumption increased with treatment Water consumption increased with treatment

Table 3.2 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F1 (F) 104 wk Arnold *et al.* (2006)	0, 8, 40, 200, 500 ppm DMA^V in feed, *ad libitum* 56/group	**Females** No treatment-related changes in urinary bladder preneoplasia or tumour incidence noted Any organ (fibrosarcomas): 3/56 (5%), 0/55, 1/56 (2%), 1/56 (2%), 6/56 (11%) **Males** No treatment-related changes in urinary bladder preneoplasia or tumour incidence noted	$P < 0.01$ (high dose)	Age at start, 5 wk Purity 99% Complete necropsies performed Survival, bw and water consumption unchanged Sporadic, small changes in food consumption early Fibrosarcomas not considered related to treatment by authors Bw reduced at 500 ppm throughout study

[a] Data also included descriptive statistics (i.e. SD).
[b] Performed during review. One-sided Fisher exact test control versus treated.
[c] Trend analysis performed after combination of female and male data for urinary bladder lesions from this same study (Arnold *et al.*, 2006).
[d] Short communication of tumour data only.
[e] On a C57BL/6 background.
[f] As stated by the authors.
[g] The lack of information on group size and the lack of descriptive statistics makes these data impossible to independently re-evaluate for statistical significance.
bw, body weight; F, female; M, male; NR, not reported; NS, not significant; wk, week or weeks

Table 3.3 Studies of cancer in experimental animals exposed to trimethylarsine oxide (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M) 2 yr Shen *et al.* (2003)	0, 50, 200 ppm trimethylarsine oxide in drinking-water, *ad libitum* 42–45; 42 controls	Liver (adenomas): 6/42 (9%), 10/42 (14%), 16/45 (24%)	$P < 0.05$ (high dose)	Age at start, 10 wk Purity, 99% Body weights, food intake, water intake, survival rate, and average survival unaltered with treatment Extensive necropsy performed Various other sites negative

bw, body weight; M, male; yr, year or years

3.3 Intravenous administration

3.3.1 Mouse

Multiple intravenous injections of sodium arsenate in male and female Swiss mice provided no evidence of elevated tumour formation (Waalkes *et al.*, 2000; see Table 3.8).

3.4 Transplacental and perinatal exposures

3.4.1 Mouse

Pregnant mice were treated subcutaneously with arsenic trioxide on a single specific day during gestation (Days 14, 15, 16 or 17), and the offspring were then treated subcutaneously on *postpartum* Days 1, 2 and 3 with arsenic trioxide. The offspring initially treated on Day 15 of gestation developed an excess of lung adenoma compared to controls, and the other groups did not (Rudnai & Borzsanyi, 1980, 1981; see Table 3.9).

Pregnant C3H mice were exposed to various doses of sodium arsenite in the drinking-water from Days 8–18 of gestation. They were allowed to give birth and their offspring were put into gender-based groups at weaning. Over the next 90 weeks, arsenic-treated female offspring developed dose-related benign and/or malignant ovarian tumours, and lung adenocarcinoma. During the next 74 weeks, a dose-related increase in the incidences of liver adenoma and/or carcinoma, and adrenal cortical adenoma was observed in the male offspring (Waalkes *et al.*, 2003).

A second study looked at the carcinogenic effects in C3H mice of various doses of sodium arsenite (two levels) in the maternal drinking-water from Days 8 to 18 of gestation, with or without subsequent 12-*O*-tetradecanoyl phorbol-13-acetate (TPA) applied to the skin of the offspring after weaning from 4–25 weeks of age. Over the next 2 years, with arsenic alone, the female offspring developed an increased incidence of ovarian tumours. The male offspring developed arsenic dose-related increases in the incidences of liver adenoma and/or carcinoma and adrenal cortical adenoma (Waalkes *et al.*, 2004).

Pregnant CD1 mice received sodium arsenite (one level) in the drinking-water from gestation Days 8 to 18, were allowed to give birth, and the female (Waalkes *et al.*, 2006a) or male (Waalkes *et al.*, 2006b) offspring were treated with diethylstilbestrol or tamoxifen subcutaneously on *postpartum* Days 1, 2, 3, 4 and 5. In female offspring over the next 90 weeks, arsenic exposure alone

Table 3.4 Studies of cancer in experimental animals exposed to monomethylarsonic acid, MMA^V (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F1 (M, F) 104 wk Arnold *et al.* (2003)	0, 10, 50, 200, 400 ppm MMA^V in feed, *ad libitum* 52/group/sex	No treatment-related changes		Age at start, 6 wk Purity, 99% Bw reduced at 400 ppm throughout study Food and water consumption similar or increased at the two higher doses Survival unremarkable Complete necropsy performed
Rat, F344 (M, F) 104 wk Arnold *et al.* (2003)	0, 50, 400, 1 300[a] ppm MMA^V in feed, *ad libitum* 60/group/sex	No treatment-related changes		Age at start, 6 wk Purity, 99% Bw reduced at two highest doses in second half of study Food consumption generally similar Water consumption similar or increased at the two higher doses Survival reduced at high dose Complete necropsy performed

[a] Due to a high mortality in male and female rats fed this level, it was reduced to 1000 ppm during Week 53, and further reduced to 800 ppm during Week 60.
bw, body weight; F, female; M, male; wk, week or weeks

Table 3.5 Studies of cancer in experimental animals exposed to sodium arsenite (oral exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, Sprague-Dawley (M, F) 167 wk (lifespan) Soffritti *et al.* (2006)	0, 50, 100, 200 mg/L $NaAsO_2$ in drinking-water, *ad libitum* from onset to 104 wk 50/group	Kidney (tumours): F– 1/50 (2%), 1/50 (2%), 5/50 (10%), 5/50 (10%)[c] M– 0/50, 2/50 (4%), 2/50 (4%), 0/50	NS for both sexes	Age at start, 8 wk Purity 98% Complete necropsy performed Reduced water and food intake especially at two highest doses Dose-related reduced bw

[a] As stated by the authors.
[b] The lack of information on group size and lack of descriptive statistics makes the data from this work impossible to re-evaluate for statistical significance.
[c] Includes three carcinomas at the high dose and one at the second highest dose in females and a carcinoma in females at the second highest dose.
Bw, body weight; F, female; M, male; NS, not significant; wk, week or weeks

increased the incidence of tumours of the ovary, uterus, and adrenal cortex. In the male offspring, prenatal arsenic exposure alone increased liver adenoma and/or carcinoma, lung adenocarcinoma, and adrenal cortical adenoma (see Table 3.10).

3.5 Studies in which arsenic modifies the effects of other agents

3.5.1 Mouse

Mice exposed to DMA^V in drinking-water after subcutaneous injection of 4-nitroquinoline 1-oxide showed an increase in lung tumour multiplicity compared to mice exposed to the organic carcinogen alone (Yamanaka *et al.*, 1996). In K6/ODC mice first treated topically with 7,12-dimethylbenz[α]anthracene (DMBA) then with DMA^V in a cream applied to the same skin area for 18 weeks, the organo-arsenical doubled the skin tumour multiplicity compared to treatment with DMBA alone (Morikawa *et al.*, 2000; see Table 3.11). [The Working Group noted that this study had too few DMA^V controls for an appropriate interpretation.]

In the studies of Germolec *et al.* (1997, 1998), oral sodium arsenite was given to Tg.AC mice with TPA by skin painting, and an approximately 4-fold increase in skin tumour response was reported.

Combined treatment with oral sodium arsenite in drinking-water and multiple exposures to excess topical UV irradiation in Crl:SKH-*hr*BR hairless mice showed that arsenic treatment alone was consistently without carcinogenic effect, but markedly enhanced UV-induced skin tumours including squamous cell carcinoma (Rossman *et al.*, 2001; Burns *et al.*, 2004; Uddin *et al.*, 2005). In another skin study, mice exposed to topical 9,10-dimethyl-1,2-benzanthracene for 2 weeks concurrently with oral sodium arsenate in drinking-water for 25 weeks showed that arsenic treatment alone was without carcinogenic effect, but enhanced skin tumour multiplicity and tumour size when combined with the organic carcinogen compared to the organic carcinogen alone (Motiwale *et al.*, 2005; see Table 3.12).

