4. Other Relevant Data

The extensive literature on cadmium has been reviewed (Friberg *et al.*, 1985, 1986b; Nordberg & Nordberg, 1988; Nordberg *et al.*, 1992; US Occupational Safety and Health Administration, 1992; WHO, 1992b). The following summary comprises illustrative studies only.

4.1 Absorption, distribution, metabolism and excretion

4.1.1 *Humans*

Cadmium may enter the body by ingestion, inhalation and, to a very limited extent, by passage through the skin, but few studies have examined fractional absorption of cadmium in humans. In one study, rice was cultured in a nutrient solution containing cadmium-115

[compound unspecified] and then cooked and administered to a healthy male subject. Whole-body counting for three days and counting in faeces and urine suggested that 5% of the cadmium had been absorbed. When cadmium-115 was administered in an acid solution [presumably on an empty stomach], the absorption was almost 30% (Yamagata *et al.*, 1975). In another study, faecal elimination of cadmium-115 was detected up to 20–30 days after oral intake of the tracer as the chloride, probably reflecting sloughing of mucosal cells containing cadmium; the remaining whole-body retention averaged 4.6% (McLellan *et al.*, 1978). A higher absorption rate has been seen in women, in whom fractional absorption of ^{115}Cd-cadmium chloride was correlated inversely with serum ferritin concentration (Flanagan *et al.*, 1978).

The extent of deposition in the lungs depends on particle size and shape, ventilatory parameters and airway geometry. The fact that smokers have higher cadmium levels in the body shows that cadmium is absorbed in the lungs (see section 1.3.9). In a study of autopsy specimens, lower pulmonary concentrations of cadmium were observed in ex-smokers than in smokers. A half-time for pulmonary cadmium of 9.4 years was calculated from these data (Paäkkö *et al.*, 1989).

Low excretion rates of cadmium lead to efficient retention in the body. Analysis of cadmium in autopsied organs shows that most of the body burden is retained in the kidneys and liver. The biological half-time in kidneys was estimated to be 12–20 years (Elinder *et al.*, 1976; Tsuchiya *et al.*, 1976; Kjellström & Nordberg, 1978; Roels *et al.*, 1981; WHO, 1992b) and that in the liver somewhat shorter (Tsuchiya *et al.*, 1976; Kjellström & Nordberg, 1978). Neutron activation analysis has been used to determine cadmium concentrations in liver and kidney of cadmium-exposed workers *in vivo*. In workers without kidney dysfunction, the cadmium concentrations in the two organs correlated well, and both correlated well with urinary cadmium excretion (Roels *et al.*, 1981). As also reflected in other studies (Lauwerys *et al.*, 1980), urinary cadmium excretion can be regarded as a measure of the body burden of this metal in individuals with normal kidney function. In 64 active and retired smelter workers without kidney dysfunction, urinary excretion of metallothionein also correlated well with the cadmium burdens of liver and kidneys (Shaikh *et al.*, 1990). In workers with cadmium-induced kidney dysfunction, urinary cadmium excretion is higher, and kidney burdens tend to decrease relative to the concentrations in the liver (Roels *et al.*, 1981).

The concentration of cadmium in the blood depends mainly on recent absorption of the metal and tends to stabilize within a few months after a change in exposure (Lauwerys *et al.*, 1980). The concentrations of cadmium in blood were measured over more than 10 years in five workers in a copper–cadmium alloy factory who had had high exposures to cadmium in the past. The data fitted a two-compartment model, with a first mean half-time of 75–128 days and a second of 7.4–16 years. Two workers with proteinuria had shorter half-times than workers without kidney dysfunction (Järup *et al.*, 1983).

Urinary excretion of absorbed cadmium is the major route of elimination, but it is also excreted in the bile (Friberg *et al.*, 1986b). In an autopsy study of deceased smelter workers, increased lung concentrations of cadmium were found. High concentrations were related particularly to tobacco smoking (Gerhardsson *et al.*, 1986).

Cadmium concentrations in the prostate (50–500 ng/g wet weight) were < 1% of those found in the kidneys (8000–39 000 ng/g wet weight) in five men aged 61–76 years, but within

the prostate the concentrations varied considerably, with the highest concentrations at the base (Lindegaard *et al.*, 1990).

A placental barrier seems to exist: at delivery, cadmium concentrations in umbilical cord blood were about half of those occurring in maternal blood, and cadmium concentrations in human placenta reached a level about 10-fold higher than that seen in maternal blood (Hubermont *et al.*, 1978). Placental transfer was also demonstrated in more recent studies (Kuhnert *et al.*, 1982, 1987).

4.1.2 *Experimental systems*

In mice given ordinary food pellets, average fractional absorption of a single dose of cadmium chloride was 0.2% of non-toxic doses; five to eight times higher absorption rates were recorded in mice on a semisynthetic diet resembling human food (Andersen *et al.*, 1992).

In a study of male Wistar rats exposed by inhalation to cadmium aerosols (see pp. 164, 166–167), the cadmium concentrations in lung tissue homogenate and lung cytosol supernatant were about twice as high for cadmium oxide as for cadmium chloride, both at the end of the 30-day exposure period and two months later. Exposure to a cadmium sulfide aerosol (a combination of sulfide and sulfate) at a 10-fold higher level (1 mg/m^3) resulted in cytosol cadmium concentrations similar to those caused by administration of cadmium oxide at 0.1 mg/m^3. The amount of absorbed cadmium that was retained in the liver and kidneys was higher if delivered as cadmium oxide than if given as cadmium chloride at the same concentration (Glaser *et al.*, 1986).

In a study of Long–Evans and Fischer 344 rats exposed to aerosols of cadmium chloride, oxide dust and sulfide dust, pulmonary retention of cadmium chloride and sulfide (half-time, 85 days and 11–76 days, respectively) was similar, whereas that of cadmium oxide dust was somewhat longer (half-time, 217 days). In contrast, there was no transfer to the kidney or liver of cadmium administered as cadmium sulfide, but the levels in faeces were high. Monkeys (*Macaca fascicularis*) did not accumulate cadmium in the kidney after inhaling cadmium sulfide dust but did so after inhaling cadmium oxide (Oberdörster & Cox, 1989).

A low-molecular-weight protein, metallothionein, occurs mainly in liver and kidney and binds cadmium. Its synthesis is induced by cadmium and other divalent metals. Metallothionein-bound cadmium released from the liver is cleared by glomerular filtration and taken up by the renal tubules (Nordberg *et al.*, 1971; Nordberg, 1972). Metallothionein production in the intestinal mucosa was induced by oral administration of zinc to Wistar rats. Subsequent oral administration of cadmium increased the retention of cadmium in the kidneys but decreased retention in the liver in comparison with non-pretreated rats (Min *et al.*, 1991). Induced mallothionein production was not detectable in rat ventral prostate, and cadmium in these cells seems to bind to other (non-inducible) proteins. In male Wistar rats, subcutaneous injection of cadmium stimulated expression of the metallothionein-I gene in the liver and the dorsal prostate, while gene expression in the ventral prostate remained unchanged (Waalkes *et al.*, 1992a,b).

Zinc deficiency may affect tissue deposition of cadmium. In male Wistar rats given a diet low in zinc (7 ppm) for nine weeks with different levels of cadmium for the last six weeks, retention of cadmium was enhanced in liver, kidney and testis, with concomitant, marked

reductions in renal and testicular zinc concentrations. Zinc deficiency also decreased cadmium-induced metallothionein retention in the kidneys (Waalkes, 1986). After acute exposure to cadmium, low doses, which probably become bound to metallothionein, are retained mainly in the kidneys, while higher doses show a retention pattern that probably reflects saturation of metallothionein binding (Lehman & Klaassen, 1986).

Metallothionein-bound cadmium-109 given orally to male C57Bl/6J mice initially showed the same fractional absorption as cadmium chloride, but the relative retention in the kidney was greater (Cherian *et al.*, 1978). Kidney retention of cadmium-109 in male CF-1 mice was similar after oral intake of metallothionein-bound cadmium generated in different ways; heat-treatment of the material did not affect the retention pattern (Maitani *et al.*, 1984).

The reported half-times of cadmium in the body vary from weeks to two years (or as long as half the lifespan of the animal); the biological half-time of cadmium in the kidney and whole body decreases when renal tubular dysfunction has developed (WHO, 1992b).

After inhaling cadmium chloride aerosols at a concentration of 100 μg/m^3 for four weeks, male Fischer 344 rats showed no significant increase in the concentration of metallothionein in lung tissue; the concentration was increased in female BALB/c mice treated similarly. Metallothionein concentrations were higher, however, in lung cells obtained by bronchoalveolar lavage from the exposed rats than in those from the mice (Oberdörster *et al.*, 1993).

The rate of cadmium uptake in Chinese hamster V79 variant cells resistant to cadmium was about 10–15% of that seen in the parental line; however, metallothionein induction and the rate of glutathione synthesis after depletion were similar in the two cell types. Depletion of glutathione enhanced the sensitivity of wild-type cells to cadmium ion but had no effect on the resistant variant. Inhibition of protein synthesis by cycloheximide did not affect cadmium uptake, but blocking of sulfhydryl groups with *N*-ethylmaleimide suppressed cadmium uptake (Ochi, 1991).