When pregnant Tg.AC mice were treated with oral sodium arsenite in drinking-water from Days 8–18 of gestation, and their offspring were topically exposed to TPA from 4–40 weeks

Table 3.6 Studies of cancer in experimental animals exposed to calcium arsenate (intratracheal instillation)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Hamster, Syrian golden (M) ~145 wk (lifespan) Pershagen & Björklund (1985)	0, ~3 mg As/kg bw in 0.15 mL saline once/wk for 15 wk 41; 29 controls	Lung (adenomas): 0/26, 4/35 (11%)	$P < 0.05$	Age at start, 8 wk Purity, ultrapure Mortality during dosing ~15%; mortality increased in arsenate group during second yr Dose approximate
Hamster, Syrian golden (M) Up to 115 wk in treated animals, and 121 wk in controls (lifespan) Yamamoto *et al.* (1987)	0, 0.25 mg As in 0.1 mL saline once/wk for 15 wk 30; 22 controls	Lung (adenomas): 0/22, 6/25 (24%) Lung (carcinomas): 1/22 (4%), 1/25 (4%) Lung (adenomas and carcinomas combined): 1/22 (4%), 7/25 (3%)	[$P < 0.01$[a]] NS *P*-value not reported but stated as significant [$P < 0.01$[a]]	Age at start, 8 wk Purity, chemical grade Instillations caused 10% mortality and reduced survival ~10% post-instillation Bw not recorded during experiment

[a] Calculated by the Working Group. One-sided Fisher exact test control versus treated.
bw, body weight; M, male; NS, not significant; wk, week or weeks

Table 3.7 Studies of cancer in experimental animals exposed to arsenic trioxide (intratracheal instillation)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Hamster, Syrian golden (M) Up to ~140 wk (lifespan) Pershagen *et al.* (1984)[a]	0 or ~3 mg As/kg bw in 0.15 mL saline once/wk for 15 wk 67; 68 controls	Larynx, trachea, bronchus, or lung (carcinomas): 0/53, 3/47 (6%) Larynx, trachea, bronchus, or lung (adenomas, adenomatoid lesions, and papillomas combined): 7/53 (13%), 24/47 (51%)	NS [$P < 0.01$]	Age at start, 7–9 wk Purity, 99.5% Doses approximate Instillation mixture for arsenic contained carbon dust and 2 mM sulfuric acid (not in controls) Significant mortality during dosing (29%) "Adenomatoid lesion" not defined, presumably focal hyperplasia

[a] Arsenic trioxide was also given with benzo[*a*]pyrene and the combination appeared to increase combined adenoma, adenocarcinoma and adenosquamous carcinoma in the bronchi and lungs compared to benzo[*a*]pyrene alone but the data are listed (total tumours/group and not incidence) such that this cannot be independently confirmed.

bw, body weight; M, male; NS, not significant; wk, week or weeks

Table 3.8 Studies of cancer in experimental animals exposed to sodium arsenate (intravenous exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Swiss CR:NIH(S) (M, F) 96 wk Waalkes *et al.* (2000)	0, 0.5 mg As/kg bw in 10 mL/kg in saline once/wk for 20 wk staring at onset; controls received saline[a] 25/group/sex	**M** Lymphomas: 1/25 (4%), 1/25 (4%)	NS	Age at start, 8 wk Purity, NR Survival and bw not remarkable No leukaemias were observed
		Testicular interstitial cell hyperplasias: 8/25 (32%), 16/25 (64%)	$P < 0.05$	
		Skin hyperkeratosis: 1/25 (4%), 5/25 (20%)	NS	
		F Lymphomas: 5/25 (20%), 3/25 (12%)	NS	
		Uterine cystic hyperplasias: 5/25 (20%), 14/25 (56%)[b]	$P < 0.05$	

[a] Based on the treatment regimen of Osswald & Goerttler (1971).

[b] A uterine adenocarcinoma was also observed with arsenate treatment that is noteworthy because of its spontaneous rarity in historical controls of this strain.

bw, body weight; F, female; M, male; NR, not reported; NS, not significant; wk, week or weeks

Table 3.9 Studies of cancer in experimental animals exposed to arsenic trioxide (perinatal exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, CFLP (NR) 1 yr Rudnai & Borzsanyi (1980), Rudnai & Borzsanyi (1981)[a]	Single dose of 1.2 mg/kg arsenic trioxide bw s.c. at gestation Day 14, 15, 16, or 17 Test offspring: 5 µg arsenic trioxide/mouse s.c. postpartum Day 1, 2 and 3 Controls untreated Offspring group sizes at start (NR)	Lung (adenomas and adenocarcinomas):[b] Control–3/17 (17%) Day 14–14/36 (39%) Day 15–12/19 (63%) Day 16–3/20 (15%) Day 17–6/20 (30%)	$P < 0.01$ (Day 15)[b]	Purity stated as "purum" Pregnancy verified by smear and when positive designated Day 0 Dam number used to derive offspring groups NR Lung and gross lesions histologically examined Survival and bw NR Gender NR and probably mixed Numbers of specific lung tumours NR

[a] In Hungarian. Tumour incidence data are numerically the same for this and the Rudnai & Borzsanyi (1980) manuscript, but vary in that the treatment day of pregnancy which lead to a significant increase in lung adenoma in the first paper (Day 15) shifted to one day later in the second paper (Day 16). Communication with the primary author revealed that this discrepancy in the re-reporting (Rudnai & Borzsanyi, 1981) is due to a difference in calling the first day on which pregnancy was indicated Day 1 of gestation rather than Day 0 as in the original report (Rudnai & Borzsanyi, 1980). Thus, the treatment regimen and data from the primary paper are herein reported.

[b] The gestational treatment day is given in parentheses before incidence or after indication of significance.

bw, body weight; NR, not reported; s.c., subcutaneously; yr, year or years

Table 3.10 Studies of cancer in experimental animals exposed to sodium arsenite (transplacental exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, C3H/HeNCr (M, F) 90 wk (*postpartum*) for F 74 wk (*postpartum*) for M Waalkes *et al.* (2003)	Maternal exposure: 0, 42.5, 85 ppm As in drinking-water, *ad libitum* from gestation Day 8–18 Offspring; 25/group/sex	**Females** Ovary (tumours): Benign–2/25 (8%), 4/23 (17%), 8/24 (33%)	$P < 0.05$ (high dose plus trend)	Purity,[a] NR 10 Pregnant mice used to derive each group of offspring Offspring weaned at 4 wk Maternal water consumption and bw unaltered Offspring bw unaltered Survival in offspring unaltered in females Survival reduced at high dose in due to liver carcinoma in males
		Malignant–0/25, 2/23 (9%), 1/24 (4%)	NS	
		Benign or malignant combined– 2/25 (8%), 6/23 (26%), 9/24 (37%)	$P < 0.05$ (high dose) $P < 0.05$ (trend)	
		Lung (carcinomas): 0/25, 1/23 (4%), 5/24 (20%)	$P < 0.05$ (high dose) $P < 0.05$ (trend)	
		Males Liver (adenomas): 9/24 (37%), 9/21 (43%), 20/23 (87%)	$P < 0.01$ (high dose)	
		Liver (hepatocellular carcinomas): 2/24 (8%), 8/21 (38%), 14/23 (61%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Liver (adenomas or hepatocellular carcinomas): 10/24 (42%), 11/21 (52%), 20/23 (87%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Liver tumours/mouse: 0.87, 1.81, 4.91	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Adrenal cortex (adenomas): 9/24 (37%), 14/21 (67%), 21/23 (91%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Adrenal adenomas/mouse: 0.71, 1.10, 1.57	$P < 0.05$ (high dose) $P < 0.05$ (trend)	

Table 3.10 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, C3H/HeNCr (M, F) 104 wk (*postpartum*) Waalkes *et al.* (2004)	Maternal exposure: 0, 42.5, 85 ppm As in drinking-water, *ad libitum* from gestation Day 8–18 Offspring exposure: topical 2 µg[b] TPA/0.1 mL acetone, twice/wk from 4–25 wk of age applied to shaved back, controls received acetone Offspring groups: 25/group/sex	**Females** Liver (adenomas or hepatocellular carcinomas):		Purity,[a] NR 10 Pregnant mice used to derive each group of offspring Litters culled at 4 d *postpartum* to no more than 8 pups Maternal water consumption and bw unaltered Small bw reductions (~10%) occurred late (> 95 wk) in the high-dose (85 ppm) female offspring TPA did not alter bw Survival unaltered Inclusion of TPA did not have an impact on skin cancers
		Without TPA–3/24 (12%), 6/23 (26%), 4/21 (19%)	NS	
		With TPA–3/24 (12%), 6/22 (27%), 8/21 (38%)	$P < 0.05$ (high dose and trend)	
		Liver tumour multiplicity (tumours/mouse):		
		Without TPA–0.13, 0.41, 0.29	NS	
		With TPA–0.13, 0.32, 0.71	$P < 0.05$ (high dose and trend)	
		Ovary (tumours):[c]		
		Without TPA–0/24, 5/23 (22%), 4/21 (19%)	$P < 0.05$ (both doses)	
		With TPA–0/24, 5/22 (23%), 4/21 (19%)	$P < 0.05$ (both doses)	
		Lung (adenomas):		
		Without TPA–1/24 (4%), 2/23 (9%), 2/21 (9%)	NS	
		With TPA–1/24 (4%), 2/22 (9%), 6/21 (29%)	$P < 0.05$ (high dose and trend)	
		Males Liver (tumours):		Arsenic group not given TPA due to liver carcinoma (males)
		Adenomas without TPA–10/24 (42%), 12/23 (52%), 19/21 (90%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Adenomas with TPA–8/23 (35%), 12/23 (52%), 16/21 (76%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Hepatocellular carcinomas without TPA–3/24 (12%), 8/23 (35%), 10/21 (48%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Hepatocellular carcinomas with TPA–2/23 (9%), 6/23 (26%), 7/21 (33%)	$P < 0.05$ (high dose and trend)	
		Adenomas or hepatocellular carcinomas without TPA–12/24 (50%), 14/23 (52%), 19/21 (90%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	

Table 3.10 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Waalkes *et al.* (2004) (contd.)		Adenomas or hepatocellular carcinomas with TPA–9/23 (39%), 15/23 (65%), 18/21 (90%)	$P < 0.05$ (high dose) $P < 0.01$ (trend)	
		Multiplicity without TPA: 0.75, 1.87, 2.14	$P < 0.05$ (both doses) $P < 0.01$ (trend)	
		Multiplicity with TPA: 0.61, 1.44, 2.14	$P < 0.05$ (both doses) $P < 0.01$ (trend)	
		Adrenal cortex (adenomas): Without TPA–9/24 (37%), 15/23 (65%), 15/21 (71%) With TPA–7/23 (30%), 15/23 (65%), 12/21 (57%)	$P < 0.05$ (high dose and trend) $P < 0.05$ (low dose)	
		Lung (adenomas): Without TPA–4/24 (17%), 6/23 (26%), 5/21 (24%) With TPA–2/23 (9%), 10/23 (43%), 5/21 (24%)	NS $P < 0.05$ (low dose)	
Mouse, CD1 (M, F) 90 wk (*postpartum*) Waalkes *et al.* (2006a, b)[k]	Maternal exposure: 0, 85 ppm As in drinking-water, *ad libitum* from gestation Day 8–18 Offspring exposure: *Postpartum* Day 1, 2, 3, 4, and 5 2 µg DES[d]/pup/d s.c., or 10 µg TAM[e]/pup/d s.c., or vehicle (corn oil; control) (control, As, DES, TAM, As + DES, As + TAM) 35/group/sex	**Females** Ovary (tumours):[h] 0/33, 7/34 (21%), 2/33 (6%), 1/35 (3%), 9/33 (26%), 5/35 (14%)	$P < 0.05$ (As, As + DES, As + TAM)	Purity 97.0% $NaAsO_2$ 12 Pregnant mice used to derive each group of offspring Litters culled after birth to no more than 8 pups Maternal water consumption unaltered Maternal and offspring bw unaltered
		Uterus (adenomas): 0/33, 3/34 (9%), 0/33, 0/35, 0/33, 0/35	NS	
		Uterus (carcinomas): 0/33, 2/34 (6%), 0/33, 2/35 (6%), 7/33 (21%), 2/35 (6%)	$P < 0.05$ (As + DES)	
		Uterus (adenomas or carcinomas): 0/33, 5/34 (15%), 0/33, 2/35 (6%), 7/33 (21%), 2/35 (6%)	$P < 0.05$ (As, As + DES)	
		Vagina (carcinomas): 0/33, 0/34, 1/33, 0/35, 5/33[g] (15%), 0/35	$P < 0.05$ (As + DES)	
		Adrenal cortex (adenomas): 1/33 (3%), 9/34 (26%), 3/33 (9%), 2/35 (6%), 8/33 (24%), 7/35 (20%)	$P < 0.05$ (As, As + DES, As + TAM)	
		Urinary bladder lesions:		

Table 3.10 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Waalkes *et al.* (2006a, b) (contd.)		Hyperplasias– 1/33 (3%), 5/34 (15%), 1/33 (3%), 0/35, 10/33 (30%), 9/35 (26%)	$P < 0.05$ (As + DES, As + TAM)	
		Papillomas– 0/33, 0/34, 0/33, 0/35, 0/33, 1/35 (3%)	NS	
		Carcinomas[i]– 0/33, 0/34, 0/33, 0/35, 3/33 (9%), 0/35	NS	
		Total proliferative lesions[j]– 1/33 (3%), 5/34 (15%), 1/33 (3%), 0/35, 13/33[g] (38%), 10/35[g] (29%)	$P < 0.05$ (As + DES, As + TAM)	
		Liver (tumours any type): 0/33, 4/34 (12%), 1/33 (3%), 0/35, 5/33 (15%), 4/35 (11%)	$P < 0.05$ (As + DES)	
		Males Liver (tumours):		Purity sodium arsenite 97.0%; DES 99%, TAM 99% Bw transiently reduced (~15%) by DES or TAM early but recovery to control levels by 5–20 wk *postpartum* Survival unaltered by prenatal arsenic alone. Survival reduced in all other treatment groups (DES, TAM, As + DES, As + TAM) from ~20 wk on compared to control[l] (males)
		Adenomas– 2/35 (6%), 8/35 (23%), 1/33 (3%), 0/30, 12/29 (41%), 9/30 (30%)	$P < 0.05$ (As, As + DES, As + TAM)	
		Hepatocellular carcinomas– 0/35, 5/35 (14%), 0/33, 0/30, 4/29 (14%), 5/30 (17%)	$P < 0.05$ (As, As + DES, As + TAM)	
		Adenomas or carcinomas– 2/35 (6%), 11/35 (31%), 1/33 (3%), 0/30, 14/29 (48%), 14/30 (47%)	$P < 0.05$ (As, As + DES,)	
		Lung (adenocarcinomas): 2/35 (6%), 9/35 (26%), 2/33 (6%), 0/30, 4/29 (14%), 6/30 (20%)	$P < 0.05$ (As)	
		Adrenal cortex (adenomas): 0/35, 13/35 (37%), 0/33, 0/30, 9/29 (31%), 11/30 (37%)	$P < 0.05$ (As, As + DES, As + TAM)	
		Urinary bladder lesions: Hyperplasias– 0/35, 3/35 (9%), 4/33 (12%), 3/30 (10%), 13/29[g] (45%), 9/30[g] (30%)	$P < 0.05$ (As + DES, As + TAM)	
		Papillomas– 0/35, 0/35, 0/33, 0/30, 0/29, 3/30 (10%)	NS	

Table 3.10 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Waalkes *et al.* (2006a, b) (contd.)		Carcinomas[i]– 0/35, 0/35, 0/33, 0/30, 1/29 (3%), 1/30 (3%)	NS	
		Papillomas or carcinomas– 0/35, 0/35, 0/33, 0/30, 1/29 (3%), 4/30[g] (13%)	$P < 0.05$ (As + TAM)	
		Total proliferative lesions[j]– 0/35, 3/35 (9%), 4/33 (12%), 3/30 (10%), 13/29[g] (45%), 14/30[g] (40%)	$P < 0.05$ (As + DES, As + TAM)	

[a] Purity given in Waalkes *et al.* (2006a) using same chemical source is 97.0%.
[b] 12-*O*-tetradecanoyl phorbol-13-acetate.
[c] Exclusively epithelial and primarily adenoma.
[d] Diethylstilbestrol
[e] Tamoxifen
[f] Included benign and malignant epithelial and mesenchymal tumours within components of the urogenital system (ovary, oviduct, uterus, cervix, vagina, kidney, and urinary bladder).
[g] Incidence for arsenic plus DES or arsenic plus TAM was significantly ($P < 0.05$) higher than arsenic alone.
[h] Primarily adenoma.
[i] Exclusively transitional cell carcinoma.
[j] Defined by the authors as the incidence of mice bearing at least one uroepithelial preneoplasia (hyperplasia), papilloma, or carcinoma.
[k] Run concurrently with and derived from the same mothers as the females in Waalkes *et al.* (2006a) study but reported separately.
[l] Reduced survival in these groups appeared dependent on moderate to extensive kidney damage due to DES and TAM in male mice and appeared unrelated to arsenic exposure.
[m] Two renal tumours also occurred in this group including, an adenoma and a renal cell carcinoma, against none in control, which are noteworthy because of their rare spontaneous occurrence in mice.
d, day or days; DES, diethylstilbestrol; F, female; M, male; NR, not reported; NS, not significant, s.c., subcutaneously; TAM, tamoxifen; wk, week or weeks

Table 3.11 Studies where arsenicals given after other agents enhance carcinogenesis while having no effect alone in experimental animals

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, ddy (M) 25 wk Yamanaka *et al.* (1996)	Initiation 10 mg 4NQO[e]/kg bw s.c. then 200 or 400 ppm DMA^V in drinking-water for 25 wk Groups: 4NQO alone, 4NQO + 200 ppm DMA, 4NQO + 400 ppm DMA 9–13/group	Macroscopic lung tumours/mouse: 0.22, 3.92, 4.38	$P < 0.05$ (high dose)	Age at start, 6 wk DMA^V purity, NR Bw and survival unremarkable DMA^V alone group not included Lung only Microscopic analysis of lung tumours not reported (largely confirmed as tumours) Small group sizes
Mouse, *K6/ODC* (C57BL/6J background) 20 wk Morikawa *et al.* (2000)	Single 50 µg dose of DMBA[f]/mouse topical dorsal skin at Week 1; then 3.6 mg DMA^V/mouse in "neutral cream" to dorsal skin twice/wk, Week 2–19 Groups: DMBA, DMBA + DMA^V 7; 8 controls (DMBA)	Macroscopic skin tumours/mouse: 9.7, 19.4	$P < 0.05$	Age at start, 10–14 wk DMA^V purity, NR Bw and survival unremarkable DMA^V-alone group had only 2 mice; skin tumours not reported Small group sizes Skin only No quantitative microscopic analysis of skin tumours
Rat, Wistar (M) 175 d Shirachi *et al.* (1983)	Sodium arsenite Partial heptectomy, 18–24 h later 30 mg DEN[a]/kg i.p.; 7 d later 160 ppm As in drinking-water Number at start, NR	Renal tumours: 0/10, 1/7 (14%), 0/9, 7/10 (70%)	$P < 0.05$	Age at start, NR Purity, NR Arsenic lowered bw and water intake Limited reporting and never reported in full