Cadmium has been observed to cross the hamster placenta on day 8 but not on day 9 of gestation (Dencker, 1975). No cadmium was seen in rat fetuses after their dams had received an injection of a sub-embryolethal dose of cadmium chloride (40 μmol [7.3 mg]/kg) on day 12 of gestation (Saltzman *et al.*, 1989). Concentrations in rat fetuses after injection of a teratogenic dose of cadmium (1.25 mg/kg) to the dam on day 12 of gestation have been reported to be 1% of those in the placenta (Webb & Samarawickrama, 1981). Christley and Webster (1983) reported similar percentages of embryonic cadmium uptake when mice were injected with cadmium at 0.66, 40 or 2400 μg/kg as cadmium chloride on gestation day 9.

4.2 Toxic effects

4.2.1 *Humans*

A worker who inhaled high concentrations of cadmium fumes died five days later. Both lungs showed acute pneumonitis (Lucas *et al.*, 1980).

Long-term exposure to cadmium may result in kidney disease. Twenty-three workers with cadmium-induced kidney dysfunction were examined at various times after their

removal from exposure. Over a five-year period, a significant increase was noted in the concentrations of β_2-microglobulin and creatinine in serum, indicating considerable progression in kidney dysfunction despite cessation of exposure (Roels *at al.*, 1989). Similar progression was observed in a population residing in a cadmium-polluted community (Kido *et al.*, 1988). Cadmium-induced kidney dysfunction may, however, be reversible, depending on the severity of the damage (Kasuya *et al.*, 1986; Saito, 1987; WHO, 1992b). In Japan, ingestion of cadmium-contaminated rice resulted in a disease (*itai-itai* or 'ouch-ouch' disease) characterized by kidney damage (mainly in proximal tubuli but also in other parts of the nephron) and osteomalacia, which mainly affected women who had given birth to many children (Shigematsu *et al.*, 1982; Williams *et al.*, 1983; Kasuya *et al.*, 1992).

Ten patients with cadmium-induced kidney dysfunction had decreased serum concentrations of 24,25-dihydroxyvitamin D; the five patients with the most severe kidney dysfunction also had decreased concentrations of 1α,25-dihydroxyvitamin D, while serum 25-hydroxyvitamin D levels were similar to those seen in five controls (Nogawa *et al.*, 1990).

A group of 101 men who had worked for at least one year at a copper–cadmium alloy manufacturing company were examined for respiratory symptoms by questionnaire, lung function testing and chest X-ray and were compared with a control group matched for age, sex and employment status; the two groups contained a similar proportion of smokers. Individual exposure to cadmium was estimated from data on cumulative exposure or from activation analysis of liver cadmium concentrations *in vivo*. The forced expiratory volume in 1 sec (FEV_1) and carbon monoxide transfer (diffusion capacity) were significantly decreased in the cadmium-exposed workers; more frequent radiographic signs of emphysema were also recorded. The difference from the controls in carbon monoxide transfer coefficient increased linearly with increasing cumulative exposure; exposure of 2000 μg/m^3-years resulted in a decrement of 0.05–0.3 mmol/min × kPa × L (Davison *et al.*, 1988).

In a study of men employed in two Belgian zinc–cadmium plants, the concentration of cadmium in the liver increased with years of past exposure (range, 3–40 years). The concentration of cadmium in the renal cortex increased up to a level of about 250 ppm after 10–15 years of exposure and decreased with longer duration of exposure. Most of the men with more than 20 years' mean exposure, but none of the men with fewer than 10 years' mean exposure, had signs of renal dysfunction. These findings were interpreted as evidence of accumulation of cadmium in the liver and kidneys up to the onset of renal dysfunction, which is followed by a progressive loss of the cadmium in the kidneys (Roels *et al.*, 1981). Ellis *et al.* (1985), in a study of workers occupationally exposed to cadmium, reported that cumulative exposure concentrations higher than 400–500 μg/m^3-years (corresponding to about 40 ppm [mg/kg] in the liver) were associated with renal abnormalities.

Workers in the cadmium recovery plant studied by Thun *et al.* (1985) (described in detail on pp. 136 and 152–153) had slightly elevated mortality from nonmalignant respiratory disease (SMR, 1.54; 95% CI, 0.88–2.51). In the study of cadmium-exposed workers in 17 plants in the United Kingdom (Kazantzis & Blanks, 1992; see pp. 154–156), the rate of mortality from bronchitis was significantly increased in the cohort as a whole (SMR, 1.20; 95% CI, 1.03–1.39) and in the highly exposed group (SMR, 3.16; 1.68–5.40). In the whole cohort, the SMR for emphysema was elevated (1.37; 95% CI, 0.84–2.12), but that for nephritis and nephrosis was not (0.77; 95% CI, 0.45–1.23). Increased mortality from

nephritis and nephrosis was, however, reported among workers in a Swedish nickel–cadmium battery plant (SMR, 3.00; not significant) (Elinder *et al.*, 1985; see pp. 150–151).

Possible excess mortality due to diabetes and 'neuralgia' [not defined] was seen over periods of 6–30 years in Japanese communities with significant cadmium pollution (Shigematsu *et al.*, 1982). In another study, mortality was recorded for an average of 6.3 years for 185 Japanese individuals over 50 years of age who had increased excretion of retinol-binding protein, indicating kidney dysfunction due to environmental cadmium pollution. The mortality rate was compared with that of a group of 2229 individuals who had no sign of proteinuria. Of the 76 deaths that occurred in the group with kidney dysfunction, five were due to respiratory disease (as compared to 1.30 expected), four in men to nephritis and renal insufficiency (0.14 expected) and three in women to diabetes (0.50 expected). These excesses were significant (Nakagawa *et al.*, 1987).

In 12 women with *itai-itai* disease, immunoglobulin serum concentrations were normal and lymphocyte transformation and phytohaemagglutinin cytotoxicity responses *in vitro* were similar to those in a control group (Williams *et al.*, 1983).

4.2.2 *Experimental systems*

Acute exposure of rodents to cadmium produces hepatotoxicity (Dudley *et al.*, 1982), while chronic administration causes kidney damage. Cadmium-induced kidney dysfunction produced in experimental animals is very similar to the low-molecular proteinuria seen in cadmium workers. Histopathological examination of kidneys from horses and sea birds exposed environmentally to cadmium showed changes indicative of chronic interstitial nephritis (WHO, 1992a). In experimental animals, acute renal toxicity can be prevented by pretreatment with small doses of the metal (Nordberg *et al.*, 1975). After repeated exposures resulting in cadmium concentrations in the kidney cortex greater than about 200 mg/kg, rats tend to develop proteinuria (WHO, 1992b); subsequently, no further accumulation of cadmium occurs in the kidneys, presumably because of the increased urinary excretion of cadmium that occurs with the induced proteinuria (Axelsson & Piscator, 1966). Interspecies differences in the critical concentrations of cadmium in the kidney have been reported (Nomiyama & Nomiyama, 1984; WHO, 1992b).

Injection into male Wistar rats of metallothionein with the same amount of bound cadmium but different amounts of bound zinc showed that renal toxicity decreased with increasing amounts of zinc (Kojima *et al.*, 1991).

Inbred strains of mice show different susceptibility to cadmium-induced hepatotoxicity: C3H/He mice are sensitive, while DBA/2 mice are resistant; however, hepatic concentrations of metallothionein isoforms were similar in the two strains after injection of cadmium chloride. Susceptibiity is therefore not mediated by metallothionein (Kershaw & Klaassen, 1991).

In a carcinogenicity study (described in detail on pp. 164, 166–167), exposure (22 h per day for 6–18 months) to different cadmium compounds by inhalation increased mortality in Wistar rats in a dose-related fashion, mainly from pulmonary toxicity (Glaser *et al.*, 1990).

Alveolar hyperplasia and interstitial fibrosis were recorded in mice and golden hamsters exposed by inhalation to similar aerosols (Heinrich *et al.*, 1989; see pp. 163–164, 167). The

earliest effect of cadmium chloride and cadmium oxide aerosols seems to be type I cell necrosis, which is followed by an increase in the number of macrophages and proliferation of type II cells. Cadmium sulfide appears to be much less toxic (Oberdörster, 1989). Dose-dependent increases in the volume density of hyperplastic areas occurred in male hamsters exposed to cadmium oxide. The volume density of hyperplastic areas was also increased in males exposed to 90 $\mu g/m^3$ cadmium sulfide and in females exposed to 30 $\mu g/m^3$ cadmium sulfate (Aufderheide *et al.*, 1990).

Many studies have been carried out to elucidate the pathogenesis of *itai-itai* disease. In female rhesus monkeys given a diet low in vitamin D, calcium (0.3%), phosphorus (0.3%) and protein (14%) with a cadmium content of 3 mg/kg (as cadmium chloride) during the first 12 months, followed by 30 mg/kg, osteomalacia developed at 12 months and proteinuria was detected at 36 months (Kimura *et al.*, 1988). When cadmium is included in hydroxyapatite, the main calcium-containing mineral in bone, the solubility of the crystal is considerably decreased (Christoffersen *et al.*, 1988).