Table 3.11 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344/DuCrj (M) 30 wk Yamamoto *et al.* (1995)	Initial pretreatment with 5 known carcinogens (termed DMBDD[b]) then 0, 50, 100, 200, 400 ppm DMA^V in the drinking-water during Week 6–30 Groups: DMBDD alone, DMBDD + 50 ppm DMA^V, DMBDD + 100 ppm DMA^V, DMBDD + 200 ppm DMA^V, DMBDD + 400 ppm DMA^V 20/group	Urinary bladder:[c]		Age at start, 7 wk DMA^V purity, 99%; DMA^V initially lowered but then increased bw; changes moderate and at high dose DMA^V increased water intake at high dose Survival unremarkable Separate 100 and 400 ppm (12 each) DMA^V alone groups were included but had no tumours or preneoplastic lesions
		Papillomas– 1/20 (5%), 12/20 (60%), 12/19 (63%), 11/20 (55%), 7/20 (35%)	$P < 0.01$ (three lowest) $P < 0.05$ (highest)	
		Transitional cell carcinomas– 1/20 (5%), 10/20 (50%), 11/19 (60%), 12/20 (60%), 13/20 (65%)	$P < 0.01$ (all DMA^V treatment groups)	
		Papillomas or carcinomas– 2/20 (10%), 17/20 (85%), 16/19 (84%), 17/20 (85%), 16/20 (80%)	$P < 0.01$ (all DMA^V treatment groups)	
		Kidney:		
		Adenomas– 1/20 (5%), 3/20 (15%), 1/19 (5%), 7/20 (35%), 3/20 (15%)	$P < 0.01$ (second highest)	
		Adenocarcinomas– 0/20, 0/20, 2/19 (10%), 1/20 (5%), 7/20 (35%)	$P < 0.01$ (high dose and trend)	
		Total– 5/20 (25%), 3/20 (15%), 6/19 (30%), 13/20 (65%), 13/20 (65%)	$P < 0.05$ (trend)	
		Liver:		
		Hepatocellular carcinomas– 0/20, 2/20 (10%), 0/19, 8/20 (40%), 8/20 (40%)	$P < 0.05$ (highest two and trend)	
		Total– 0/20, 2/20 (10%), 2/19 (10%), 17/20 (85%), 13/20 (65%)	$P < 0.05$ (highest two) $P < 0.01$ (trend)	
		Total thyroid gland tumours: 3/20 (15%), 2/20 (10%), 8/19 (40%), 6/20 (30%), 9/20 (45%)	$P < 0.05$ (highest) $P < 0.01$ (trend)	

Table 3.11 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Rat, F344 (M) 36 wk Wanibuchi *et al.* (1996)	Pretreatment with BBN[d] 0.05% in drinking-water for 4 wk then 0, 2, 10, 25, 50, or 100 ppm DMA^V in drinking-water for 32 wk Groups: BBN alone, BBN + 2 ppm DMA^V, BBN + 10 ppm DMA^V, BBN + 50 ppm DMA^V, BBN + 100 ppm DMA^V 20/group	Urinary bladder: Papillary/nodular hyperplasias– 14/20 (70%), 13/20 (65%), 14/20 (70%), 18/19 (95%), 20/20 (100%), 20/20 (100%)	$P < 0.05$ (highest two doses)	Age at start, ~6 wk DMA^V purity, 99% Separate 0 and 100 ppm control and DMA^V alone groups were included (12 each) but showed no urinary bladder tumours or preneoplastic lesions Bw, water intake and survival unremarkable Urinary bladder only
		Papillomas– 3/20 (15%), 2/20 (10%), 7/20 (35%), 11/19 (58%), 13/20 (65%), 17/20 (85%)	$P < 0.01$ (highest three doses)	
		Carcinomas– 1/20 (5%), 2/20 (10%), 3/20 (15%), 7/19 (37%), 10/20 (50%), 12/20 (60%)	$P < 0.05$ (third highest dose) $P < 0.01$ (highest two doses)	

[a] Diethylnitrosamine

[b] The organic carcinogen treatment consisted of a single dose of diethylnitrosamine (100 mg/kg, i.p.) at the start of the experiment) and *N*-methyl-*N*-nitrosourea (20 mg/kg, s.c.) on experimental Days 5, 8, 11 and 14. Thereafter, rats received 1,2-dimethylhydrazine (40 mg/kg, s.c.) on Days 18, 22, 26, and 30). During the same period (experimental Days 0–30) the rats received *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine (0.05% in the drinking-water Weeks 1 and 2) and *N*-bis(2-hydroxypropyl)nitrosamine (0.1% in the drinking-water, Weeks 3 and 4). Altogether this was defined as DMBDD treatment. Rats received no treatment for 2 wk after DMBDD exposure and before DMA exposure.

[c] For brevity, only significant proliferative lesions are noted for each tissue

[d] *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine

[e] 4-Nitroquinoline

[f] 7,12-dimethylbenz[α]anthracene

[g] Estimated from graphical presentation.

d, day or days; DMA, dimethylarsinic acid; F, female; i.p., intraperitoneal; M, male; NR, not reported; s.c., subcutaneously; wk, week or weeks

Table 3.12 Studies where arsenicals given concurrently with other agents enhance carcinogenesis while having no effect alone in experimental animals

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Tg.AC homozygous (F) 14 wk Germolec *et al.* (1997)	0 or 0.02% As in drinking-water, *ad libitum* throughout experiment 0 or 2.5 µg TPA[a]/mouse in acetone topical to shaved dorsal skin twice/wk, Week 5 and 6 Groups: control, As alone, TPA, As + TPA 20/group	Macroscopic skin papillomas/mouse: none in control or arsenic alone, intermediate in TPA alone (~0.5/mouse),[b] "4-fold higher" (~2.1/mouse)[b] in arsenic + TPA	NR	Age at start, NR Purity, NR Survival unremarkable Specific quantitative microscopic analysis of skin tumours not included but confirmed as papillomas at termination Skin lesions only Incomplete reporting makes independent statistical analysis impossible
Mouse, Tg.AC homozygous (F) 24 wk Germolec *et al.* (1998)	0 or 0.02% As in drinking-water, *ad libitum* throughout experiment 0, 1.25, 2.5 µg TPA/mouse in acetone topical to shaved dorsal skin twice/wk, Week 5 and 6 Groups: control, As alone, 1.25 TPA, 2.5 TPA, As + 1.25 TPA, As + 2.5 TPA 20/group	Macroscopic skin papillomas/mouse: 0 in control, As alone, and 1.25 TPA alone; As + 1.25 TPA maximal ~5/mouse,[b] 2.5 TPA ~3/mouse,[b] in arsenic + 2.5 TPA ~7/mouse[b]	NR	Age at start, 8 wk Purity, NR Survival impacted by high-dose TPA co-treatment but specifics not given Quantitative microscopic analysis of skin tumours not included but confirmed as papillomas at termination Skin lesions only Incomplete reporting makes independent statistical analysis impossible

Table 3.12 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Crl: SKl-*hr*BR (hairless) (F) 29 wk Rossman *et al.* (2001)	0, 10 mg/L sodium arsenite in drinking-water throughout experiment plus topical 1.7 kJ/m^2 solar irradiation (85% UVB, < 1% UVC, 4% UVA, remainder visible; termed UVR[c]) 3x/wk starting 3 wk after As until termination Groups: control, As alone, UVR alone, As + UVR 5–15; 5 controls	Skin (tumours): Macroscopic and microscopic analysis–0/5, 0/5 (control and As alone) Macroscopic analysis– Time to first occurrence: As + UVR earlier than UVR Microscopic analysis– Total tumours all mice: 53 (UVR), 127 (As + UVR) Highly invasive squamous cell carcinoma: 14/53 (26%; UVR), 64/127 (50%; As + UVR) Tumour volume: UVR smaller than As + UVR	 $P < 0.01$ $P < 0.01$ $P < 0.01$	Age at start, 3wk Purity, NR Survival and bw unremarkable Small control groups
Mouse, SKl (hairless), (NR) 29 wk Burns *et al.* (2004)	Experiment 1: 0, 1.25, 2.50, 5.00, 10.0 mg/L sodium arsenite in drinking-water from onset plus topical 0 or 1.0 kJ/m^2 solar irradiation (UVR[c]) 3x/wk, starting 3 wk after As to termination Experiment 2: 10.0 mg/L sodium arsenite in drinking-water from onset plus topical 1.7 kJ/m^2 UVR[c] 3x/wk starting 3 wk after As to termination	Experiment 1: Skin tumours/mouse[d]: 2.4 (UVR), 5.4 (1.25 As + UVR), 7.21 (2.5 As + UVR), 11.1 (5.0 As + UVR), 6.8 (10.0 As + UVR) Experiment 2: Skin tumours/mouse:[d] 3.5 (UVR), 9.6 (As + UVR) Skin tumour incidence: 0/10, 0/10 (control and As alone both experiments)	[$P < 0.01$ all groups vs UVR alone[e]] [$P < 0.01$[f]]	Age, 3 wk Survival and bw unremarkable Specific quantitative microscopic analysis of skin tumours not reported but confirmed as primarily squamous cell carcinomas at termination Experiment 1 shows clear arsenic dose–response in enhancement through 5.0 mg/L by various criteria

Table 3.12 (continued)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Crl: SKl-*hr*BR (hairless) (F) Duration, NR Uddin *et al.* (2005)	0, 5 mg/L sodium arsenite in drinking-water from onset; diet unsupplemented or with added vitamin E (62.5 IU/kg diet; basal 49.0 IU/kg) or *p*-XSC[g] (10 mg/kg diet) from onset. Topical 1.0 kJ/m^2 UVR[c] 3x/wk starting 3 wk after As to termination. Groups: UVR alone, UVR + As, UVR + As + Vitamin E, UVR + As + *p*-XSC[h] 10; 30 controls (UVR)	Macroscopic skin tumours/mouse: 3.60 (UVR alone), 7.00 (UVR + As), 3.27 (UVR + As + Vitamin E), 3.40 (UVR + As + *p*-XSC)	$P < 0.01$ (UVR vs UVR + As) $P < 0.01$ (UVR + As vs UVR + As + either dietary supplement)	Age at start, 3 wk Sodium arsenite, purity (NR), *p*-XSC Purity > 99% Survival and bw unremarkable Small control groups Vitamin E and *p*-XSC added as antioxidants Specific quantitative microscopic analysis of skin tumours not reported but random sampling (10 tumours/group) confirmed primarily squamous cell carcinomas at termination No untreated control or arsenic alone groups included
Mouse, Swiss-bald hairless (M) 25 wk Motiwale *et al.* (2005)	Treatment with 2 mg BA[i] /mL 25 µL topical once/wk for 2 wk Sodium arsenate 0 or 25 mg/L drinking-water for 25 wk Groups: Control, BA, As, BA + As 10/group	Macroscopic skin tumours/mouse: 0, 2.0, 0, 3.2[b] % large papillomas (≥ 3 mm) of total papillomas: 0, 16, 0, 65[d]	$P < 0.05$ (As + BA vs BA) $P < 0.05$ (As + BA vs BA)	Age at start, 8 wk Purity, NR Survival unremarkable Small group sizes Quantitative microscopic skin tumour incidence or multiplicity not reported though histologically confirmed

[a] 12-*O*-tetradecanoyl-13-acetate.
[b] Estimated from graphical presentation. No descriptive statistics included.
[c] UVR as defined in Rossman *et al.* (2001) above.
[d] Data included descriptive statistics.
[e] Using Dunnett's multiple comparison test and not including arsenic alone and untreated control groups
[f] Using Student's*t*-test.
[g] 1,4-Phenyl*bis*(methylene)selenocyanate a synthetic organoselenium compound.
[h] Some control groups are not discussed for the sake of brevity (UVR + Vitamin E and UVR +*p*-XSC).
[i] 9,10-dimethyl-1,2-benzanthracene.
F, female; M, male; NR, not reported; wk, week or weeks

of age, although arsenic treatment alone had no effect, it markedly increased the multiplicity of squamous cell carcinoma when combined with TPA compared to TPA alone (Waalkes *et al.*, 2008; see Table 3.13).

Prenatal sodium arsenite exposure via maternal drinking-water when combined with postnatal topical TPA exposure increased the liver tumour incidence and multiplicity in an arsenic-dose-related fashion (female offspring), and lung tumours (male offspring) compared to controls; effects not seen with TPA or arsenic alone (Waalkes *et al.*, 2004). Prenatal arsenic exposure followed by postnatal diethylstilbestrol increased uterine carcinoma, vaginal carcinoma, urinary bladder total proliferative lesions, and liver tumours in female offspring compared to controls; effects not seen with diethylstilbestrol or arsenic alone. In female offspring, prenatal arsenic exposure followed by postnatal tamoxifen administration similarly increased urinary bladder total proliferative lesions (Waalkes *et al.*, 2006a).

In male offspring, prenatal arsenic exposure followed by postnatal diethylstilbestrol increased the liver tumour response and urinary bladder total proliferative lesions effects when compared to controls; effects not seen with diethylstilbestrol or arsenic alone. In male offspring, prenatal arsenic exposure followed by postnatal tamoxifen increased liver tumour response, urinary bladder total tumours, and urinary bladder total proliferative lesions (Waalkes *et al.*, 2006b).

3.5.2 Rat

Rats that underwent partial hepatectomy followed by diethylnitrosamine injection and one week later by oral administration of sodium arsenite in the drinking-water for approximately 24 weeks showed an increased incidence of renal tumours, but arsenic treament alone had no effect (Shirachi *et al.*, 1983).

In a comprehensive study, rats were given an initial pretreatment with a mixture of organic carcinogens (including diethylnitrosamine, *N*-methyl-*N*-nitrosourea, 1,2-dimethylhydrazine, *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine, and *N*-bis(2-hydroxypropyl)nitrosamine) by various routes, no treatment for 2 weeks and then DMA^V (at four levels) in the drinking-water for 24 weeks, rats developed an increased incidence of tumours of urinary bladder with the combined carcinogen treatment and arsenical (Yamamoto *et al.*, 1995).

In another study in rats, *N*-butyl-*N*-(4-hydroxybutyl)nitrosamine in the drinking-water was used as an initiator for 4 weeks followed by four levels of DMA^V for 32 weeks, and the combined treatment increased urinary bladder hyperplasia, papilloma, and carcinoma, but the arsenical treatment alone had no effect (Wanibuchi *et al.*, 1996).

3.6 Gallium arsenide

A single study (NTP, 2000) was judged to provide evidence for the carcinogenicity of gallium arsenide in rodents. In this report, $B6C3F_1$ mice and F344 rats were exposed via inhalation to various levels of gallium arsenide particulate for up to ~2 years, and the tumour response was assessed in various tissues (see Table 3.14).

3.6.1 Mouse

No treatment-related tumours were observed, but in both males and females, dose-related increases in the incidence in lung epithelial alveolar hyperplasia were reported.

3.6.2 Rat

In female rats, dose-related responses were reported for the incidence of lung alveolar/bronchiolar tumours and atypical hyperplasia

Table 3.13 Studies where arsenic given before another agent enhances carcinogenesis while having no effect alone in experimental animals

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, Tg.AC (M, F) Homozygous 40 wk (*postpartum*) Waalkes *et al.* (2008)	Maternal exposure: 0, 42.5, 85 ppm arsenic in drinking-water, *ad libitum*, gestation Day 8–18	Skin (tumours): Papillomas/mouse[a]– 0.5 (control), 0.9 (42.5 As), 0.12 (85 As), 17 (TPA[b]), 17 (42.5 As + TPA), 11 (85 As + TPA)	$P < 0.05$ (all TPA groups vs control; TPA alone vs 85As + TPA)	Age, 4 wk (offspring) Purity, NR Litters culled at 4 d *postpartum* to no more than 8 pups 10 pregnant mice used to randomly derive each group Maternal water consumption and body unaltered Offspring weaned at 4 wk Offspring bw unaltered by arsenic All skin tumours were histopathologically diagnosed for stage and number per animal Some mice were killed because of tumour burden during experiment but were not lost to observation Only skin tumours reported
	Offspring exposure:[a] TPA, 2 µg/0.1 mL acetone, topical twice/wk, applied to shaved dorsal skin, 4–40 wk of age (36 wk of TPA exposure)	Squamous cell carcinomas/mouse:[a] 0.04 (control), 0.06 (42.5 As), 0.04 (85 As), 0.57 (TPA), 1.31 (42.5 As + TPA), 1.49 (85 As + TPA)	$P < 0.05$ (all TPA groups vs control; all As + TPA groups vs TPA alone $P < 0.01$ (trend with As in TPA-treated mice)	
	Offspring groups (M, F):[c] Without TPA: (0, 42.5, 85 ppm arsenic) With TPA: (0, 42.5, 85 ppm arsenic) 50/group	Incidence of mice with 3 or more squamous cell carcinomas: 0/49 (control), 0/47 (42.5 As), 0/48 (85 As), 1/47 (2%; TPA), 9/48 (19%; 42.5 As + TPA), 14/49 (29%; 85 As + TPA)	$P < 0.05$ (all TPA + As groups vs control or TPA alone) $P < 0.01$ (trend with As in TPA-treated mice)	

[a] Manuscript included descriptive statistics.
[b] 12-*O*-tetradecanoyl-13-acetate.
[c] Because initial analysis of tumours showed no gender-based differences between similarly treated groups of males and females, they were pooled for final assessment and are reported as such. Initial groups were made up of 25 M and 25 F mice.
bw, body weight; F, female; M, male; NR, not reported; vs; versus; wk, week or weeks

Table 3.14 Studies of cancer in experimental animals exposed to gallium arsenide (inhalation exposure)