In female B6C3F1 mice given water containing 0, 10, 50 or 250 ppm (mg/L) cadmium chloride for 90 days, T- and B-lymphocyte proliferation was significantly reduced. Increased susceptibility to herpes 2 virus was also recorded (Thomas *et al.*, 1985). In SPF female rats of the Brown–Norway and Lewis strains given subcutaneous injections of 0.8 mg/kg bw cadmium chloride five times a week for 15 days, the amount of cadmium that reached the thymus was similar; however, only Brown–Norway rats had a significant decrease in S-phase thymocytes and increases in the number of thymus cells in G_2 phase and in mitosis (Morselt *et al.*, 1988).

At concentrations below 10 μmol/L [1 mg/L], cadmium selectively inhibited concanavalin A-induced T-cell proliferation but not bacterial lipopolysaccharide-induced B-cell proliferation of spleen cells from male BALB/c mice. The effect could be prevented by adding 30 μmol zinc to the culture medium, but the intracellular cadmium concentration and the cadmium-induced metallothionein level were not affected (Otsuka & Ohsawa, 1991).

Natural killer cell-mediated cytotoxicity and antibody-dependent cellular cytotoxicity of human peripheral blood lymphocytes *in vitro* were inhibited by cadmium concentrations of 1 μM [0.1 mg/L] and above. The inhibition of natural killer activity could be prevented partially by adding calcium or zinc to the culture medium, zinc being most effective (Cifone *et al.*, 1991).

4.3 Reproductive and developmental effects

In a review of occupational exposures and defects of the central nervous system, Roeleveld *et al.* (1990) noted that cadmium could induce malformations of the brain in experimental animals but that no data were available on the effects of prenatal or postnatal exposure to cadmium in humans.

4.3.1 *Humans*

In a study of 77 pregnant smokers and 125 nonsmokers who delivered infants in Cleveland Metropolitan General Hospital (USA), samples of blood were obtained from the mothers within 1 h of delivery and from the umbilical cord immediately after delivery;

placental samples were obtained immediately after delivery. Cadmium concentrations were determined in maternal whole blood, placenta and placental, maternal and cord-vein plasma; zinc was determined in maternal and cord-vein red blood cells. Smoking status was confirmed by measuring plasma thiocyanate. The potential confounding variables that were taken into account in the analysis included maternal age, gravidity, parity, gestational age, sex of offspring, race, maternal red blood cell count, maternal haemoglobin concentration, haematocrit and cord-vein haemoglobin concentration. The birth weights of the infants of smokers were significantly reduced (3143 g *versus* 3534 g), and maternal whole blood cadmium and thiocyanate concentrations were negatively related to birth weight. After the confounding variables had been controlled for, thiocyanate concentration explained 5.8% of the birth weight variance among the infants of smokers, maternal whole blood cadmium concentration explained 8.5%, and cord-vein red blood cell zinc concentration explained 1.7%. All of variables together explained more than 30% of the variance in birth weight (Kuhnert *et al.*, 1987). [The Working Group noted that it was not clear whether the differences in birth weight could be fully explained by differences in smoking, since smoking increases blood cadmium levels, and thiocyanate measurements are only qualitative measures of smoking.]

The relationship between placental cadmium concentration and the birth weight of the children of a population of nonsmoking women living near a lead smelter in former Yugoslavia was compared with that in a neighbouring town. There were 106 placentas from the smelter region and 55 from the control region. The analysis was adjusted for ethnicity, gender of children, maternal age, height, parity and education, mid-pregnancy blood lead levels and alcohol consumption. The average placental cadmium concentrations were 0.73 nmol [82 ng]/g dry weight in the exposed area and 0.50 nmol [56 ng]/g in the control area. There was no association between placental cadmium levels and either birth weight or gestational age (Loiacono *et al.*, 1992).

4.3.2 *Experimental systems*

The effects of cadmium and cadmium compounds on reproduction in experimental systems have been reviewed (Barlow & Sullivan, 1982; Carmichael *et al.*, 1982; Pařízek, 1983; Shepard, 1992).

Haemorrhagic necrosis of the ovaries was observed in Cr:RGH hamsters, in one strain of mice (DBA), but not in three others, and in immature Fischer 344/NCr and WF/NCr rats injected with 47.5 μmol/kg [8.7 mg/kg] cadmium chloride (Rehm & Waalkes, 1988). A single intraperitoneal injection of 2 mg/kg cadmium chloride to (101 × C3H)F_1 or (SEC × C57Bl)F_1 × X^{Gsy} female mice had no dominant lethal or other effect on fertility, except that it induced superovulation (Suter, 1975).

Dietary exposure to up to 10 (Lorke, 1978) or 68.8 ppm (Zenick *et al.*, 1982) cadmium chloride did not affect reproductive performance in male rats. Injection of cadmium chloride to adult male rats induced an acute vascular response in the testis, leading to oedema and, ultimately, necrosis of the seminiferous epithelium (Pařízek, 1960). Vas deferens sperm concentration, release of human chorionic gonadotropin-stimulated testosterone 14 days after exposure and testicular weight 60 days after exposure were found to be the most sensitive of a variety of reproductive parameters in exposed male rats. Younger (30- or

50-day-old) male rats were less sensitive than older (70-day-old) rats to the effects of cadmium (Laskey *et al.*, 1984, 1986). Rat Sertoli cells in culture were at least four times more sensitive to cadmium than interstitial (primarily Leydig) cells, suggesting a direct action of cadmium on cells in the seminiferous epithelium (Clough *et al.*, 1990). Laskey and Phelps (1991) also showed a direct effect on rat Leydig cell function following exposure *in vitro* to cadmium chloride.

Metallothionein was not induced by cadmium in rat, mouse or monkey testis or in hamster ovary (Ohta *et al.*, 1988; Waalkes & Perantoni, 1988; Waalkes *et al.*, 1988b,c,d), which may determine the susceptibility of these organs to cadmium (Waalkes & Goering, 1990). In contrast, Abel *et al.* (1991) demonstrated a cadmium-induced increase in metallothionein concentration in a murine Leydig cell line and in purified rat Leydig cells.

Female mice received cadmium in their diet for six consecutive 42-day rounds of pregnancy and lactation. Litter size at birth and pup growth were reduced at 50 but not at 25 ppm [mg/kg] (Whelton *et al.*, 1988). When male and female rats were gavaged with up to 10 mg/kg bw cadmium chloride per day for six weeks prior to mating and females during pregnancy, the high dose reduced the incidence of copulation and of pregnant females and the numbers of implants and live fetuses. Fetuses of dams given the high dose were anaemic. No effect on male fertility was reported (Sutou *et al.*, 1980a,b).

In multigeneration studies in rats in which cadmium was incorporated into the diet, offspring body weight was reduced at 100 ppm [mg/kg] (Lorke, 1978; Löser, 1980b) and the number of litters per female was reduced in a group receiving a diet containing 6.9 μg/kg bw more than the control levels of 4.4 μg/kg bw (Wills *et al.*, 1981). In a multigeneration study in which rats received up to 5 ppm (mg/L) cadmium in the drinking-water, reductions in male body weights (day 130), liver weights (1 ppm, days 50 and 130), epididymal sperm content (5 ppm, day 130), serum progesterone in term F_1 females (5 ppm), kidney weights in F_1 neonates (5 ppm) and F_2 litter weights [no data presented] were reported. A significant decrease in the incidence of preimplantation death was observed in the F_1 females given 5.0 ppm (Laskey *et al.*, 1980). Exposure of rats by inhalation to 100 μg/m^3 cadmium chloride (as an aerosol) for three generations increased lung weight in males and females of all three generations, increased leukocyte counts in males of the first two generations and in females of all three generations, increased proteinuria in males of the first and third generations and decreased body weight in males of the second and third generations and in females of the third generation. No effect on reproduction was reported (Weischer & Greve, 1979).

Pre- and postimplantation mouse and rat embryos cultured *in vitro* were severely affected by the presence of microgram per millilitre concentrations of cadmium chloride or sulfate (Schmid *et al.*, 1983; Warner *et al.*, 1984; Yu *et al.*, 1985; Abraham *et al.*, 1986; Yu & Chan, 1987; Naruse & Hayashi, 1989; Müller *et al.*, 1990).

Danielsson and Dencker (1984) found decreased vitamin B_{12} transport to the fetuses of mice within 1 h of injection of an embryolethal dose of cadmium chloride (4 mg/kg bw) on gestation day 16; lower doses did not affect fetal development, but vitamin B_{12} transport was reduced within 24 h of exposure to doses as low as 0.5 mg/kg. Transport of α-aminobutyric acid and deoxyglucose across the placenta were largely unaffected by the treatment. A teratogenic dose of cadmium (1.25 mg/kg bw) reduced thymidine incorporation into embryonic DNA at 4 h and leucine incorporation into embryonic protein at 20 h (Webb &

Samarawickrama, 1981). Injection of rats on gestation day 12 or 18 with 40 μM/kg [7.3 mg/kg] cadmium chloride reduced blood flow from the uterus to the chorioallantoic placenta beginning some time between 12 and 16 h after exposure (Levin & Miller, 1981; Levin *et al.*, 1987; Saltzman *et al.*, 1989).

Lobes of placentas from normal-term deliveries of nonsmoking women were dually perfused *in vitro* with cadmium at 0, 10, 20 or 100 nmol/ml [0–11 μg/ml] for up to 12 h. The synthesis and release of human chorionic gonadotropin was decreased by all concentrations of cadmium, beginning at 4 h, and necrosis of the fetal vasculature was seen 5–8 h after perfusion with the high dose. Zinc transfer to the fetal circuit was decreased by addition of 10 nmol/ml cadmium to the maternal perfusate (Wier *et al.*, 1990).