Species, strain (sex) Duration Reference	Dosing regimen Animals/group at start	Incidence of tumours	Significance	Comments
Mouse, B6C3F$_1$ (M, F) 105 wk for M 106 wk for F NTP (2000)	0, 0.1, 0.5, 1.0 mg/m^3 6 h/d, 5 d/wk 50/group/sex	**Females** Lung (epithelial alveolar hyperplasias):2/50 (4%), 5/50 (10%), 27/50 (54%), 43/50 (86%) Lung[a] (adenomas or carcinomas): 7/50 (14%), 4/50 (8%), 4/50 (8%), 6/50 (12%) **Males** Lung (epithelial alveolar hyperplasias):4/50 (8%), 9/50 (18%), 39/50 (78%), 45/50 (90%) Lung[a] (adenomas or carcinomas): 15/50 (30%), 14/50 (28%), 16/50 (32%), 13/50 (26%)	$P \leq 0.01$ (high dose) $P \leq 0.01$ (mid-dose) NS $P \leq 0.01$ (high dose) $P \leq 0.01$ (mid-dose) NS	Age at start, 6 wk Purity > 98% MMAD, 0.9–1.0 µm GSD, 1.8–1.9 µm Chamber controls used No reduced bw with treatment Survival unaltered No increases in tumour incidence
Rat, F344 (F) 105 wk NTP (2000)	0, 0.01, 0.1, 1.0 mg/m^3 6 h/d, 5 d/wk 50/group/sex	**Females** Lung[a] (adenomas): 0/50, 0/50, 2/50 (4%), 7/50 (14%) Lung (carcinomas): 0/50, 0/50, 2/50 (4%), 3/50 (6%) Lung (adenomas or carcinomas): 0/50, 0/50, 4/50 (8%), 9/50 (18%) Adrenal medulla:[b] 4/50 (8%), 6/49 (12%), 6/50 (12%), 13/49 (27%) Mononuclear cell leukaemia: 22/50 (44%), 21/50 (42%), 18/50 (36%), 33/50 (66%) **Males** Lung (atypical hyperplasias): 0/50, 2/49 (4%), 5/50 (10%), 18/50 (36%) Lung[a] (adenomas): 1/50 (2%), 0/49, 3/50 (6%), 2/50 (4%) Lung (carcinomas): 2/50 (4%), 0/49, 2/50 (4%), 1/50 (2%) Lung (adenomas or carcinomas): 3/50 (6%), 0/49, 5/50 (10%), 3/50 (6%)	$P \leq 0.01$ (high dose) $P \leq 0.01$ (trend) NS $P \leq 0.01$ (high dose) $P \leq 0.01$ (trend) $P \leq 0.01$ (high dose) $P \leq 0.01$ (trend) $P \leq 0.05$ (high dose) $P \leq 0.01$ (trend) $P \leq 0.01$ (high dose) $P \leq 0.05$ (mid-dose) NS NS NS	Age at start, 6 wk Purity > 98% MMAD, 0.9–1.0 µm GSD, 1.8–1.9 µm Chamber controls used Minimal decrease in body weight at high dose in second yr Survival unaltered No increases in tumour incidence in males

[a] All lung tumours were of avelolar/bronchiolar origin.

[b] All tumours were benign pheochromocytoma except one which was malignant in the low-dose group.

d, day or days; F, female; h, hour or hours; M, male; NS, not significant; wk, week or weeks; yr, year or years

of the alveolar epithelium. In male rats, though treatment-related tumours were not observed, a dose-related increase in the incidence of atypical hyperplasia of the lung alveolar epithelium occurred. Atypical hyperplasia of the lung alveolar epithelium is considered potentially preneoplastic. In the female rats, dose-related increases in the incidence of adrenal medulla pheochromocytomas and an increase in mononuclear cell leukaemia at the highest dose were also reported (NTP, 2000).

3.6.3 Hamster

Another study using intratracheal instillation of gallium arsenide in hamsters (Ohyama *et al.*, 1988) was judged inadequate due to critical design flaws (short duration, small groups, etc.) with no indication of tumours.

3.7 Synthesis

Oral administration of sodium arsenate and DMA^V induced lung tumours in mice. Calcium arsenate induced lung tumours in hamsters by oral and intratracheal administration. Pre- and postnatal exposure in mice to arsenic trioxide, through subcutaneous injections (maternal and postnatal), induced lung tumours in the offspring. Transplacental exposure via maternal oral exposure in mice to sodium arsenite during gestation induced lung, liver, ovary and adrenal tumours in the offspring in several studies, and the uterus in one study. Early life transplacental and perinatal exposure to sodium arsenite appears to be a time of particular sensitivity in terms of carcinogenesis.

Oral exposure to DMA^V induced urinary bladder tumours in several studies in rats and among studies in mice, only one showed negative results. Oral trimethylarsine induced liver tumours in rats. Chronic oral exposure to MMA^V did not produce tumours in rats and mice. [The Working Group considered that previous traditional bioassays for arsenicals for adult rodents were frequently negative in their final evaluations.]

Inhalation of gallium arsenide causes lung and adenal tumours in rats but not in mice.

In multiple studies, initiating, promoting or co-carcinogenic activity was demonstrated in the urinary bladder, skin, female reproductive tract, kidney, lung, liver and thyroid after exposure to inorganic arsenicals or DMA^V in drinking-water or by transplacental exposure.

4. Other Relevant Data

4.1 Absorption, distribution, metabolism, and excretion

Most inorganic arsenic compounds are readily absorbed after oral exposure (about 80–90% for soluble compounds, and a smaller percentage for less soluble compounds), less well absorbed after inhalation (better for small particulates and soluble arsenicals), and least well absorbed after dermal exposure (NRC, 1999; IARC, 2004). Large airborne arsenic-containing particulates that are deposited in the upper airways may also be absorbed in the intestine if they are later swallowed. Hamsters exposed to gallium arsenide by the oral route or by intratracheal instillation showed the presence of As^{III} in blood and urine, but the majority of the gallium arsenide was excreted in faeces, indicating that absorption was limited by its insolubility. Absorption was about 30 times higher after intratracheal installation than by the oral route (Carter *et al.*, 2003).

The transport of As^V is thought to take place via phosphate transporters (Csanaky & Gregus, 2001). The sodium-coupled phosphate transporter NaPi-IIb may be responsible in part for the intestinal and hepatic uptake of As^V (Villa-Bellosta & Sorribas, 2008). As^{III} enters the cell by aquaglyceroporins 9 and 7 (Liu *et al.*, 2004),

although another major pathway for the uptake of As^{III} and MMA^{III} (see below) is probably via hexose permeases (Rosen & Liu, 2009). Because As^{V} is rapidly reduced to As^{III} once it enters the cell (Carter *et al.*, 2003), the faster rate of cellular uptake of As^{III}, compared with As^{V}, may be part of the explanation for the greater toxicity of As^{III} (Bertolero *et al.*, 1987; Dopp *et al.*, 2004). However, the much higher chemical reactivity of As^{III}, compared to that of As^{V} is the major explanation. Some data suggests that glyceraldehyde 3-phosphate dehydrogenase (GAPDH) functions as a cytosolic As^{V} reductase *in vivo* (Németi *et al.*, 2006), although there are other candidate enzymes for this reaction (Aposhian *et al.*, 2004). As^{III} can react with cellular glutathione (GSH), either spontaneously or enzymatically, to form the tri-glutathione complex $As(SG)_3$ (Leslie *et al.*, 2004; Rey *et al.*, 2004).

As^{III} is metabolized by stepwise methylation, mainly in the liver. Although some details of inorganic arsenic metabolism remain uncertain (Aposhian & Aposhian, 2006), it is clear that the enzyme arsenic (+3 oxidation state) methyltransferase (AS3MT) is involved (Thomas *et al.*, 2007). Two schemes have been proposed for the methylation.

Reduction: As^{V} + thiol → As^{III}
Oxidative methylation: As^{III} + SAM → monomethylarsonate (MMA^{V})
Reduction: MMA^{V} + thiol → MMA^{III}
Oxidative methylation: MMA^{III} + SAM → dimethylAs^{V} (DMA^{V})
Reduction: DMA^{V} + thiol → DMA^{III}

Scheme 1: Inorganic arsenic metabolic pathway in mammals. As^{III} methylation is catalysed by AS3MT using *S*-adenosylmethionine (SAM) as a methyl donor and thioredoxin (or, less efficiently, other thiols such as glutaredoxin or lipoic acid) as a reductant. MMA^{III}: monomethylarsonous acid; MMA^{v}: monomethylarsonic acid; DMA^{III}: dimethylarsinous acid; DMA^{v}: dimethylarsinic acid

$As(SG)_3$ + SAM → MMA^{III} $(SG)_2$
MMA^{III} $(SG)_2$ + SAM → DMA^{III} (SG)

Scheme 2: The use of $As(SG)_3$ (tri-glutathione complex) as a substrate for methylation (Hayakawa *et al.*, 2005). Each of the glutathione (GSH) complexes can also decompose to yield GSH and MMA^{III} or DMA^{III}, which can then form MMA^{V} and DMA^{V}, respectively.

Neither reaction scheme necessarily goes to completion *in vivo*.

Evidence shows that exposure to arsine gas (AsH_3) results in the same metabolites as described above, but arsenobetaine found in seafood does not get metabolized in humans (Crecelius, 1977; Luten *et al.*, 1982; Le *et al.*, 1993, 1994; Buchet *et al.*, 1996; Schmeisser *et al.*, 2006). Information is not currently available on the other organo-arsenic compounds in seafood (Lai *et al.*, 2004).

Dimethylthioarsinic acid ($DMMTA^{V}$) and dimethyldithioarsinic acid ($DMDTA^{V}$) can be formed from DMA^{III} in red blood cells, and possibly in other cells (Naranmandura *et al.*, 2007; Suzuki *et al.*, 2007). These compounds have been observed in the urine of arsenic-exposed individuals (Raml *et al.*, 2007). They may have been misidentified as MMA^{III} and DMA^{III} in most studies (Hansen *et al.*, 2004).

Most organisms detoxify inorganic arsenic by cellular efflux (Rosen & Liu, 2009). In fibroblasts and other non-methylating cells, protection against arsenic takes place by specific mechanisms for $As(SG)_3$ efflux catalysed by multidrug-resistance-associated protein-transport ATPases MRP1 and MRP2, and maybe others (Kala *et al.*, 2000; Leslie *et al.*, 2004). These efflux pumps may also remove methylated arsenic–glutathione (As–GSH) complexes.

The rat is not a good model for the human in studying the toxicokinetics of arsenic because rat haemoglobin has a much higher affinity for trivalent arsenic species compared with human haemoglobin (Lu *et al.*, 2004). In mice, chronic

exposure (12 weeks) to As^{V} via drinking-water led to total tissue arsenic accumulation in the following ranking: kidney > lung > bladder > > > skin > blood > liver (Kenyon *et al.*, 2008). Monomethylated arsenic species (MMAs) predominated in the kidney, and dimethylated arsenic species (DMAs) predominated in the lung. Urinary bladder and skin had about equal ratios of inorganic arsenic and DMAs. The proportions of different arsenic species in urinary bladder tissue did not match those in urine.

In a study of intratracheal instillation of gallium arsenide, although substantial levels of arsenic were detected in blood and urine, no gallium was detected except for the amount that was left in the lung (Carter *et al.*, 2003).

Human exposure to arsenic is mainly via drinking-water. Trivalent arsenicals are eliminated via the bile, and pentavalent arsenicals are mainly eliminated by urinary excretion (Gregus *et al.*, 2000; Kala *et al.*, 2000; Csanaky & Gregus, 2002). Most population groups exposed mainly via drinking-water excrete 60–70% DMAs and 10–20% MMAs, the remainder 10–30% being inorganic compounds (Vahter, 2000). [The Working Group noted that this study did not include thiolated compounds, which had not yet been discovered.] Interindividual differences in methylation patterns may reflect genetic polymorphisms in AS3MT, and/or variability in the activities of different reductants (Thomas *et al.*, 2007).

4.2 Genetic and related effects

Arsenicals do not react directly with DNA, but cells treated with low concentrations of trivalent arsenicals show increased oxidative DNA damage (Wang *et al.*, 2002; Schwerdtle *et al.*, 2003; Shi *et al.*, 2004; Ding *et al.*, 2005; Wang *et al.*, 2007a). As^{III} and MMA^{III} are equally potent inducers of oxidative DNA damage in human urothelial cells, where they are equally toxic (Wang *et al.*, 2007a). Cytotoxic concentrations of trivalent arsenicals also cause DNA strand breaks and/or alkali-labile sites (Kligerman *et al.*, 2003; Klein *et al.*, 2007). In mice, DMA^{V} causes lung-specific DNA damage attributed to the DMA peroxy radical $(CH_3)_2AsOO$ (Yamanaka & Okada, 1994), which can also induce DNA strand breaks and DNA–protein crosslinks in cultured cells (Tezuka *et al.*, 1993).

Gallium arsenide and other arsenicals are not mutagenic in the Ames test (NTP, 2000; IARC, 2004). There was no increase in frequency of micronucleated erythrocytes in mice exposed to gallium arsenide by inhalation for 14 weeks (NTP, 2000).

Despite the fact that low (non-toxic) concentrations of trivalent arsenicals cause oxidative DNA damage such as 8-hydroxy-2′-deoxyguanosine, which is expected to cause G→T transversions, neither As^{III}, MMA^{III} nor DMA^{III} are significant point mutagens (Rossman, 2003; Klein *et al.*, 2007). This may be due to the efficient removal of oxidative DNA lesions (Fung *et al.*, 2007; Pu *et al.*, 2007b). At toxic concentrations, As^{III} increased large-deletion mutations in human/hamster hybrid cells through a mechanism mediated by reactive oxygen species (Hei *et al.*, 1998). MMA^{III} and DMA^{III} are weakly mutagenic in mouse lymphoma L5178Y cells, but only at toxic concentrations, and yield mostly deletions (Moore *et al.*, 1997; Kligerman *et al.*, 2003).

Using a transgenic cell line that readily detects deletions as well as point mutations, statistically significant mutagenesis was never observed for DMA^{III}, and was only seen for As^{III} or MMA^{III} at toxic concentrations. MMA^{III} yielded a mutant fraction about 4-fold over background at 11% survival, and 79% of these mutants were deletions (Klein *et al.*, 2007).

As^{III}, MMA^{III}, and DMA^{III} can induce chromosomal aberrations *in vitro* (Oya-Ohta *et al.*, 1996; Kligerman *et al.*, 2003). Statistically significant increases in chromosomal aberrations occur only at toxic doses (Klein *et al.*, 2007), except as a secondary effect of genomic

instability in long-term, low-dose treatment protocols (Sciandrello *et al.*, 2004). An analysis of micronuclei induced by As^{III} in human fibroblasts shows that at lower (relatively non-toxic) doses, As^{III} acts as an aneugen by interfering with spindle function and causing micronuclei with centromeres, but at high (toxic) doses, it acts as a clastogen, inducing micronuclei without centromeres (Yih & Lee, 1999). Aneuploidy is seen after treatment with As^{III} concentrations lower than those that cause chromosomal aberrations (Yih & Lee, 1999; Ochi *et al.*, 2004; Sciandrello *et al.*, 2002, 2004). Aneuploidy associated with disruption of spindle tubulin has been reported in other cells treated with arsenicals (Huang & Lee, 1998; Kligerman & Tennant, 2007; Ramírez *et al.*, 2007). Disrupted mitotic spindles and induced persistent aneuploidy were maintained even 5 days after As^{III} removal (Sciandrello *et al.*, 2002). Humans exposed to high concentrations of inorganic arsenic in drinking-water also show increased micronuclei in lymphocytes, exfoliated bladder epithelial cells and buccal mucosa cells, and sometimes chromosomal aberrations and sister chromatid exchange in whole-blood lymphocyte cultures (Basu *et al.*, 2001). Micronuclei and chromosomal aberrations are also induced in mice after intraperitoneal treatment with As^{III} (IARC, 2004).

Long-term low-dose treatment of human osteosarcoma cells with As^{III} (but not MMA^{III}) resulted in increased mutagenesis and transformation as a secondary effect of genomic instability (Mure *et al.*, 2003). In Chinese hamster V79–13 cells grown in the presence of low concentrations of As^{III}, genomic instability (measured by chromosomal aberrations in later generations) followed earlier changes in DNA methylation and aneuploidy (Sciandrello *et al.*, 2002, 2004). Other studies report gene amplification (Lee *et al.*, 1988; Rossman & Wolosin, 1992), and changes in gene expression, e.g. by DNA methylation changes (Liu *et al.*, 2006b; Klein *et al.*, 2007; Reichard *et al.*, 2007; Liu & Waalkes, 2008). Alterations of DNA methylation, along with histone modification, were seen in cells treated with As^{III} and MMA^{III} (Jensen *et al.*, 2008; Zhou *et al.*, 2008). Global DNA hypomethylation, along with hypermethylation of specific genes, was demonstrated in several As^{III}-transformed cells (Benbrahim-Tallaa *et al.*, 2005a; Liu & Waalkes, 2008). Oxidative damage to DNA has been shown to cause changes in DNA methylation (Cerda & Weitzman, 1997), suggesting a mechanism by which As^{III} may induce this effect. Changes in DNA methylation patterns could also result from altered SAM pools or downregulation of DNA methyltransferases (Hamadeh *et al.*, 2002; Benbrahim-Tallaa *et al.*, 2005a; Reichard *et al.*, 2007; Liu & Waalkes, 2008). Altered DNA methylation has also been observed in arsenic-exposed humans (Chanda *et al.*, 2006; Marsit *et al.*, 2006).

Although not a mutagen, As^{III} can enhance the mutagenicity of other agents (Rossman, 2003; Danaee *et al.*, 2004; Fischer *et al.*, 2005). Co-mutagenesis may occur by interference with both nucleotide-excision repair and base-excision repair (Hartwig *et al.*, 2002; Rossman, 2003; Danaee *et al.*, 2004; Wu *et al.*, 2005; Shen *et al.*, 2008). Nucleotide-excision repair was blocked in human fibroblasts with the following potency: $MMA^{III} > DMA^{III} > As^{III}$ (Shen *et al.*, 2008). As^{III} is not a very effective inhibitor of DNA-repair enzymes (Snow *et al.*, 2005). Rather, it appears to affect DNA-damage signalling events that control DNA repair. One of these is poly(ADP-ribose) polymerase (PARP) (Hartwig *et al.*, 2003; Qin *et al.*, 2008). PARP-1, the major PARP, is involved in base-excision repair by interacting with DNA-repair protein XRCC1, DNA polymerase β, and DNA ligase ^{III}. This might explain the inhibition of the ligation step of base-excision repair by As^{III} (Li & Rossman, 1989). MMA^{III} and DMA^{III} are more effective PARP inhibitors than is As^{III} (Walter *et al.*, 2007). The inhibition of PARP (and other proteins such as XPA) may be

mediated by the displacement of zinc (Zn) at Zn fingers (Schwerdtle *et al.*, 2003; Qin *et al.*, 2008).