Exposure of QS/CH mice to 40 ppm (mg/L) cadmium in the drinking-water throughout gestation resulted in reduced maternal water intake and fetal growth retardation during gestation; the newborn mice were severely anaemic. Fetal body weights were reduced by concentrations of 10 ppm and above (Webster, 1978). No effect on fetal viability, weight or morphology was reported in a study in which albino rats received 100 ppm (mg/L) cadmium as cadmium acetate in the drinking-water throughout gestation (Saxena *et al.*, 1986). Fetal growth retardation was observed in the offspring of Sprague–Dawley rats receiving 50 or 100 ppm (mg/L) cadmium as cadmium chloride in the drinking-water from day 6 to 20 of pregnancy; no effect was seen with 5 ppm. The higher doses also reduced the average daily body weight gain of dams; after adjustment for maternal weight at day 20, fetal weight deficit was seen only at 50 ppm. No gross defect was noted (Sorell & Graziano, 1990). Exposure of Wistar rats by inhalation to 0.2–0.6 mg/m^3 cadmium (median aerodynamic diameter, 0.6 μm) throughout gestation decreased maternal weight gain and increased lung weight. The fetuses of dam given the high dose were retarded in growth, and both high- and low-dose groups had nonsignificant decreases in haematocrit (Prigge, 1978). No effect on fetal development was reported following dietary exposure of Long–Evans rats to up to 100 ppm (mg/kg in diet) on days 6–15 of gestation (Machemer & Lorke, 1981). Exposure of rats during gestation by oral gavage to doses of 40 mg/kg bw per day and above was severely toxic to the dams; doses as low as 2 mg/kg per day had some maternal effects (Machemer & Lorke, 1981; Barański *et al.*, 1982). Reductions in fetal body weight were seen in Wistar rats with doses as low as 8 mg/kg per day (Barański *et al.*, 1982) and in Long–Evans rats at 30 mg/kg per day (Machemer & Lorke, 1981). Fetal hydropericardium was seen with 4 mg/kg per day and above (Barański *et al.*, 1982), and at 30 mg/kg per day a variety of fetal defects (e.g. dysplasia of the facial bones and of the rear limbs, oedema, cleft palate) were observed in rats (Machemer & Lorke, 1981).

Parenteral administration of < 10 mg/kg of cadmium salts on single days during pregnancy induced a wide range of malformations (e.g. craniofacial, eyes, limbs) in hamsters (Gale, 1979), mice (Layton & Layton, 1979; Webster & Messerle, 1980; Murdoch & Cowen, 1981; Messerle & Webster, 1982; Feuston & Scott, 1985; Naruse & Hayashi, 1989; De *et al.*, 1990; Padmanabhan & Hameed, 1990) and rats (Parzyck *et al.*, 1978; Samarawickrama & Webb, 1979, 1981; Holt & Webb, 1987). Direct injection of cadmium into rat fetuses late in gestation resulted in lower fetal mortality than was expected from the body burden (Levin & Miller, 1980). Daston and coworkers (Daston & Grabowski, 1979; Daston, 1981a,b, 1982) demonstrated selective retardation in morphological and biochemical maturation of fetal rat

lung at doses of cadmium chloride as low as 2 mg/kg per day injected intraperitoneally on days 12–15 of gestation. Respiratory distress was seen in the offspring at birth.

The postnatal consequences of exposure to cadmium *in utero* have been studied by several investigators. Barański *et al.* (1983) reported no effect on postnatal growth of rats following exposure of dams to up to 4 mg/kg per day by oral gavage beginning five weeks prior to and during gestation, but they observed reduced exploratory locomotor activity in females at two months of age after exposure of dams to doses as low as 0.04 mg/kg per day. Ali *et al.* (1986) followed the offspring of rats that had received cadmium in the drinking-water (4.2 or 8.4 μg/ml) during gestation and found impaired postnatal growth, delayed development of cliff avoidance and swimming behaviour, elevated locomotor activity on postnatal days 14 and 21 and reduced locomotor activity on postnatal day 60. Lehotzky *et al.* (1990) injected rats subcutaneously with cadmium chloride at 0.2, 0.62 or 2 mg/kg bw per day on days 7–15 of gestation and found reduced litter size at birth but no effect on growth. Horizontal motor activity was decreased on day 38, among offspring of dams given 0.62 or 2 mg/kg and in all groups on day 90. Saillenfait *et al.* (1991) examined renal function in the offspring of rats exposed to up to 2.5 mg/kg bw cadmium chloride by intraperitoneal injection on days 8, 10, 12 and 14 of gestation. Indications of compromised renal function were observed in offspring of each sex on postnatal day 3 and in male offspring on postnatal day 49 but not on postnatal day 12.

4.4 Genetic and related effects (see also Table 14, pp. 195 *et seq.* and Appendices 1 and 2)

4.4.1 *Humans*

The genetic effects of cadmium and cadmium compounds in exposed humans have been reviewed (Vainio & Sorsa, 1981; Fleig *et al.*, 1983; Bernard & Lauwerys, 1986).

(*a*) *Itai-itai* patients

Twelve female *itai-itai* patients had markedly higher incidences of chromosomal aberrations of all types in peripheral blood lymphocytes than a group of nine age-matched control subjects (six females and three males [no further detail provided]). The patients were women aged 52–72 years who had been living in cadmium-polluted areas of Japan for more than 30 years and had been exposed to cadmium in the diet (water, rice, fish). Eight of the patients were sampled two to three times at three-month intervals. All types of chromatid and chromosomal aberrations were observed in the exposed women; the mean frequency of cells with any abnormality was 26.7% (range, 8.9–51.2%) in the exposed and 2.6 (range, 1.5–3.8%) in controls. The incidence of aneuploidy was four times or more that of the control group [smoking habits were not described] (Shiraishi, 1975).

In contrast, Bui *et al.* (1975) found no significant difference in the frequencies of cells with structural aberrations in cultures from blood of four female *itai-itai* patients and from four controls (three females, one male) living in an area of Japan known not to be cadmium-polluted; both had high frequencies of structural aberrations: 6.6 and 6.0%, respectively. The average age of the patients was 65 and that of controls, 75 years; blood cadmium levels ranged from 16 to 29 ng/g whole blood in exposed and 4.4–6.1 ng/g in controls. The samples were assayed in Sweden 96 h after sampling. The subjects were not

suffering from viral diseases and had not been exposed to X-rays or cytostatic drugs. [The Working Group noted the long delay between sampling and culturing. Two of six samples were haemolysed and therefore discarded.]

(*b*) *Environmental and dietary exposure*

Nogawa *et al.* (1986) examined the frequency of sister chromatid exchange in peripheral lymphocytes from two groups of Japanese men and women. Group 1 (eight men and 16 women) lived in the cadmium-polluted Kakehashi river basin in Ishikawa Prefecture and had been diagnosed as having cadmium-induced renal damage. The comparison group 2 (two men and four women) came from Uchinada-machi, which was not contaminated by cadmium. The mean age was 76.6 years in group 1 and 68.3 years in group 2. The men, but not the women, in both groups had smoked tobacco. None of the subjects had used any known clastogenic drug or had undergone radiotherapy, and none had clinical evidence of viral infection at the time of examination. The mean cadmium concentrations in whole blood from men and women were 9.6 ± 5.8 (μg/L) in group 1 and not detectable in group 2; the mean concentrations in urine were 9.1 μg/g creatinine in group 1 and 2.7 μg/g creatinine in group 2. No difference was seen between the groups in the number of sister chromatid exchanges per cell: group 1, 8.0 ± 0.94; group 2, 9.0 ± 3.13.

Tang *et al.* (1990) investigated the frequency of chromosomal aberrations in a cadmium-polluted region of China. Twenty-one men (urinary cadmium concentration, 3.32 ± 1.46 μg/L) and 19 women (urinary cadmium, 3.83 ± 1.82 μg/L) living at Suichang in Zhejiang Province (soil cadmium, 1.103 ppm) for 11–62 years were compared with nine men (urinary cadmium, 2.34 ± 1.59 μg/L) and two women (urinary cadmium, 1.85 ± 0.65 μg/L) from an unpolluted region in the same general area (soil cadmium, 0.20 ppm). None of the subjects had been exposed to chromosome damaging drugs or radiotherapy and did not have viral infections. The frequency of abnormal cells, including structural aberrations, aneuploidy and endoreduplication, was not significantly different in the exposed group (5.80 ± 3.44) than in the controls (2.80 ± 1.99). (Statistical analysis using transformed data gave $p < 0.01$.) More individuals in the cadmium-polluted group (63.5%) had a high aberration prevalence (> 5%) than in controls (18.2%), and more severe structural aberrations, such as dicentrics, translocations and multiradials, were observed in the exposed group. A significant dose–effect relationship between urinary cadmium content and chromosomal aberration frequency was observed (linear regression equation given). Most men in the region were smokers, while none of the women smoked; no effect of smoking was observed.

(*c*) *Occupational exposure*

Deknudt and Léonard (1975) examined chromosomal aberrations in peripheral lymphocytes from three groups of workers in a cadmium plant: group 1, 23 cadmium workers with an average exposure of 12 years; group 2, 12 rolling-mill workers with an average exposure of 11 years; group 3, 12 controls (administrative department in the same plant). The materials to which exposure was considered to be relevant were: group 1, lead (60% w/w) and cadmium (10% w/w) in the absence of zinc; and group 2, mostly zinc but also low levels of lead (max. 4% w/w) and cadmium (max. 1% w/w). Both lead and cadmium concentrations in blood were measured in groups 1 and 2 at the time of sampling for cytogenetic analysis; the

mean concentrations (in μg/L) were: group 1—lead, 446 ± 122.9; cadmium, 31.7 ± 33.11; group 2—lead, 208 ± 44.3; cadmium, 6.3 ± 5.51. Much of the variation in the concentration of cadmium of group 1 was due to a single individual who had 179 μg/L blood. [The Working Group noted that neither lead nor cadmium concentrations were measured in the blood of controls.] The proportions of cells (per 100 examined) with structural abnormalities were: group 1, 2.00; group 2, 3.96; and group 3, 3.04. The numbers of chromatid exchanges and chromosomal translocations, rings or dicentrics per 100 cells were: group 1, 0.89; group 2, 0.54; and group 3, 0.13. The exposed groups thus showed no increase in total aberrations but had a significantly increased frequency of more severe aberrations; however, the individual with a very high blood cadmium level had no aberration or gap. Seven workers in group 1 who had previously been employed in coal mines for 2.5–13 years had a mean rate of severe aberrations of [1.36/100 cells], compared with [0.69/100 cells] in the remainder of the group. [This effect was, however, due almost entirely to the rate of a single individual.] [The Working Group noted the absence of any record of other relevant exposures, such as tobacco smoking, viruses, X-rays and medicaments.]

Bui *et al.* (1975) examined chromosomal aberrations in peripheral lymphocytes from five men who had been employed in the electrode department of an alkaline battery factory for 5–24 years. The average cadmium concentration in the general air of the department during 1969–72 was 35 μg/m^3, and about twice this value was estimated in personal air samples. The control group consisted of three male office workers of about the same age as the exposed workers and from the same factory. Cadmium concentrations were measured in urine and blood [but it is not clear whether this was done at the same time as blood sampling for chromosomal analysis]. The subjects were not known to be suffering from viral disease and had not been exposed to X-rays or known clastogenic drugs. The mean cadmium concentrations in whole blood were 37.7 ± 15.5 ng/g in the exposed and 2.3 ± 0.9 ng/g in the controls; the concentrations in urine were 11.5 ± 11.5 μg/g creatinine in exposed and 2.5 ± 1.3 μg/g creatinine in controls. Lymphocytes were examined after culture times of both 48 h and 72 h: At neither time was there an increase in the frequency of cells with either structural chromosomal aberrations or numerical changes in the exposed group when compared with the control group.

Chromosomal aberrations were studied in peripheral lymphocytes from 24 male workers at a zinc smelting plant who had spent 3–6.5 years in zinc electrolysis, where they were exposed to fumes and dust containing zinc, lead and cadmium (Bauchinger *et al.*, 1976). The exposed workers had a mean lead blood concentration of 192.9 ± 66.2 μg/L and a cadmium concentration of 3.95 ± 2.68 μg/L but had no clinical sign of metal toxicity and had had no previous exposure to cytostatic drugs or X-irradiation. Fifteen (11 men, 4 women) unexposed healthy members of the general population not exposed to these metals were used as controls; the blood levels of lead and cadmium in this group were not measured but were assumed to be the average for industrial workers—120–130 μg/L lead and 1.5 μg/L cadmium. The numbers of cells with structural aberrations was significantly increased in the exposed group ($p < 0.001$, Mann–Whitney rank test). The percentages of cells with structural aberrations were 1.35 ± 0.99 (0.018 ± 0.015 assigned breaks/cell) for exposed workers and 0.47 ± 0.92 (0.0053 ± 0.011 assigned breaks/cell) for the controls.

No significant difference in chromosomal or chromatid aberration frequency was observed between 40 workers in a cadmium pigment plant (blood cadmium, 19.5 μg/L; range, < 2–140 μg/L) and 13 administrative and laboratory personnel at the same plant, used as controls (blood cadmium, < 2–29 μg/L), although four cells (out of 3740) with chromatid interchanges were observed in the exposed group only. No correlation was found between extent of damage and exposure levels or duration [data not shown]. Exposures ranged from six weeks to 34 years, and workers had not previously been exposed to chromosome damaging drugs or radiation (O'Riordan *et al.*, 1978).

Fleig *et al.* (1983) also found no significant difference in the incidence of chromosomal aberrations (chromosome and chromatid type) in 14 workers exposed to cadmium-containing dusts for 6–25 years in cadmium pigment and stabilizer production plants (1.5% of cells with structural aberrations) when compared with 14 age-matched office workers (1.3% of cells with structural aberrations). The concentrations of cadmium in the blood of the workers (14–38 μg/L) were measured three years before the study; the levels for controls were not stated. The exposed workers had not been exposed to chromosome damaging drugs or radiotherapy.

Dziekanowska (1981) reported small increases in the incidence of chromosomal aberrations (8.91 ± 4.99), especially structural rearrangements (dicentrics, translocations), and disturbance of spiralization in 11 cadmium-exposed workers compared with 32 healthy non-smelter controls (6.66 ± 2.38). No difference was found in the frequency of sister chromatid exchange (cadmium-exposed group, 15.14 ± 4.7; controls, 16.9 ± 5.82). [The Working Group noted the high control value for sister chromatid exchange. It is not clear whether smoking habits were considered.]

The rates of abnormal metaphases (excluding gaps) were significantly higher in peripheral blood lymphocytes of a group of 40 male workers (10 nonsmokers, 24 smokers, 6 ex-smokers) exposed to fumes and dusts in the production of cadmium, zinc, copper and silver alloys in a single factory (2.6%) than in controls matched for age and smoking habits (1.7%, $p < 0.05$), whereas the total rates of abnormal metaphases did not differ between the two groups. Chromosome-type aberrations accounted for most of the observed increase. The mean cadmium concentration in blood, measured at the time of cytogenetic assay, was 5.10 ± 5.15 μg/L (range, 0.3–28.3), and the urinary concentration was 10.63 ± 7.99 μg/L (range, 1.5–31.6) in workers; levels for controls were not stated. When a cumulative exposure index was calculated for each subject (mean yearly atmospheric cadmium concentration × years of exposure), only high-intensity, long-term exposure was associated with a significant increase in the frequency of chromosome-type aberrations: Six of seven complex aberrations (dicentrics and rings) observed were found in the eight subjects of this group. The workers had not been exposed to radiation therapy, treatment with cytotoxic drugs, recent viral diseases or occupational exposure to known clastogens (Forni *et al.*, 1990). [The Working Group noted that neither the exposure levels nor the blood and urine concentrations of other metals were measured.]

4.4.2 *Experimental systems*

The genetic effects of cadmium compounds in experimental systems have been reviewed (Degraeve, 1981; Hansen & Stern, 1984; Sunderman, 1984; Baker, 1985; IARC, 1987b;

Swierenga *et al.*, 1987), as have the mechanistic aspects of the effects (Léonard, 1988; Magos, 1991; Snow, 1992; Rossman *et al.*, 1992).

Most experimental systems have been used to study cadmium chloride. Some data are also available on cadmium acetate, cadmium oxide, cadmium sulfate, cadmium nitrate and cadmium sulfide, and the genetic and related effects of those compounds are listed separately in Table 14. The results are summarized here according to the solubility of the compounds in water, before they are added to biological media. Thus, cadmium sulfide, oxide and carbonate are very poorly soluble, while all of the other cadmium compounds are water-soluble at all concentrations tested. Water solubility does not, however, necessarily reflect solubility *in vivo*.

(*a*) *Cadmium compounds readily soluble in water (acetate, chloride, nitrate, sulfate)*

Cadmium chloride induced DNA strand breaks but not prophage in bacteria. Both cadmium chloride and cadmium sulfate, but not cadmium nitrate, induced differential toxicity in *Bacillus subtilis* and *Escherichia coli* strains. The compounds did not induce bacterial mutation reliably; precipitation in the bacterial media may have affected bio-availability. A few positive responses were reported with cadmium chloride and sulfate tested in *Salmonella typhimurium* strains (particularly TA102) and with cadmium nitrate in *E. coli* DG1153.

Cadmium chloride and cadmium sulfate induced gene conversion in *Saccharomyces cerevisiae*, but cadmium chloride did not induce reverse mutation in *S. cerevisiae* or aneuploidy in either *S. cerevisiae* or *Aspergillus nidulans*.

Cadmium chloride induced micronuclei in *Vicia faba* and water hyacinth and aneuploidy in Chinese spring wheat.

Cadmium chloride and cadmium nitrate did not induce mutation in *Drosophila melanogaster*, and cadmium chloride did not induce aneuploidy in one study but did in another, more sensitive assay.

Cadmium acetate and cadmium chloride induced DNA strand breaks in several cultured, non-human mammalian cell lines. Cadmium sulfate induced DNA strand breaks in primary cultures of rat hepatocytes, and cadmium chloride and cadmium nitrate induced unscheduled DNA synthesis in the same type of cell. Cadmium chloride did not induce DNA strand breaks in primary cultures of rat Leydig cells, which are an important target *in vivo* (see section 4.2).