Another important signal pathway affected by As^{III} is that mediated by tumour-suppressor gene *Tp53*. As^{III} was shown to prevent the activation of the P53 protein and the downstream expression of p21 after genotoxic insult (Vogt & Rossman, 2001; Tang *et al.*, 2006; Shen *et al.*, 2008). This has the effect of overriding the growth arrest at G1 (normally an opportunity for DNA repair to take place before DNA replication) in cells with DNA damage, and might explain part of the co-mutagenic effect (Vogt & Rossman, 2001; Hartwig *et al.*, 2002; Mudipalli *et al.*, 2005). p53 is also required for proficient global nucleotide-excision repair (Ferguson & Oh, 2005). The inhibition of thioredoxin reductase by As^{III}, MMA^{III} and DMA^{III} (Lin *et al.*, 1999) would cause the accumulation of oxidized thioredoxin, which may be partially responsible for p53 malfunction, as is shown in yeast (Merwin *et al.*, 2002). The upregulation of positive growth genes such as cyclin D by low concentrations of As^{III} would also tend to drive cells to cycle inappropriately (Trouba *et al.*, 2000; Vogt & Rossman, 2001; Luster & Simeonova, 2004).

In addition to inhibiting particular proteins, As^{III} (at slightly toxic concentrations) can down-regulate expression of some DNA repair genes (Hamadeh *et al.*, 2002; Andrew *et al.*, 2006; Sykora & Snow, 2008). However, very low, non-toxic concentrations, may have the opposite effect of upregulating DNA repair, concomitant with antioxidant defenses (Snow *et al.*, 2005; Sykora & Snow, 2008).

4.3 Co-carcinogenic and *in utero* carcinogenic effects

There are several non-genotoxic actions of As^{III} (sometimes demonstrated also for its trivalent metabolites) that may contribute to arsenic-induced carcinogenesis. The effects of As^{III} on preventing blockage of the cell cycle after genotoxic insult by a second agent were discussed above. In addition, low concentrations of As^{III} in the absence of a second agent can also stimulate cell proliferation *in vitro* (Germolec *et al.*, 1997; Trouba *et al.*, 2000; Vogt & Rossman, 2001; Benbrahim-Tallaa *et al.*, 2005b; Komissarova *et al.*, 2005), and *in vivo* (Germolec *et al.*, 1998; Burns *et al.*, 2004; Luster & Simeonova, 2004). The concentration-dependent increase in proliferation of human keratinocytes after 24 hours of treatment with arsenicals followed the potency trend: $DMA^{III} > MMA^{III} > As^{III}$ (Mudipalli *et al.*, 2005). As^{III} upregulates pro-growth proteins such as cyclin D1, c-myc, and E2F-1 (Trouba *et al.*, 2000; Vogt & Rossman, 2001; Ouyang *et al.*, 2007). The increased proliferation in mouse skin by As^{III} alone (in drinking-water) is not sufficient to induce skin cancer (Burns *et al.*, 2004), but may contribute to its co-carcinogenesis with solar ultraviolet. As^{III} was found to block the differentiation of skin cells, resulting in increased numbers of keratinocyte stem cells, the cells that proliferate (Patterson & Rice, 2007; Waalkes *et al.*, 2008). Because tumours may arise from stem cells, this would increase the pool of target cells for cancer of the skin.

Another mechanism for arsenic-related carcinogenesis might be acquired resistance to apoptosis. Long-term growth of human skin cells (HaCaT) in the presence of low concentrations of As^{III} resulted in cells with a generalized resistance to apoptosis (Pi *et al.*, 2005). This may allow the survival of cells with DNA damage, thus facilitating tumorigenesis. Even short-term exposure to As^{III} affected the apoptotic response to solar UV in a mouse keratinocyte cell line (Wu *et al.*, 2005) or to UVB in normal human keratinocytes (Chen *et al.*, 2005b). It is possible that the loss of the P53 function partially mediates the reduction in apoptotic response (Chen *et al.*, 2005b).

Numerous studies report increased inflammation after As^{III} exposure (NRC, 1999; Straub

et al., 2007). The transcription factor NF-κB is involved in the inflammatory response, and As^{III} causes oxidant-dependent activation of NF-κB (Barchowsky *et al.*, 1999). Activation of the NF-κB inflammatory signalling pathway was seen in infants born to As^{III}-exposed mothers in Bangladesh (Fry *et al.*, 2007).

As^{III} can disrupt the signalling of the estrogen receptor, glucocorticoid receptor, and of other steroids *in vivo* and *in vitro* (Benbrahim-Tallaa *et al.*, 2005b, 2007; Liu *et al.*, 2007; Davey *et al.*, 2008). Submicromolar concentrations of As^{III} stimulate the transcription of several steroid receptors, but slightly higher concentrations (1–3 μM) are inhibitory (Bodwell *et al.*, 2006). Exposure of mice *in utero* to As^{III} in a protocol leading to hepatocarcinogenesis resulted in altered expression of numerous genes involved in estrogen signalling or steroid metabolism, as well as hypomethylation of estrogen receptor α (Liu & Waalkes, 2008).

Angiogenesis, which provides a blood supply to developing tumours, is stimulated by very low concentrations of As^{III} (Mousa *et al.*, 2007; Straub *et al.*, 2007). This activity can be blocked by selenium compounds (Mousa *et al.*, 2007), which also blocks As^{III}-induced co-carcinogenesis with UV and delays mutagenesis (Uddin *et al.*, 2005).

Many of these effects depend on altered gene expression that can result from genetic and epigenetic effects discussed above. Changes in gene expression by As^{III} can also be mediated by the alteration of miRNA patterns (Marsit *et al.*, 2006). Some short-term changes in gene expression (e.g. changes in the expression of DNA-repair proteins or DNA methyltransferases) can result in long-term changes. Genome-wide changes in gene expression and signal transduction induced by arsenicals have been reported in several publications (Su *et al.*, 2006; Kumagai & Sumi, 2007; Ghosh *et al.*, 2008).

4.4 Synthesis

In the human body, inorganic arsenic compounds are converted to As^{III} and As^{V}. As^{V} is rapidly converted to As^{III}. As^{III} species are more toxic and bioactive than are As^{V} species, both because of the greater chemical reactivity of As^{III}, and because As^{III} enters cells more easily.

For inorganic arsenic and its metabolites, the evidence points to weak or non-existent direct mutagenesis, which is seen only at highly cytotoxic concentrations. On the other hand, long-term, low-dose exposure to inorganic arsenic – more relevant to human exposure – is likely to cause increased mutagenesis as a secondary effect of genomic instability, perhaps mediated by increased levels of reactive oxygen species, as well as co-mutagenesis with other agents. The major underlying mechanisms observed at low concentrations include the rapid induction of oxidative DNA damage and DNA-repair inhibition, and slower changes in DNA-methylation patterns, aneuploidy, and gene amplification. Gene amplification, altered DNA methylation, and aneuploidy lead to altered gene expression, and genomic instability. Inhibition of DNA repair leads to co-mutagenicity as well. These effects are consistent with the animal carcinogenicity data, in which As^{III} is a transgenerational carcinogen – with exposure being present during many cell generations – and in results observed in co-carcinogenicity studies.

For bladder tumours induced by high doses of DMA^{V} in the rat, the mechanism is likely to involve sustained cytotoxicity followed by stress-related cell proliferation, leading to genomic instability.

Inflammation and cytotoxicity may play a role in lung tumours induced by gallium arsenide in female rats.

5. Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of mixed exposure to inorganic arsenic compounds, including arsenic trioxide, arsenite, and arsenate. Inorganic arsenic compounds, including arsenic trioxide, arsenite, and arsenate, cause cancer of the lung, urinary bladder, and skin. Also, a positive association has been observed between exposure to arsenic and inorganic arsenic compounds and cancer of the kidney, liver, and prostate.

There is *sufficient evidence* in experimental animals for the carcinogenicity of dimethylarsinic acid, calcium arsenate, and sodium arsenite.

There is *limited evidence* in experimental animals for the carcinogenicity of sodium arsenate, gallium arsenide, arsenic trioxide, and trimethylarsine oxide.

There is *inadequate evidence* in experimental animals for the carcinogenicity of monomethylarsonic acid and arsenic trisulfide.

In view of the overall findings in animals, there is *sufficient evidence* in experimental animals for the carcinogenicity of inorganic arsenic compounds.

Arsenic and inorganic arsenic compounds are *carcinogenic to humans (Group 1).*

Dimethylarsinic acid and monomethylarsonic acid are *possibly carcinogenic to humans (Group 2B).*

Arsenobetaine and other organic arsenic compounds not metabolized in humans, are *not classifiable as to their carcinogenicity to humans (Group 3).*

The Working Group made the overall evaluation on 'arsenic and inorganic arsenic compounds' rather than on some individual arsenic compounds, based on the combined results of epidemiological studies, carcinogenicity studies in experimental animals, and data on the chemical characteristics, metabolism, and modes of action of carcinogenicity.

Elemental arsenic and inorganic arsenic species share the same metabolic pathway: arsenate→arsenite→methylarsonate→dimethylarsenite. Thus, independent of the mechanisms of the carcinogenic action, and independent of which of the metabolites is the actual ultimate carcinogen, different inorganic arsenic species should be considered as carcinogenic.

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