Cadmium chloride and cadmium sulfate are mutagenic to cultured, non-human mammalian cells. The mutagenic activity of the chloride salt has been demonstrated at the *hprt* locus in Chinese hamster V79 cells and at the *tk* locus in mouse lymphoma L5178Y cells.

In non-human mammalian cells *in vitro*, cadmium chloride induced a dose-dependent increase in sister chromatid exchange frequency in one study but not in two others, in which only single doses were used; in one of the two studies, neither cadmium acetate nor cadmium nitrate induced sister chromatid exchange. A much higher degree of reproducibility has been observed in the induction of chromosomal aberrations by cadmium chloride and cadmium sulfate and in the induction of cell transformation by cadmium acetate and cadmium chloride. The chloride also induced aneuploidy in some cultured cells.

In cultured human cells, cadmium acetate and cadmium chloride induced DNA strand breaks, but cadmium chloride did not induce chromosomal aberrations. Cadmium acetate was reported to have induced aberrations in one study at very high doses. In the only pertinent study in which a human cell line was used, cadmium chloride induced aneuploidy, as demonstrated by the presence of centromeres in micronuclei. Cadmium chloride, but not cadmium sulfate, induced sister chromatid exchange in human lymphocytes.

Conflicting results have been reported for the genetic effects of cadmium chloride in mice: micronuclei and chromosomal aberrations have been observed in bone-marrow cells in several studies but not in others. Cadmium chloride did not induce aneuploidy in bone-marrow cells or spermatocytes of mice treated *in vivo*, but it induced aneuploidy in oocytes of Syrian hamsters and, in two of three studies, of mice. Cadmium chloride did not induce dominant lethal mutation in male rodents in five of six studies with mice or in a single study with rats and did not induce germ-line cell translocations in mice, either cytologically or in breeding experiments. Cadmium chloride induced morphologically abnormal sperm in mice in three of four studies. The discrepancies in the results of the different studies do not appear to be due to dose levels or frequency or route of treatment.

(*b*) *Cadmium compounds sparingly soluble in water*

Cadmium oxide [particle size not given] did not induce mutation in *S. typhimurium*, and cadmium carbonate [particle size not given] did not induce micronuclei in cells of *Vicia faba*.

Only cadmium sulfide, which exists in crystalline and amorphous forms, has been tested in cultured mammalian cells. Crystalline cadmium sulfide induced DNA strand breaks [particle size not given] and cell transformation [particle size, 0.64 μm], whereas amorphous cadmium sulfide [particle size, 0.64 μm] did not induce cell transformation. Cadmium sulfide [form unspecified] induced chromosomal aberrations in cultured human lymphocytes.

Considerations with regard to genotoxic mechanisms

As metal ions may be precipitated as their insoluble phosphates by *ortho*-phosphate ions in normal bacteriological culture medium and may not be detected as mutagens, modified media were used in some studies (e.g. Pagano & Zeiger, 1992). Ochi *et al.* (1984) reported a higher chromosomal aberration incidence after treatment in saline than in serum-containing medium, and that a post-treatment recovery period of Chinese hamster cells, which allows DNA synthesis to resume, was needed for efficient detection of cadmium-induced chromosomal aberrations.

Cadmium compounds are very toxic *in vitro*. In a screening study for cytotoxicity in BALB/c 3T3 cells, cadmium ranked second only to methylmercury in toxic potency (Borenfreund & Babich, 1987). Prostatic fibroblasts were more sensitive to cadmium toxicity than prostatic epithelial cells from the same species (Terracio & Nachtigal, 1986).

It was reported in many studies that exposure to cadmium induced DNA strand breaks (see Table 14). Ochi and Ohsawa (1983) reported single-strand breaks and, possibly, DNA–protein cross-links in Chinese hamster cells. *In vitro*, cadmium–metallothionein, but not cadmium alone, caused DNA strand breaks (Müller *et al.*, 1991). [The Working Group noted that the significance of this observation for the cell is questionable, since zinc

pretreatment (which causes induction of metallothionein) resulted in a reduction of cadmium toxicity and DNA strand breaks (Coogan *et al.*, 1992).]

The frequencies of cadmium-induced DNA strand breaks and chromosomal aberrations are reduced in cells treated with antioxidants, suggesting a relationship between single-strand breaks and active oxygen species. Various scavengers of active oxygen species were assayed for their ability to block chromosomal aberrations induced by cadmium chloride; no effect was seen with superoxide dismutase or dimethylfuran (a scavenger of singlet oxygen), but catalase blocked the induction of aberrations in a dose-dependent manner. D-Mannitol, a scavenger of hydroxyl radicals, also blocked aberration induction, as did the antioxidant butylated hydroxytoluene (a diffusible radical scavenger) (see IARC, 1986b). These results suggest that cadmium chloride is genotoxic by producing hydrogen peroxide, which can form hydroxyl radicals in the presence of iron or copper ions (Rossman *et al.*, 1992). Cadmium chloride treatment also reduced the cellular glutathione level (Ochi *et al.*, 1983; Ochi & Ohsawa, 1985; Ochi *et al.*, 1987; Snyder, 1988). Selenium may also inhibit the clastogenic effects of cadmium in mouse bone marrow, but the interaction, if confirmed, appears to be complex (Mukherjee *et al.*, 1988a). [The Working Group considered this an interesting observation, which could contribute to an understanding of the difficulty in reproducing the genetic effects of cadmium compounds *in vivo*, since selenium levels in rodent diets differ with time and place.]

Various studies have shown that cadmium compounds synergistically increase the effects of other chemicals. For example, cadmium increased the induction of micronuclei by NDMA in mice (Watanabe *et al.*, 1982), enhanced ultraviolet-induced mutagenesis in V79 Chinese hamster cells (Hartwig & Beyersmann, 1989), but not in *E. coli* (Rossman & Molina, 1986), enhanced meiotic nondisjunction induced by γ-irradiation in *Drosophila* oocytes (Kogan *et al.*, 1978) and enhanced benzo[*a*]pyrene-induced transformation of Syrian hamster embryo cells (Rivedal & Sanner, 1981). Inhibition of DNA repair by cadmium has been suggested as a mechanism for these interactions (e.g. Zasukhina & Sinelschikova, 1976). Cadmium inhibits human DNA polymerase β (a polymerase implicated in DNA replication) (Popenoe & Schmaeler, 1979) and O^6-methylguanine-DNA methyl transferase (Bhattacharyya *et al.*, 1988). Other effects on DNA repair have been reviewed (Rossman *et al.*, 1992).

Cadmium ion induces a number of genes in animal cells. Doses of 5–10 μM [917–1834 μg] cadmium chloride induced transient accumulation of c-*jun* and c-*myc* mRNA 2–4 h after treatment of L6J1 rat myoblasts (Jin & Ringertz, 1990). Cadmium chloride inhibited differentiation of *Drosophila* embryonic cultures, while inducing the entire set of heat-shock proteins (Bournias-Vardiabasis *et al.*, 1990). It also induced haem oxygenase in human skin fibroblasts (Keyse & Tyrrell, 1989) and rat small intestinal epithelium (Rosenberg & Kappas, 1991) and metallothionein in Leydig cells (Abel *et al.*, 1991). The induction of hepatocytic transdifferentiation by cadmium in rat pancreas (Konishi *et al.*, 1990) and characteristics of the granulocyte phenotype in promyelocytic leukaemic cells (Richards *et al.*, 1988) also suggest that it can modify gene expression.

Various researchers have reported that cadmium affects the spindle apparatus (possibly through interactions with thiol compounds, which have a high affinity for cadmium ion [$pK_d \sim 17$] [Verbost *et al.*, 1989]). Kogan *et al.* (1978) and Ramel and Magnusson (1979)

Table 14. Genetic and related effects of cadmium and cadmium compounds

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
***Itai-itai* patients**				
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	–		0.029 (blood, max.) 0.031 (per g urinary creatinine, max.)	Bui *et al.* (1975)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	+		NR	Shiraishi (1975)
AVH, Aneuploidy, human lymphocytes *in vivo*	+		NR	Shiraishi (1975)
Environmental/dietary exposure				
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	–		0.01 (blood) 0.01 (per g urinary creatinine)	Nogawa *et al.* (1986)
SLH, Chromosomal aberrations, human lymphocytes *in vivo*	+		NR 0.003 (urine, men) 0.004 (urine, women)	Tang *et al.* (1990)
Occupational exposure				
SLH, Sister chromatid exchange, human lymphocytes *in vivo*	–		NR	Dziekanowska (1981)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	?[b]		0.032 (blood)	Deknudt & Léonard (1975)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	–		0.061 (blood) 0.031 (per g urinary creatinine, max.)	Bui *et al.* (1975)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	(+)[b]		0.004 (blood)	Bauchinger *et al.* (1976)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	–		0.020 (blood)	O'Riordan *et al.* (1978)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	(+)		NR	Dziekanowska (1980)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	–		0.038 (blood)	Fleig *et al.* (1983)
CLH, Chromosomal aberrations, human lymphocytes *in vivo*	+		0.0003–0.0283 (blood) 0.0015–0.0316 (urine)	Forni *et al.* (1990)

Table 14 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium acetate				
DIA, DNA strand breaks, cross-links, hamster fibroblasts *in vitro*	+	0	0.11	Casto (1983)
SIC, Sister chromatid exchange, Chinese hamster DON cells *in vitro*	-	0	0.13	Ohno *et al.* (1982)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay *in vitro*	+	0	0.04	DiPaolo & Casto (1979)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay *in vitro*	(+)	0	0.21	Rivedal & Sanner (1981)
T7S, Cell transformation, SA7/Syrian hamster embryo cells *in vitro*	+	0	0.11	Casto *et al.* (1979)
DIH, DNA strand breaks, cross-links, human cells *in vitro*	+	0	21	Casto (1983)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	(+)	0	11.2	Gasiorek & Bauchinger (1981)
Cadmium chloride				
PRB, λ Prophage induction/SOS/strand breaks/cross-links	-	0	7.2	Rossman *et al.* (1984)
ECB, *Escherichia coli*, DNA strand breaks	+	0	0.34	Mitra & Bernstein (1978)
BSD, *Bacillus subtilis rec* strains, differential toxicity	+	0	280	Nishioka (1975)
BSD, *Bacillus subtilis rec* strains, differential toxicity	+	0	28	Kanematsu *et al.* (1980)
ERD, *Escherichia coli* differential toxicity	+	+	60	De Flora *et al.* (1984a)
SAF, *Salmonella typhimurium* TA1537, forward mutation to 8-azaguanine resistance	+	0	56	Mandel & Ryser (1984)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	150	Bruce & Heddle (1979)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	0	1120	Tso & Fung (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	0	56	Mandel & Ryser (1984)

Table 14 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium chloride (contd)				
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	610	Mortelmans *et al.* (1986)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SA2, *Salmonella typhimurium* TA102, reverse mutation	(+)	(+)	8	De Flora *et al.* (1984b)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	+	0	56	Mandel & Ryser (1984)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	610	Mortelmans *et al.* (1986)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	150	Bruce & Heddle (1979)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	+	0	56	Mandel & Ryser (1984)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	610	Mortelmans *et al.* (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	150	Bruce & Heddle (1979)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	610	Mortelmans *et al.* (1986)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	NR	De Flora *et al.* (1984b)
SAS, *Salmonella typhimurium* TA1975, reverse mutation	(+)	–	56	Mandel & Ryser (1984)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–[c]	0	22.4	Pagano & Zeiger (1992)
SCG, *Saccharomyces cerevisiae*, gene conversion	+	0	11.2	Fukunaga *et al.* (1982)
SCG, *Saccharomyces cerevisiae*, gene conversion	+	0	61	Schiestl *et al.* (1989)
SCR, *Saccharomyces cerevisiae*, reverse mutation	–	0	34	Fukunaga *et al.* (1982)
SCN, *Saccharomyces cerevisiae*, aneuploidy	–	0	50	Whittaker *et al.* (1989)
SCN, *Saccharomyces cerevisiae*, aneuploidy	–	0	9	Albertini (1990)
ANN, *Aspergillus nidulans*, aneuploidy	–	0	610	Crebelli *et al.* (1991)
PLI, *Vicia faba*, micronuclei	+	0	45	De Marco *et al.* (1988)

Table 14 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium chloride (contd)				
PLI, Water hyacinth root tips, micronuclei	+	0	0.006	Rosas *et al.* (1984)
PLN, Chinese spring wheat, aneuploidy	+	0	0.61	Sandhu *et al.* (1991)
DMM, *Drosophila melanogaster*, somatic mutation or recombination	-		240	Rasmuson (1985)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	-		30	Inoue & Watanabe (1978)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	-		112	Kogan *et al.* (1978)
DMX, *Drosophila melanogaster*, sex-linked recessive lethal mutations	-		30	Chung & Kim (1982)
DMN, *Drosophila melanogaster*, aneuploidy	-		38	Ramel & Magnusson (1979)
DMN, *Drosophila melanogaster*, aneuploidy	+		12	Osgood *et al.* (1991)
DIA, DNA strand breaks, Chinese hamster ovary cells *in vitro*	+	0	11	Robison *et al.* (1982)
DIA, DNA strand breaks, Chinese hamster ovary cells *in vitro*	-	0	112	Hamilton-Koch *et al.* (1986)
DIA, DNA strand breaks, cross-links, Chinese hamster V79 cells *in vitro*	+	0	2.24	Ochi & Ohsawa (1983)
DIA, DNA strand breaks, TRL-1215 rat liver cells *in vitro*	+	0	56	Coogan *et al.* (1992)
DIA, DNA strand breaks, rat primary Leydig cells *in vitro*	-	0	45	Koizumi *et al.* (1992)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus, *in vitro*	+	0	0.11	Ochi & Ohsawa (1983)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus, *in vitro*	(+)	0	0.22	Hartwig & Beyersmann (1989)
G9H, Gene mutation, Chinese hamster lung V79 cells, *hprt* locus, *in vitro*	+	0	0.001	Kanematsu *et al.* (1990)

Table 14 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium chloride (contd)				
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus, *in vitro*	(+)	0	0.07	Amacher & Paillet (1980)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus, *in vitro*	+	0	0.09	McGregor *et al.* (1988)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	-	0	0.045	Deaven & Campbell (1980)
SIC, Sister chromatid exchange, Don Chinese hamster cells *in vitro*	-	0	0.11	Ohno *et al.* (1982)
SIC, Sister chromatid exchange, Chinese hamster ovary cells *in vitro*	+	0	0.001	Howard *et al.* (1991)
MIA, Micronucleus test (aneuploidy), Chinese hamster lung Cl-1 cells	+	0	1.22	Antoccia *et al.* (1991)
CIC, Chromosomal aberrations, Chinese hamster V79 cells *in vitro*	+	0	0.11	Deaven & Campbell (1980)
CIC, Chromosomal aberrations and polyploidy, Chinese hamster V79 cells *in vitro*	+	0	0.11	Ochi *et al.* (1984)
CIC, Chromosomal aberrations, Chinese hamster V79 cells *in vitro*	+	0	1.12	Ochi & Ohsawa (1985)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	0	0.06	Lakkad *et al.* (1986)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	0	0.01	Howard *et al.* (1991)
CIT, Chromosomal aberrations, mouse mammary carcinoma cells *in vitro*	-	0	3.58	Umeda & Nishimura (1979)
TBM, Cell transformation, BALB/c 3T3 mouse cells *in vitro*	+	0	0.17	Saffiotti & Bertolero (1989)

Table 14 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium chloride (contd)				
TCL, Cell transformation, rat ventral prostate cells *in vitro*	+	0	0.003 × 7 days	Terracio & Nachtigal (1986)
TCL, Cell transformation, Indian muntjac skin fibroblasts *in vitro*	+	0	0.56 × 20 months	Chibber & Ord (1990)
T7S, Cell transformation, SA7/Syrian hamster embryo cells *in vitro*	+	0	0.22	Casto *et al.* (1979)
DIH, DNA strand breaks, human lymphocytes *in vitro*	+	0	2.8	Zasukhina & Sinelschikova (1976)
DIH, DNA strand breaks, human lymphocytes *in vitro*	-	0	5.6	McLean *et al.* (1982)
DIH, DNA strand breaks, human diploid (HSBP) fibroblasts *in vitro*	+	0	14	Hamilton-Koch *et al.* (1986)
DIH, DNA strand breaks, human diploid (HSBP) fibroblasts *in vitro*	+	0	14	Snyder (1988)
MIH, Micronuclei (aneuploidy), human LEO fibroblasts *in vitro*	+	0	0.03	Bonatti *et al.* (1992)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	+	0	0.56	Han *et al.* (1992)
CHL, Chromosomal aberrations, human lymphocytes *in vitro*	-	0	5.6	Deknudt & Deminatti (1978)
SVA, Sister chromatid exchange, mouse bone-marrow cells *in vivo*	+	0	0.51, ip × 1	Mukherjee *et al.* (1988b)
SVA, Sister chromatid exchange, pregnant mouse bone-marrow cells *in vivo*	-	0	7, sc × 1	Nayak *et al.* (1989)
SVA, Sister chromatid exchange, mouse fetal liver and lung cells *in vivo*	-	0	7, transplacentally × 1	Nayak *et al.* (1989)
MVM, Micronuclei, mice *in vivo*	-	0	9.15, ip	Bruce & Heddle (1979)
MVM, Micronuclei, mice *in vivo*	-	0	50, in drinking-water × 7 days	Watanabe *et al.* (1982)

Table 14 (contd)

Test system	Result		Dose (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium chloride (contd)				
MVM, Micronuclei, mice *in vivo*	+	0	0.92, ip × 1	Kozachenko *et al.* (1987)
MVM, Micronuclei, mice *in vivo*	(+)	0	4.12, ip × 1	Mukherjee *et al.* (1988b)
MVM, Micronuclei, mice *in vivo*	-	0	0.06, po × 2	Volkova & Karplyuk (1990)
MVM, Micronuclei, mice *in vivo*	-	0	6.10, ip × 1	Adler *et al.* (1991)
MVM, Micronuclei, mice *in vivo*	+	0	0.43, ip × 1	Han *et al.* (1992)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	-	0	44, in diet × 1 month	Deknudt & Gerber (1979)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	+	0	0.26, ip × 1	Mukherjee *et al.* (1988b)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	+		1.07, po × 7–21 days	Mukherjee *et al.* (1988a)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	-		30.5, ip × 1	Chopikashvili *et al.* (1989)
CBA, Chromosomal aberrations, mouse bone-marrow cells *in vivo*	+		0.43, ip × 1	Han *et al.* (1992)
CGC, Chromosomal aberrations, mouse spermatocytes *in vivo*	-		1.83, ip × 1	Gilliavod & Léonard (1975)
DLM, Dominant lethal mutation, mice *in vivo*	-		4.3, ip × 1	Epstein *et al.* (1972)
DLM, Dominant lethal mutation, mice *in vivo*	-		1.07, ip × 1	Gilliavod & Léonard (1975)
DLM, Dominant lethal mutation, mice *in vivo*	-		1.22, ip × 1	Suter (1975)
DLM, Dominant lethal mutation, mice *in vivo*	-		2.44, ip × 1	Ramaiya & Pomerantseva (1977)
DLM, Dominant lethal mutation, mice *in vivo*	-		2.44 ip × 1	Pomerantseva *et al.* (1980)
DLM, Dominant lethal mutation, mice *in vivo*	(+)		1.83, po × 5 days	Bleyl & Lewerenz (1980)

Table 14 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium chloride (contd)				
DLR, Dominant lethal mutation, rats *in vivo*	-		6.10, po × 6 weeks	Sutou *et al.* (1980b)
MHT, Heritable translocation, mice *in vivo*	-		1.07, ip × 1	Gilliavod & Léonard (1975)
AVA, Aneuploidy, mouse oocytes *in vivo*	(+)		3.66, sc × 1	Shimada *et al.* (1976)
AVA, Aneuploidy, mouse oocytes *in vivo*	(+)		3.66, sc × 1	Watanabe *et al.* (1977)
AVA, Aneuploidy, mouse oocytes *in vivo*	-		3.66, ip × 1	Mailhes *et al.* (1988)
AVA, Aneuploidy, Syrian hamster oocytes *in vivo*	+		0.61, sc × 1	Watanabe *et al.* (1979)
AVA, Aneuploidy, mouse spermatocytes *in vivo*	(+)		3.66, ip × 1	Miller & Adler (1992)
SPM, Sperm morphology, mice *in vivo*	+		2.44, ip × 1	Pomerantseva *et al.* (1980)
SPM, Sperm morphology, mice *in vivo*	-		9, ip, × 5	Bruce & Heddle (1979)
SPM, Sperm morphology, mice *in vivo*	+		0.51, ip × 5	Mukherjee *et al.* (1988b)
SPM, Sperm morphology, mice *in vivo*	+		0.37, ip × 1	Han *et al.* (1992)
***, Inhibition of DNA synthesis, mouse testis *in vivo*	+		10, ip × 1	Friedman & Staub (1976)
***, Decreased chromosome length, human lymphocytes *in vitro*	+	0	1.12, 4 h	Andersen *et al.* (1983)
***, Stimulation of DNA synthesis in mouse liver and other organs *in vivo*	+		1, ip × 1	Hellman (1986)
Cadmium nitrate				
BSD, *Bacillus subtilis rec* strains, differential toxicity	-	0	280	Nishioka (1975)
BSD, *Bacillus subtilis rec* strains, differential toxicity	+	0	28	Kanematsu *et al.* (1980)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	0	NR	Arlauskas *et al.* (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	0	NR	Arlauskas *et al.* (1985)

Table 14 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium nitrate (contd)				
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	0	NR	Arlauskas *et al.* (1985)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	0	NR	Arlauskas *et al.* (1985)
SA9, *Salmonella typhimurium* TA98, reverse mutation	–	0	NR	Arlauskas *et al.* (1985)
ECR, *Escherichia coli* DG1153, reverse mutation	–[d]	0	NR	Arlauskas *et al.* (1985)
SIC, Sister chromatid exchange, Chinese hamster DON cells *in vitro*	–	0	0.18	Ohno *et al.* (1982)
DMM, *Drosophila melanogaster*, somatic mutation or recombination	–		132	Rasmuson (1985)
Cadmium sulfate				
ERD, *Escherichia coli* differential toxicity	+	+	67	De Flora *et al.* (1984a)
BSD, *Bacillus subtilis rec* strains, differential toxicity	+	0	28	Kanematsu *et al.* (1980)
SAS, *Salmonella typhimurium* TA97, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SA8, *Salmonella typhimurium* TA98, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SA0, *Salmonella typhimurium* TA100, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SA2, *Salmonella typhimurium* TA102, reverse mutation	(+)	(+)	7	De Flora *et al.* (1984b)
SA2, *Salmonella typhimurium* TA102, reverse mutation	–	0	0.03	Marzin & Phi (1985)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	–	–	NR	De Flora *et al.* (1984a)
SCG, *Saccharomyces cerevisiae*, gene conversion	+	0	54	Schiestl *et al.* (1989)
DIA, DNA strand breaks, rat hepatocytes *in vitro*	+	0	3.36	Sina *et al.* (1983)
G5T, Gene mutation, mouse lymphoma L5178Y cells, *tk* locus *in vitro*	+	0	0.08	Oberly *et al.* (1982)
CIC, Chromosomal aberrations, Chinese hamster fibroblasts *in vitro*	+	0	11.2	Röhr & Bauchinger (1976)

Table 14 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium sulfate (contd)				
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	0	0.11	Armstrong *et al.* (1992)
CIC, Chromosomal aberrations, Chinese hamster ovary cells *in vitro*	+	0	0.22	Bean *et al.* (1992)
SHL, Sister chromatid exchange, human lymphocytes *in vitro*	-	0	0.69	Bassendowska-Karska & Zawadzka-Kos (1987)
HMA, Chromosomal aberrations, mouse ascites tumour cells *in vivo*	-		0.02, parenterally × 1	Bishun & Pentecost (1981)
Cadmium sulfide				
DIA, DNA strand breaks, Chinese hamster ovary cells *in vitro*[e]	+	0	8 × 24 h	Robison *et al.* (1982)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay *in vitro*[e]	+	0	0.78	Costa *et al.* (1982)
TCS, Cell transformation, Syrian hamster embryo cells, clonal assay *in vitro*[f]	-	0	3.90	Costa *et al.* (1982)
CHL, Chromosomal aberrations, human lymphocytes *in vitro* (unspecified)	+	0	0.05 × 4 h	Shiraishi *et al.* (1972)
Cadmium oxide				
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	0	1466	Mortelmans *et al.* (1986)
SA5, *Salmonella typhimurium* TA1535, reverse mutation	-	0	147	Mortelmans *et al.* (1986)
SA7, *Salmonella typhimurium* TA1537, reverse mutation	-	0	147	Mortelmans *et al.* (1986)

Table 14 (contd)

Test system	Result		Dose[a] (LED/HID)	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Cadmium oxide (contd)				
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	0	1466	Mortelmans *et al.* (1986)
Cadmium carbonate				
PLI, *Vicia faba*, micronuclei	-[g]	0	0	De Marco *et al.* (1988)

+, considered to be positive; (+), considered to be weakly positive in an inadequate study; -, considered to be negative; ?, considered to be inconclusive (variable responses in several experiments within an adequate study); 0, not tested

[a]LED, lowest effective dose; HID, highest ineffective dose. In-vitro tests, μg/ml; in-vivo tests, mg/kg bw. Doses given as concentration of element, not concentration of compound. ip, intraperitoneally; sc, subcutaneously; po, orally, by gavage; NR, not reported

[b]Exposed to lead and cadmium

[c]Positive at 12.5–25 μM in distilled deionized water

[d]Positive in fluctuation assay for *E. coli* DG1153 at 0.67 μg/ml

[e]Crystalline cadmium sulfide

[f]Amorphous cadmium sulfide

[g]Induced by 8×10^{-4} M in the presence of equimolar nitrilotriacetic acid 3Na salt

***Not displayed on profiles

reported non-disjunction of meiotic chromosomes in *D. melanogaster* after exposure to cadmium, suggesting damage to the mitotic apparatus. Lakkad *et al.* (1986) observed chromosomal damage after exposure of Chinese hamster ovary cells to very low concentrations of cadmium *in vitro*, which included micronuclei, lagging chromosomes, chromatid bridges and multinucleated cells, suggesting spindle damage. A project for the validation of tests for aneuploidy coordinated by the Commission of the European Communities included cadmium chloride among 10 known or presumed spindle poisons: Cadmium-induced spindle disturbances and aneuploidy were observed in test systems ranging from yeast to human cells and in mice *in vivo* (Table 14). Cadmium chloride also inhibited the assembly of purified *Drosophila* microtubules *in vitro* (Sehgal *et al.*, 1990).

The ionic charge and radius of Cd^{2+} are comparable to those of Ca^{2+} (Chao *et al.*, 1984). Thus, Cd^{2+} could conceivably replace Ca^{2+} at cellular Ca^{2+} binding sites and lead to disturbances in cellular calcium homeostasis. Verbost *et al.* (1989) observed inhibition of Ca^{2+}-ATPase-mediated Ca^{2+} extrusion in erythrocyte ghosts by Cd^{2+} at nanomolar concentrations, with involvement of thiol groups. [The Working Group noted that this effect occurred at very low concentrations and could have many consequences for cellular metabolism.]